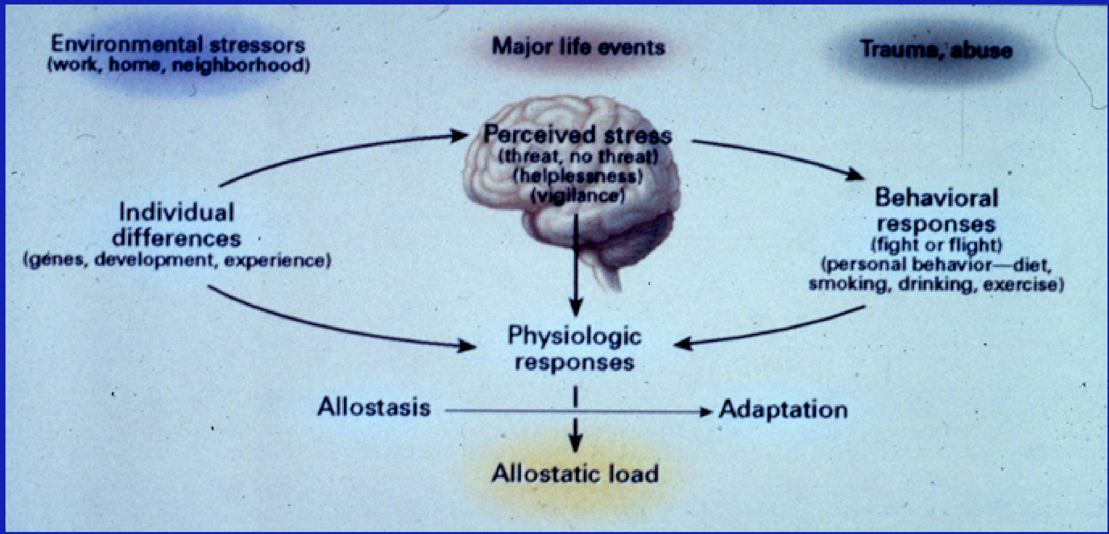
The Neurobiology of Stress and Adaptation

Part 1

The Big Picture



Stress and adaptation: central role of the brain

-Protective and damaging effects of stress mediators

-Scared stiff - neural basis of fear and anxiety

- Stress hormones have beneficial effects, acting via receptors

- Structural plasticity of the brain.

-Stress effects on behavior and structural plasticity
    - Hippocampus
    - Amygdala
    - Prefrontal cortex

-Sex differences in response to stress

- Importance of the mother - long-lasting effects of early experience -

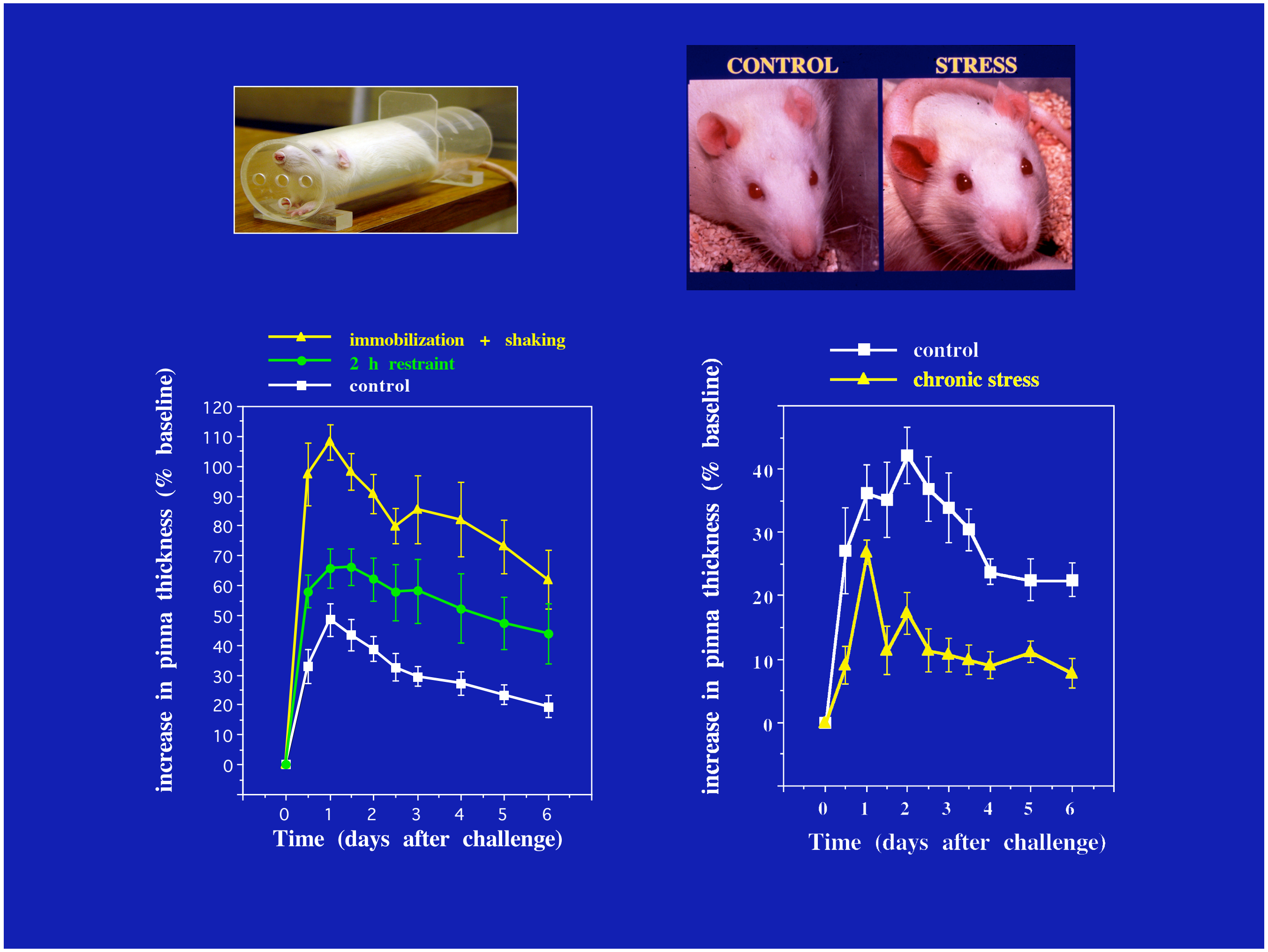
Types of stress

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

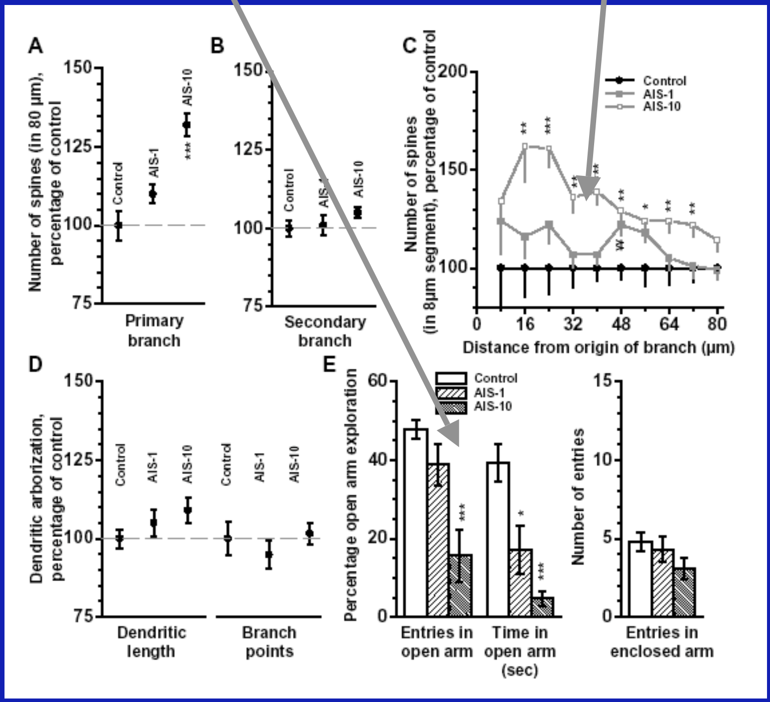
Tolerable stress:
-Adverse life events but good social and emotional support
-Depression is a risk

Toxic stress:
-Chaos, abuse, neglect
-Absence of social and emotional support
-Depression is a likely outcome
-More likely to occur to people with less education and income*

* Adverse childhood experiences (ACE) from toxic stress:
long-lasting - emotional, cognitive, behavioral, systemic consequences


CONTROL
STRESS
immobilization + shaking
2 h restraint
control
increase in pinna thickness (% baseline)
120
110
100
90
80
70
60
50
40
30
20
10
0
0 1 2 3 4 5 6
Time (days after challenge)
control
chronic stress
increase in pinna thickness (% baseline)
40
30
20
10
0
0 1 2 3 4 5 6
Time (days after challenge)

A single immobilization causes delayed spine synapse induction and increased anxiety



Sumantra Chattarji, Bangalore and MIT

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

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 atheroslerosis 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

Sleep deprivation as a chronic stressor:

Disturbed allostasis and allostatic load

Increased blood pressure;
decreased parasympathetic tone.

Elevated evening cortisol, glucose, insulin.

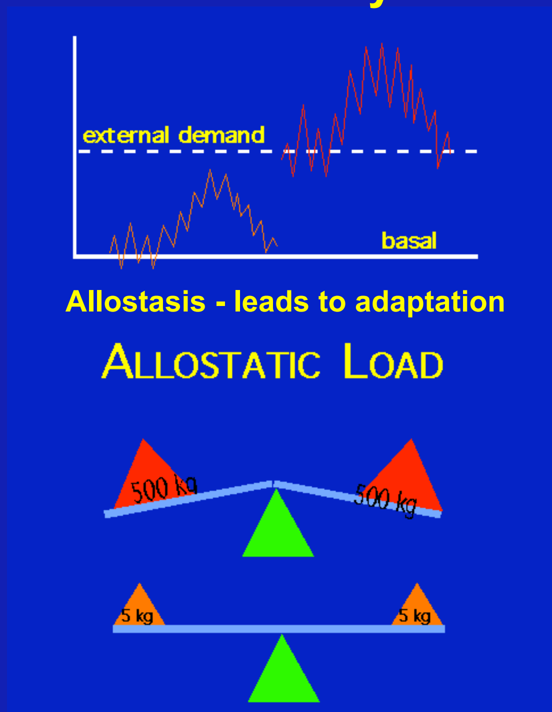
Elevated inflammatory cytokines.

Increased appetite, which can increase 1-3
after over-eating.

Depressed mood.

Impaired cognitive function.

Stress - a challenge to the body



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

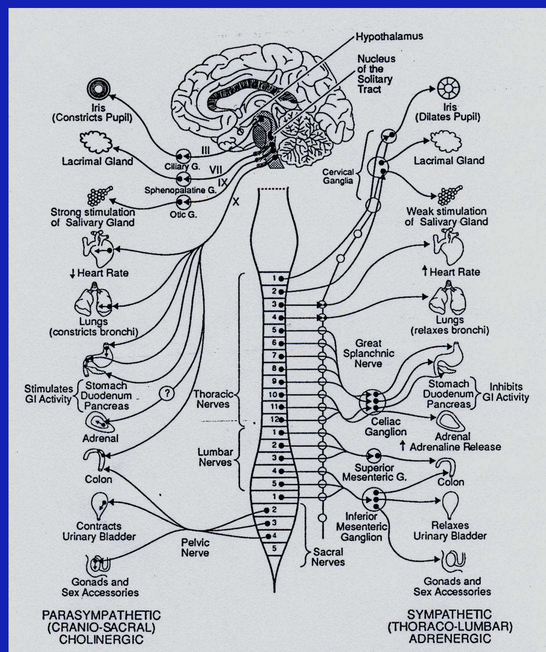
Biological Mediators of Allostasis

Autonomic nervous system

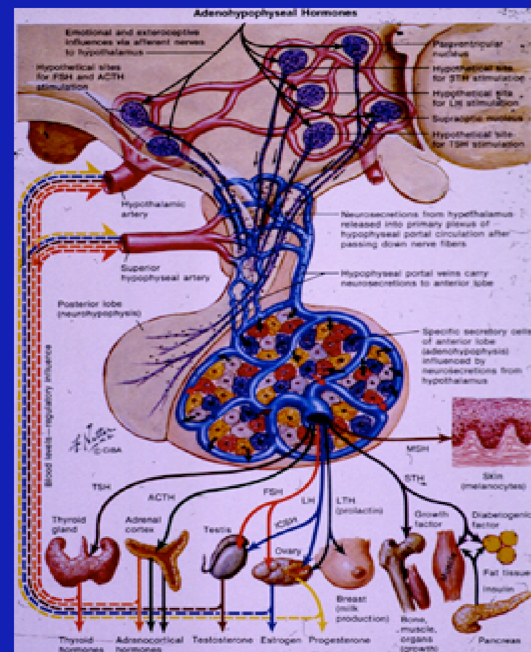
Hormones

Cytokines - immune system “hormones”

Neurotransmitters



Autonomic nervous system



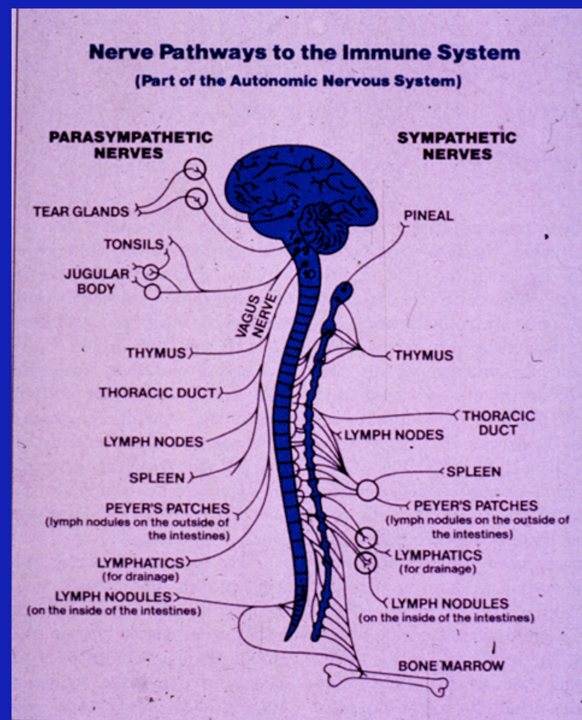
Neuroendocrine System

Brain to immune

Acute stress - enhancement

Chronic stress- immunosuppression

Containment of inflammation



Immune to Brain

Cytokines and sleep

Sickness behavior

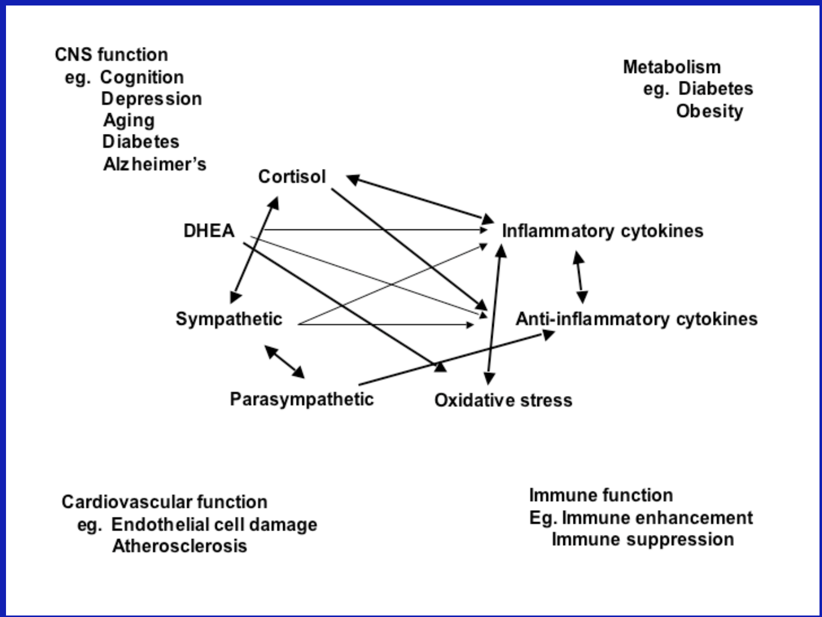
Inflammatory cascade

HPA regulation

Neuroprotection

The immune system is innervated and responds to virtually every hormone in the body

Mediators of stress and adaptation



NON-LINEARITY!!

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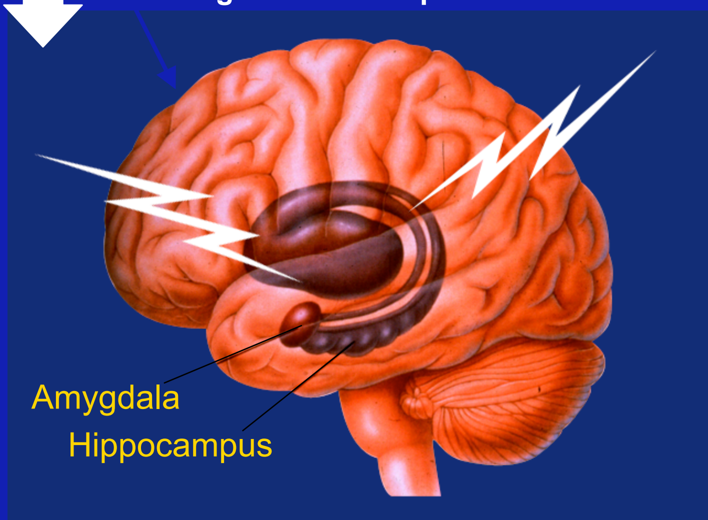
The Human Brain Under Stress:
Control of the Stress Response

Prefrontal cortex
Top down control
Balancing of stress response

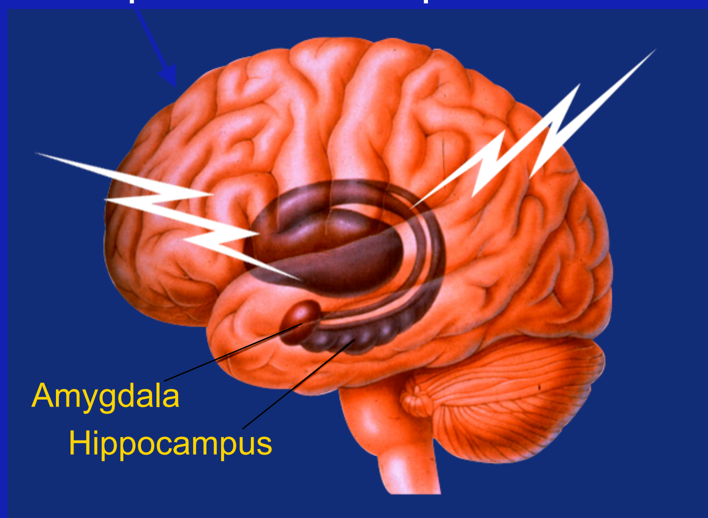


Hippocampus
Shut-off of stress response

Amygdala
Turns on stress response

The Human Brain Under Stress:
Role in cognitive function and emotion

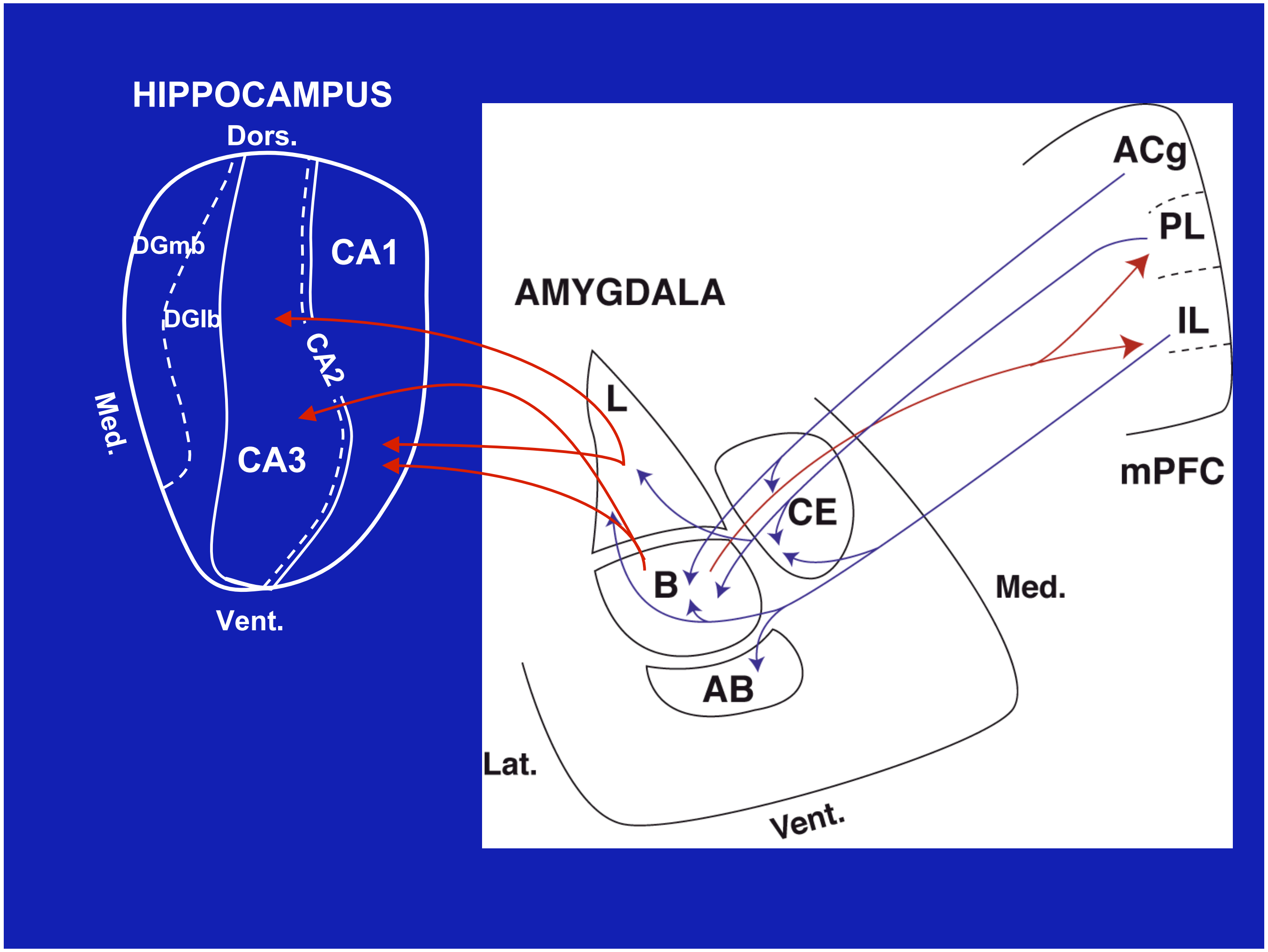
Prefrontal cortex
Decision making, working memory,
Top down control of impulsive behavior

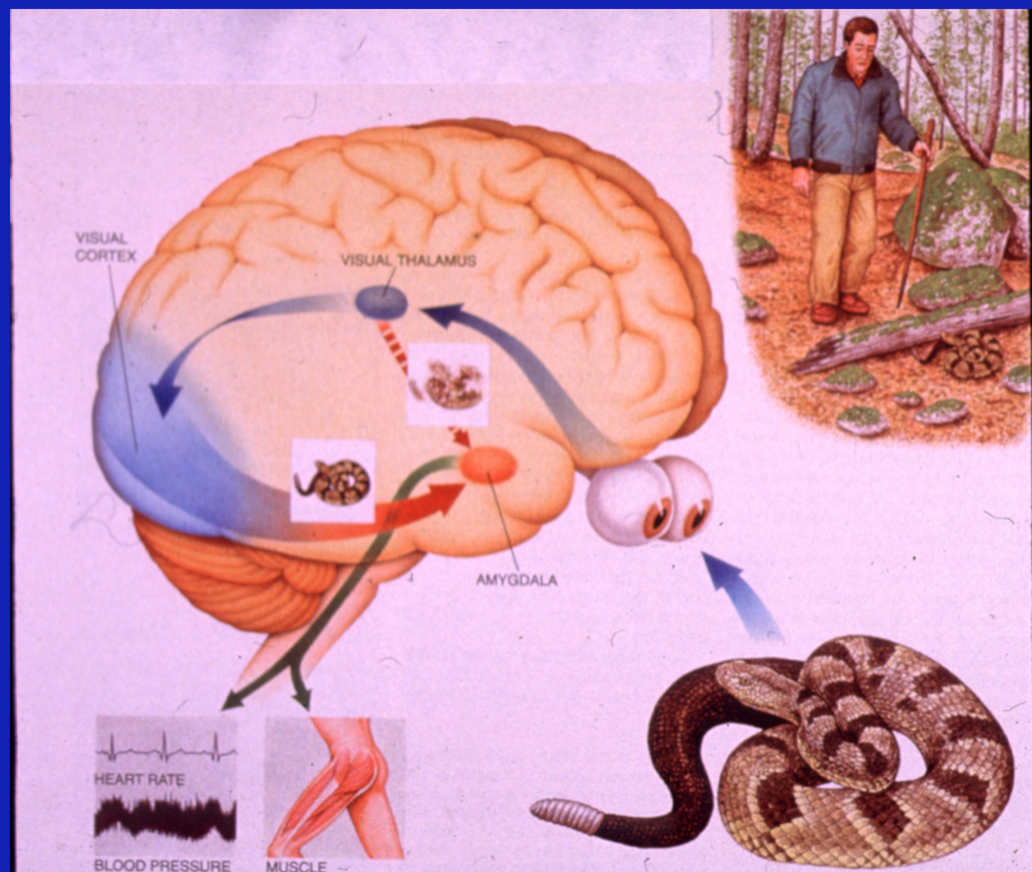


Hippocampus
Contextual, episodic, spatial memory

Amygdala
Emotion. fear, anxiety,

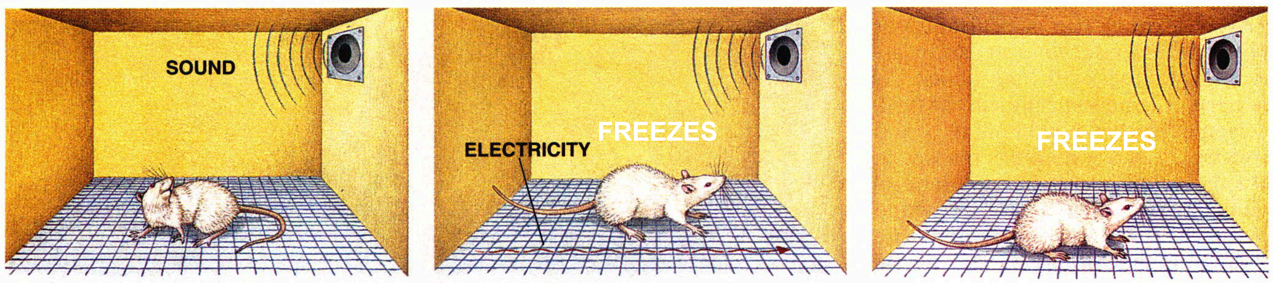
Aggression


HIPPOCAMPUS
Dors.
DGmb
DGlb
CA1
CA2
CA3
Med.
Vent.
AMYGDALA
L
B
CE
AB
Lat.
Vent.
Med.
ACg
PL
IL
mPFC



Joseph Ledoux, New York University

Fear Conditioning



tone | tone+shock | tone

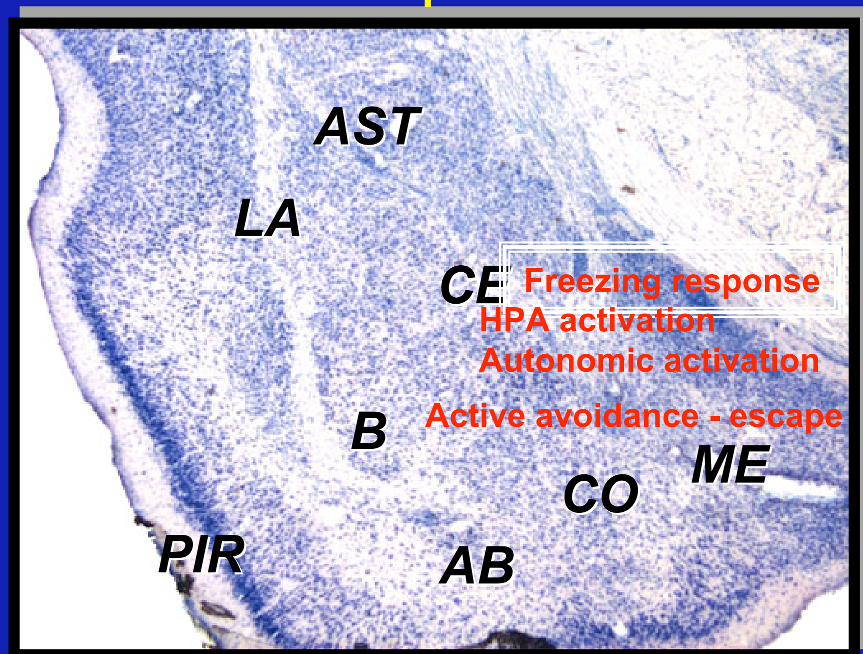
Conditioned Fear Responses

freezing (muscle tension)

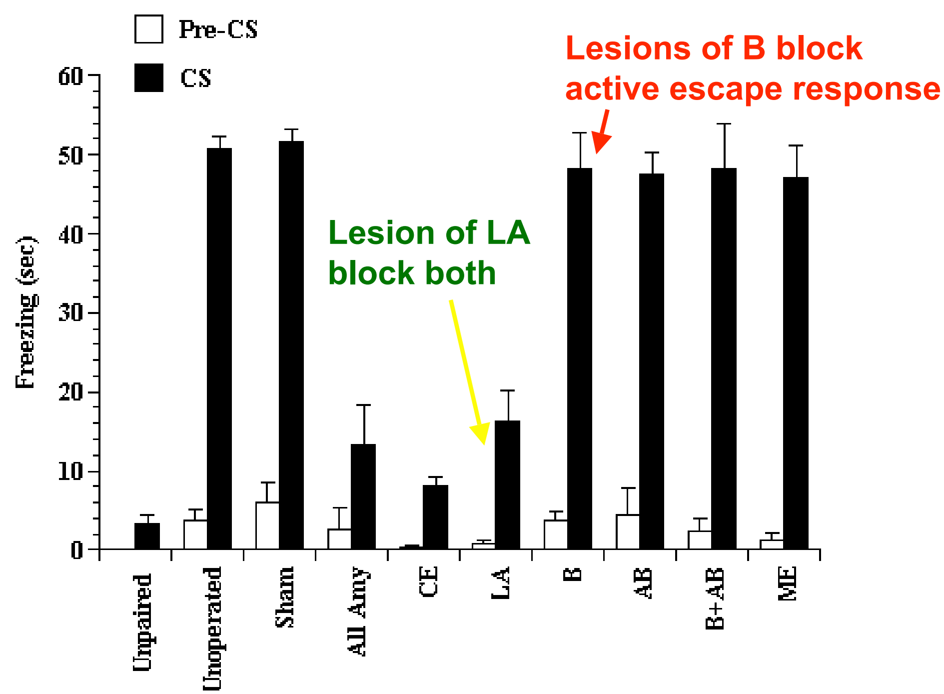
increase in BP, HR, & respiration

stress hormone release

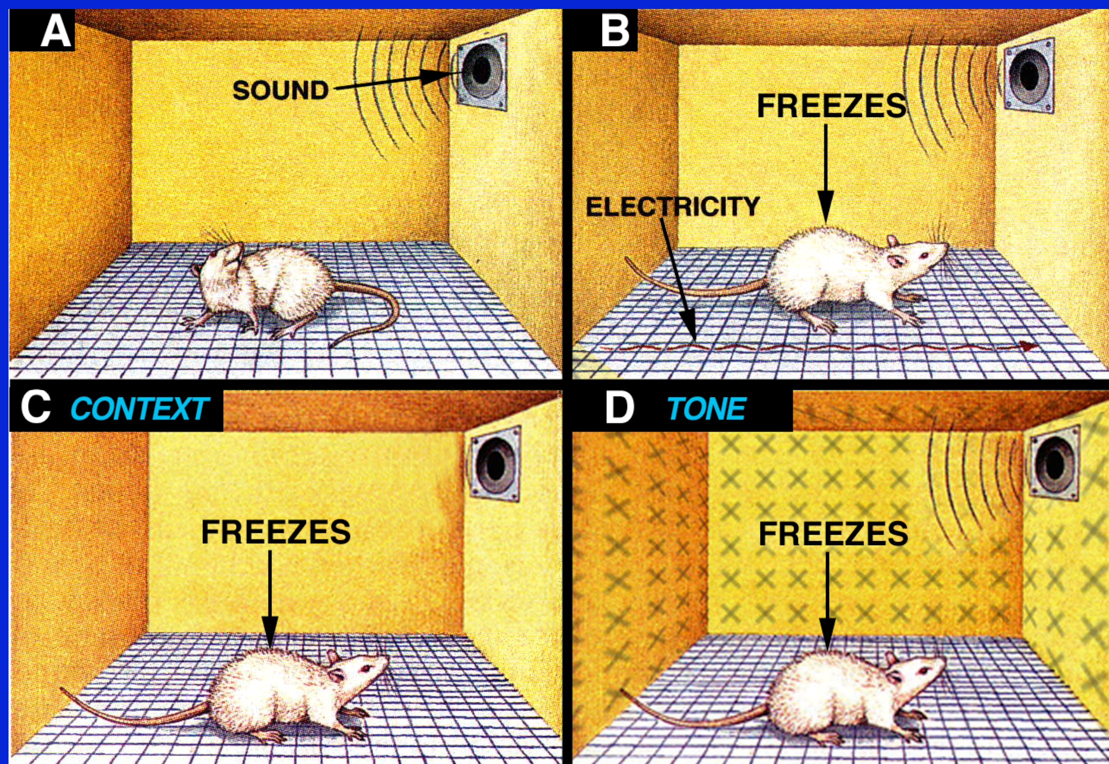
Which Areas of the Amygdala Are Required?



Only the Lateral and Central Nuclei are Necessary for Fear Conditioning



CONTEXTUAL FEAR CONDITIONING



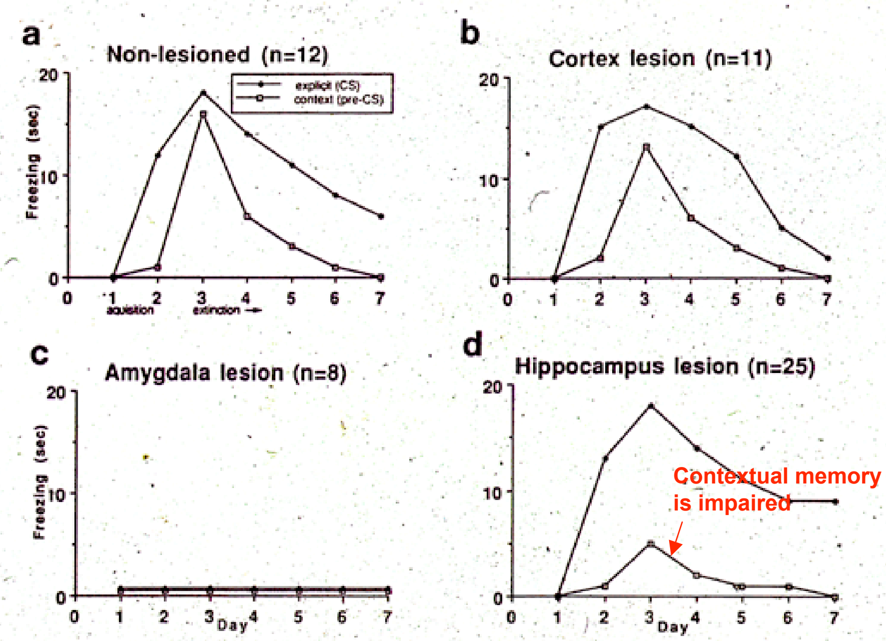


Figure 2. Effects of lesions of the amygdala and hippocampus on the acquisition of conditioned freezing responses to a cued conditioned stimulus (CS) and to contextual stimuli. (Lesions of the amygdala [c] interfere with conditioning to the cued CS and to the context, whereas lesions of the hippocampus [d] only interfere with contextual conditioning, compared with controls [a]. Lesions of the cortex above the hippocampus [b] have no effect on either form of conditioning. Conclusions are based on analysis of variance and post hoc tests.)

Lesions of hippocampus block contextual fear conditioning

Fear learning and the problem of consolidation and reconsolidation

Basic observation: "reminder" of context leads to recall in amnestic animal. Was memory really ever gone? Or did it grow back from a trace?

Table 1. Systemic or ICV administration of protein synthesis inhibitors after memory reactivation

Finding	Inhibitor application[a]	Species	Refs
Contextual fear conditioning memory is disrupted by protein synthesis inhibitors administered either after training or after reactivation	IP	Mouse	[51]
Transcription and translation are required for both consolidation and reconsolidation of a classical conditioning task	Bath	Mollusk (*Hermissenda*)	[31]
Protein synthesis is required for both consolidation and reconsolidation	Pericardial sac	Crab (*Chasmagnathus*)	[52]
Protein synthesis inhibitors impair passive avoidance memory after recall	ICV	Chick	[42]
Both consolidation and reconsolidation of a contextual fear memory require protein synthesis	IP	Mouse	[32]
A reactivated inhibitory avoidance memory is disrupted by protein synthesis inhibition	IP	Rat	[21]
Passive avoidance memory is disrupted by a protein synthesis inhibitor administered after reactivation	ICV	Chick	[36]
A reactivated passive avoidance memory is disrupted by protein synthesis inhibitors (this also occurs after training)	SC	Mouse	[4]

[a]Abbreviations: ICV, intracerebroventricular; IP, intraperitoneal; SC, subcutaneous.

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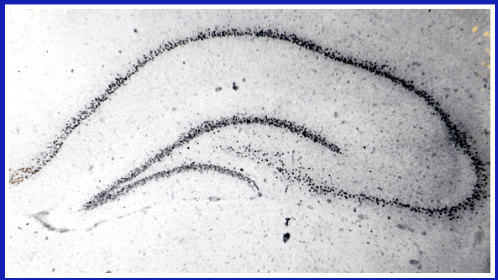
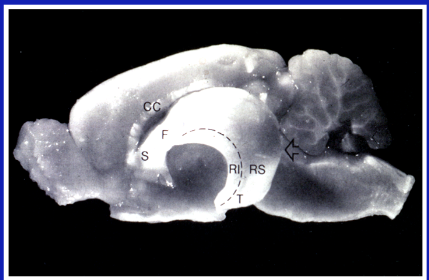
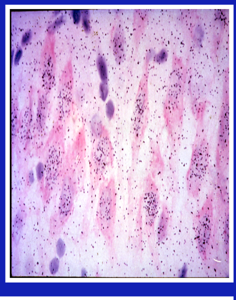
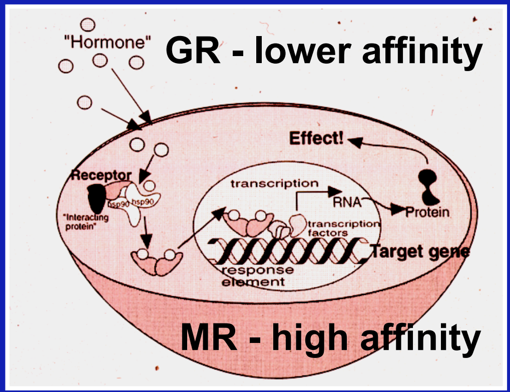
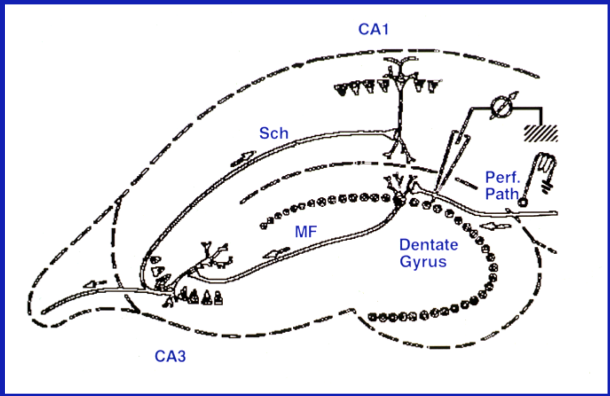
Hippocampus:
Target for Adrenal Steroids











Distribution of Adrenal Steroid Receptors in Brain Regions

•Hippocampus	MR and GR
•Amygdala	GR and some MR
•Septum	GR and some MR
•Hypothalamus	GR mostly; low levels of MR
•Cerebral cortex	GR mostly; low levels of MR
•Midbrain	GR mostly; low levels of MR
•Brainstem	GR mostly; patches of MR
•Cerebellum	GR mostly

Non-nuclear glucocorticoid receptors: association with PSD

L. R. Johnson et al. / Neuroscience 136 (2005) 289–299 293

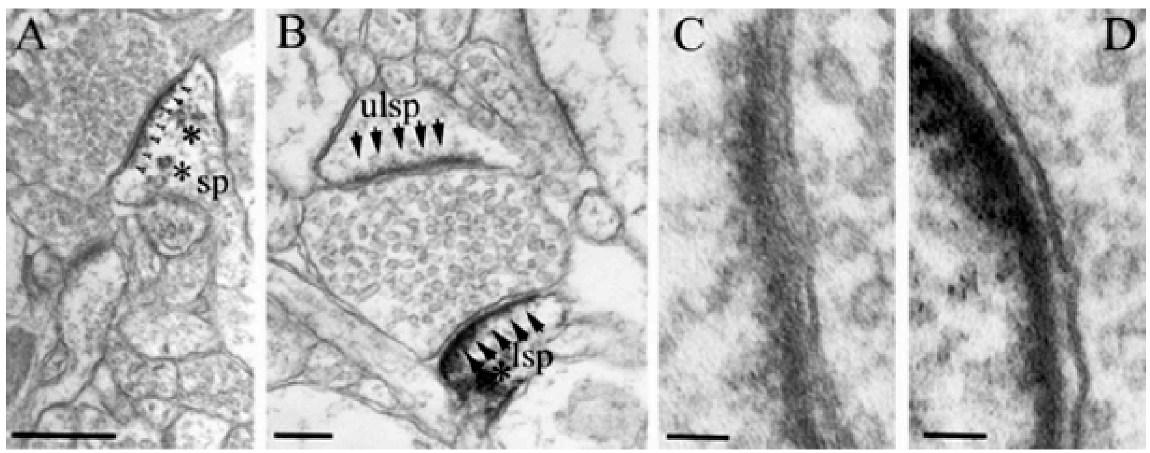
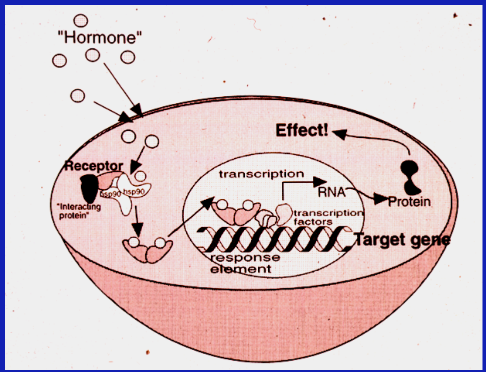
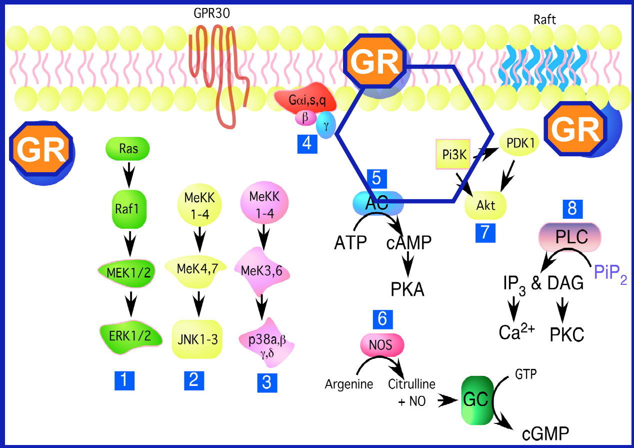


Fig. 3. GR immunolabeling of the PSD. (A) GR-ir labeling of the PSD (arrowheads) of an asymmetrical synapse located on the head of a LA spine (sp). GR-ir spine organelles are also present in the spine head (asterisk). (B) A presynaptic terminal simultaneously forms two asymmetric synapses onto spines (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

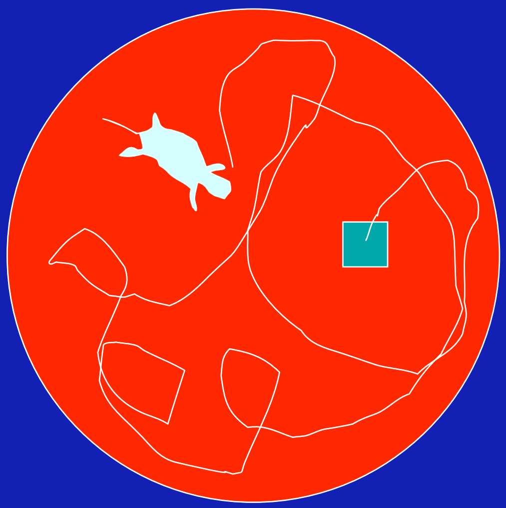
Genomic and non-genomic actions of glucocorticoids





Morris Water Maze - *finding hidden platform*

Rat/mouse learns by finding shortest path to platform using either global spatial cues or local contextual clues



Glucocorticoid receptors (GR) facilitate Morris Water Maze learning;
Defective GR prevent the beneficial action

Glucocorticoid effects on object recognition memory require training-associated emotional arousal

Shoki Okuda*†‡, Benno Roozendaal*, and James L. McGaugh*

*Center for the Neurobiology of Learning and Memory, and Department of Neurobiology and Behavior, University of California, Irvine, CA 92697-3800; and †Banyu Tsukuba Research Institute, Banyu Pharmaceutical Co., Ltd., Tsukuba, Ibaraki 300-2611, Japan

Contributed by James L. McGaugh, November 24, 2003

Considerable evidence implicates glucocorticoid hormones in the regulation of memory consolidation and memory retrieval. The present experiments investigated whether the influence of these hormones on memory depends on the level of emotional arousal induced by the training experience. We investigated this issue in male Sprague–Dawley rats by examining the effects of immediate posttraining systemic injections of the glucocorticoid corticosterone on object recognition memory under two conditions that differed in their training-associated emotional arousal. In rats that were not previously habituated to the experimental context, corticosterone (0.3, 1.0, or 3.0 mg/kg, s.c.) administered immediately after a 3-min training trial enhanced 24-hr retention performance in an inverted-U shaped dose–response relationship. In contrast, corticosterone did not affect 24-hr retention of rats that received extensive prior habituation to the experimental context and, thus, had decreased novelty-induced emotional arousal during training. Additionally, immediate posttraining administration of corticosterone to nonhabituated rats, in doses that enhanced 24-hr retention, impaired object recognition performance at a 1-hr retention interval whereas corticosterone administered after training to well-habituated rats did not impair 1-hr retention. Thus, the present findings suggest that training-induced emotional arousal may be essential for glucocorticoid effects on object recognition memory.

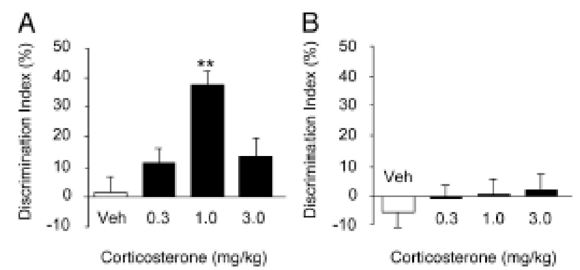
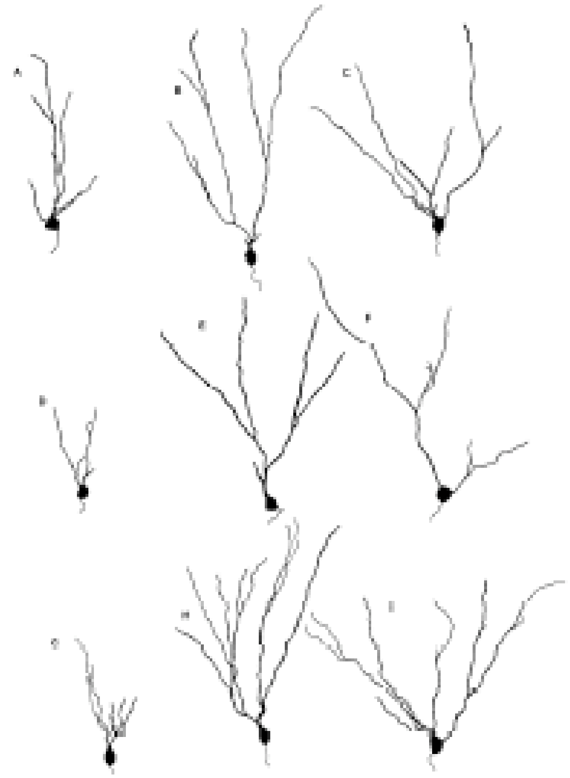


Fig. 1. Posttraining administration of corticosterone enhanced 24-hr object recognition performance of rats in the WITHOUT-habituation (*A*) but not the WITH-habituation (*B*) condition. Rats received a single injection of corticosterone or vehicle immediately after the 3-min training trial. Corticosterone administered in a dose of 1.0 mg/kg significantly enhanced 24-hr object recognition memory of rats in the WITHOUT-habituation condition but failed to affect memory of rats in the WITH-habituation condition. **, $P < 0.0001$ compared with the corresponding vehicle control group (n = 11–13 per group).

“Trophic” effect of Corticosterone!!



Glucocorticoids prevent dentate gyrus cell death 369

Table 1

Morphological variable	Sham operation $n = 5$	Adrenalectomy $n = 6$	Adrenalectomy plus corticosterone $n = 4$
Cell body area of granule cells located in the suprapyramidal blade (μm^2)	181.8 ± 2.7	145.7 ± 4.8*	171.9 ± 6.2
Cell body area of granule cells located in the infrapyramidal blade (μm^2)	196.9 ± 12.8	142.2 ± 4.4*	189.4 ± 7.3
Number of dendritic branch points of granule cells located in the genu	4.9 ± 0.9	2.9 ± 0.4*	4.2 ± 0.2
Number of dendritic branch points of single primary dendrite granule cells	6.4 ± 0.6	4.7 ± 0.3*	5.7 ± 0.4
Number of dendritic branch points of multiple primary dendrite granule cells	5.8 ± 0.5	4.2 ± 0.4*	6.2 ± 0.5
Length of dendrites within 100-μm section of granule cells located in the genu	493.8 ± 61.6	323.1 ± 33.2	392.1 ± 46.7
Length of dendrites within 100-μm section of single primary dendrite granule cells	653.1 ± 64.4	675.7 ± 42.8	759.5 ± 28.2
Length of dendrites within 100-μm section of multiple primary dendrite granule cells	926.0 ± 29.0	765.7 ± 76.4	839.6 ± 48.1
Number of pyknotic cells in dentate gyrus/10^6 μm^2	6.4 ± 1.0	2163.8 ± 556.0*	6.9 ± 2.2

Values represent mean ± standard error. These data were analysed by one-way ANOVA with *post hoc* comparisons (see text). Asterisks equal significant difference ($P < 0.05$) from sham operated.

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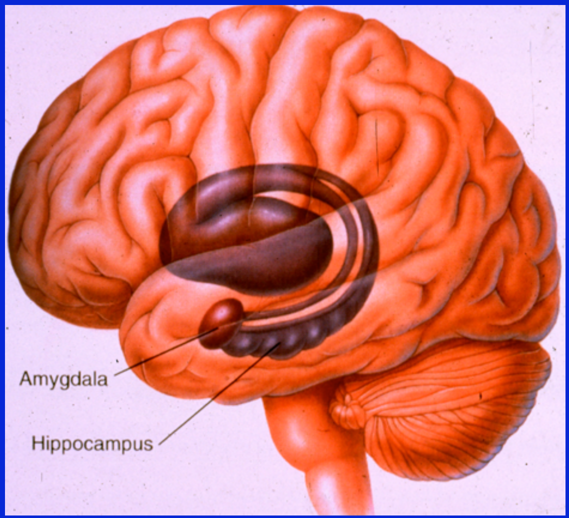
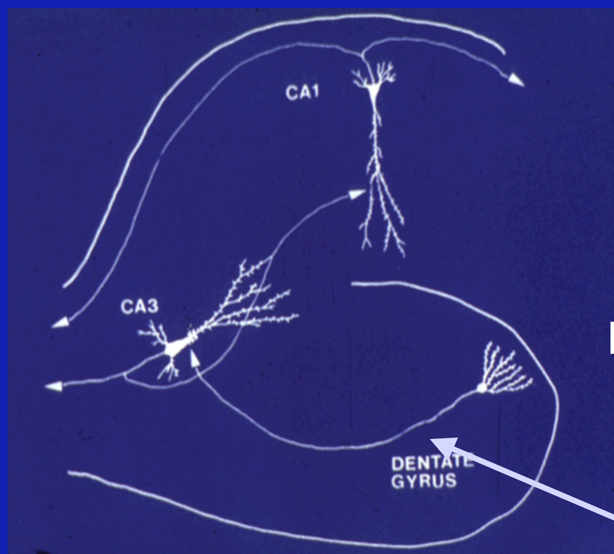
Hippocampus: Study of London Cab Drivers

- **Activation of hippocampus in a spatial task.**
- **Posterior hippocampus - larger volume with longer time on job.**
- **Anterior hippocampus - smaller volume with longer time on job.**
- **Maguire et.al. Proc.Nat.Acad.Sci.US 97: 4398-4403, 2000**



Tri-synaptic circuit in hippocampus



Entry point via entorhinal ctx

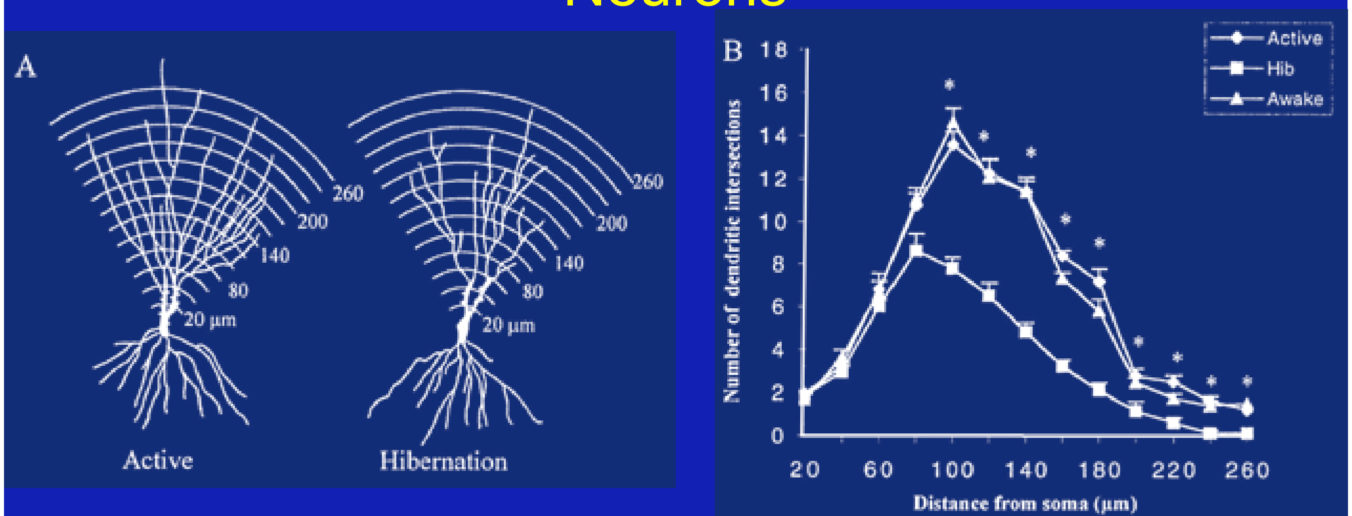
Reciprocal loop : DG - CA3

Memory function of DG - CA3

Vulnerability to damage

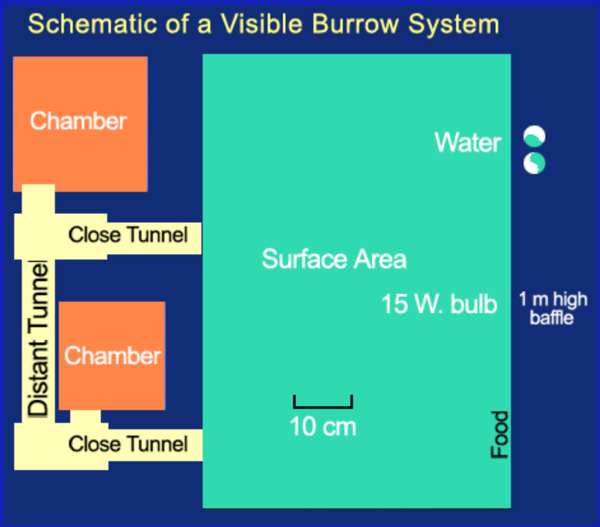
Entorhinal input

Remodeling of Dendrites of Hippocampal Neurons

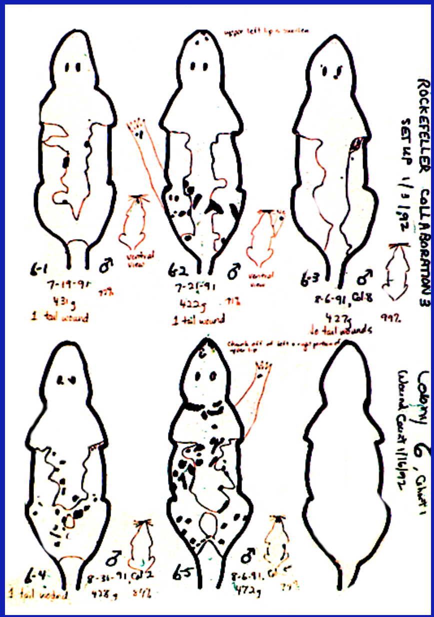


Hibernation in hamsters - remodeling of hippocampal CA3 neurons

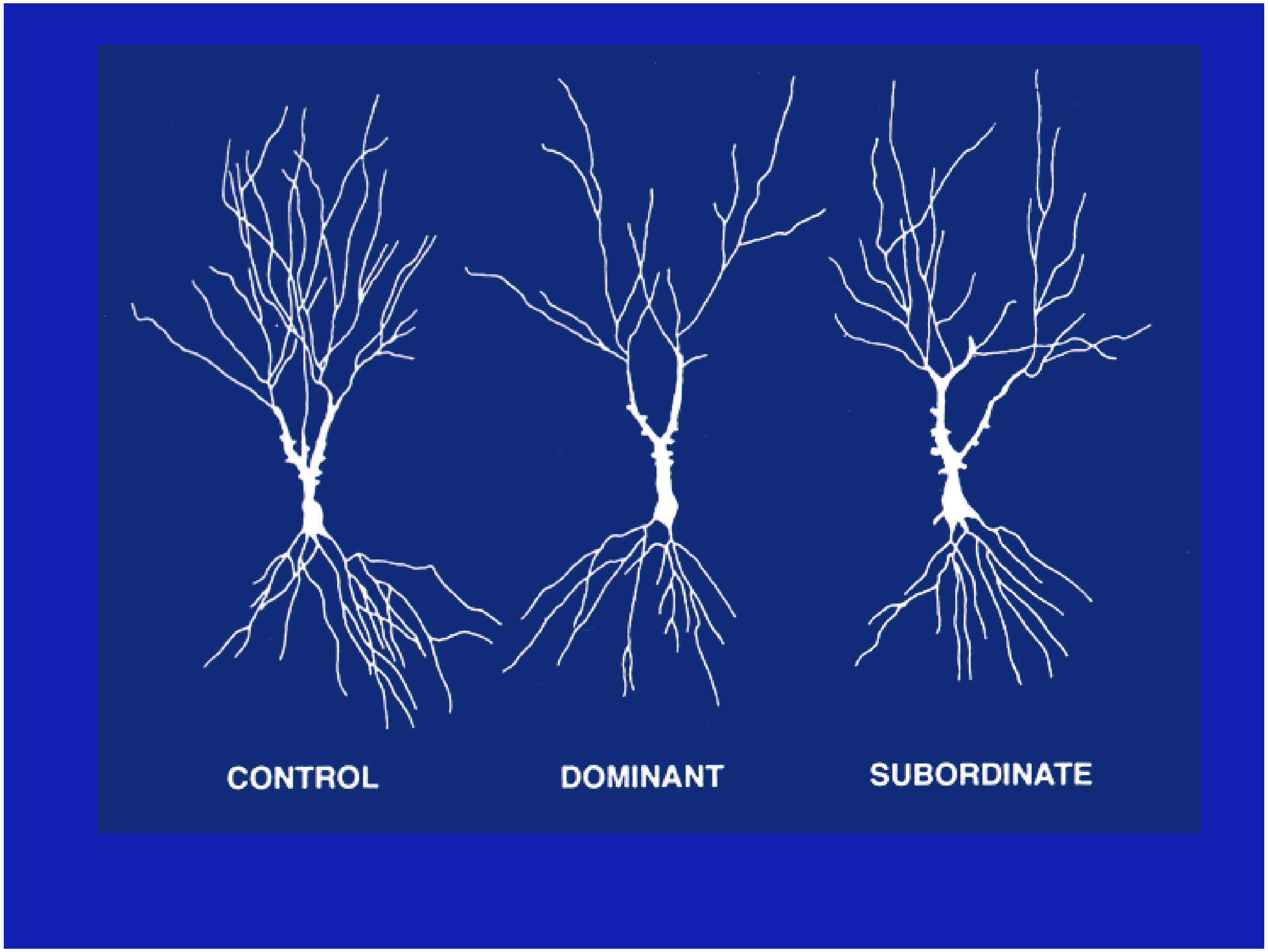
Chronic Stress: VBS



5 males, 2 females
Dominant has fewest scars



<u>Subordinates</u> - low testosterone and high stress hormones; numerous changes in brain chemistry.
<u>Dominants</u> - elevated testosterone and elevated stress hormones compared to cage controls.


CONTROL
DOMINANT
SUBORDINATE

Neurogenesis in dentate gyrus:
GFAP expressing progenitors

ORGANIZATION OF THE VERTEBRATE DENTATE GYRUS 373

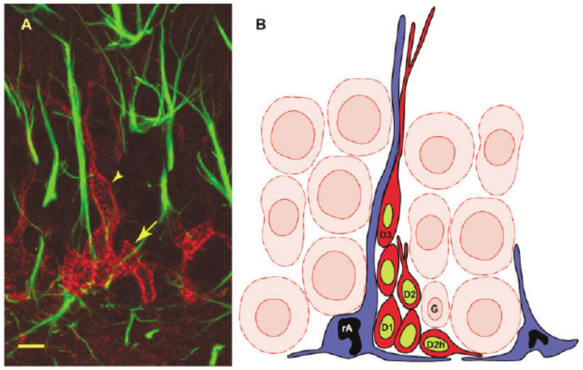


Fig. 9. Model of subgranular zone (SGZ) organization in the coronal plane. A: Confocal image of a coronal brain section immunostained against glial fibrillary acidic protein (GFAP, green) and PSA-NCAM (red). Note the cluster of D1 cells (arrow) at the base of the SGZ and a D2v cell (arrowhead) apposed to a GFAP-positive process. B: Model showing the organization of the SGZ. Astrocytes (rA, blue cytoplasm and black nucleus) with tangential processes at the base of the SGZ. D cells (red cytoplasm and green nucleus) form clusters and as cells mature, they move into the GCL to reside next to older granule neurons (light orange cytoplasm and nucleus). Scale bar = 7 µm in A.

9000 neurons per day in DG.

Survival increased by learning.

Proliferation increased by exercise.

IGF-1 mediates exercise effect.

Stress suppreses neurogenesis.

Antidepressants increase neurogenesis.

Elizabeth Gould, Tracey Shors
Fred Gage, and colleagues
Heather Cameron

Bettina Seri, Arturo Alvarez-Buylla

The Journal of Neuroscience, April 15, 2000, *20*(8):2926–2933

Circulating Insulin-Like Growth Factor I Mediates Effects of Exercise on the Brain

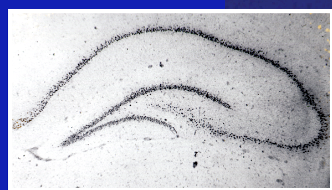
Eva Carro,[1] Angel Nuñez,[2] Svetlana Busiguina,[1] and Ignacio Torres-Aleman[1]

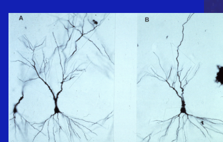
[1]Laboratory of Neuroendocrinology, Cajal Institute, Consejo Superior de Investigaciones Cientificas, 28002 Madrid, Spain, and [2]Department of Morphology, School of Medicine, Autonoma University, 28029 Madrid, Spain

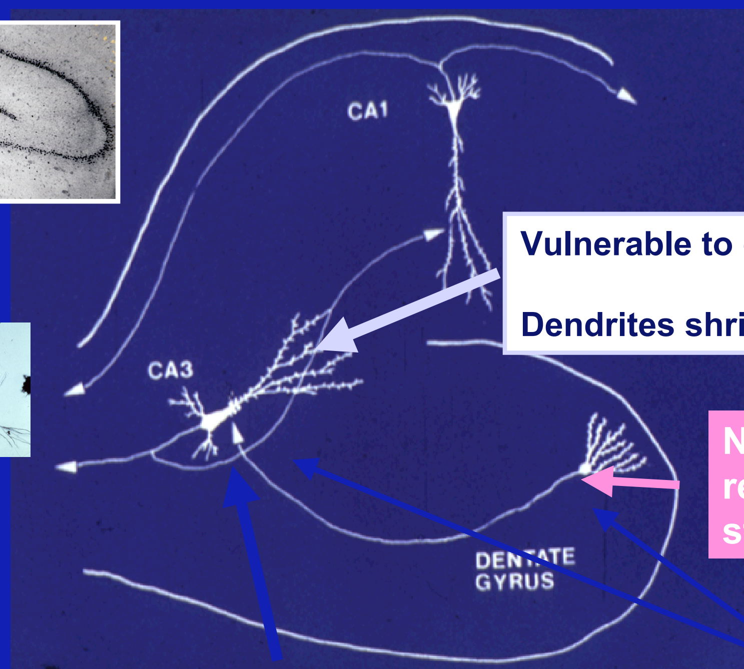
Physical exercise increases brain activity through mechanisms not yet known. We now report that in rats, running induces uptake of blood insulin-like growth factor I (IGF-I) by specific groups of neurons throughout the brain. Neurons accumulating IGF-I show increased spontaneous firing and a protracted increase in sensitivity to afferent stimulation. Furthermore, systemic injection of IGF-I mimicked the effects of exercise in the brain. Thus, brain uptake of IGF-I after either intracarotid injection or after exercise elicited the same pattern of neuronal accumulation of IGF-I, an identical widespread increase in neuronal c-Fos, and a similar stimulation of hippocampal brain-derived neurotrophic factor. When uptake of IGF-I by brain cells was blocked, the exercise-induced increase on c-Fos expression was also blocked. We conclude that serum IGF-I mediates activational effects of exercise in the brain. Thus, stimulation of the uptake of blood-borne IGF-I by nerve cells may lead to novel neuroprotective strategies.

Key words: insulin-like growth factor I; exercise actions on brain function; blood-CSF pathway; neuronal activation; c-Fos; brain-derived neurotrophic factor

Stress:Dentate gyrus - CA3:
plasticity and vulnerability







Vulnerable to damage.

Dendrites shrink with stress

Neurogenesis reduced by stress

Mossy fiber terminals: glutamate release

Entorhinal Cortex input

Glucocorticoids - excitatory amino acids and damage to hippocampus

- **Ischemic damage - stroke model**

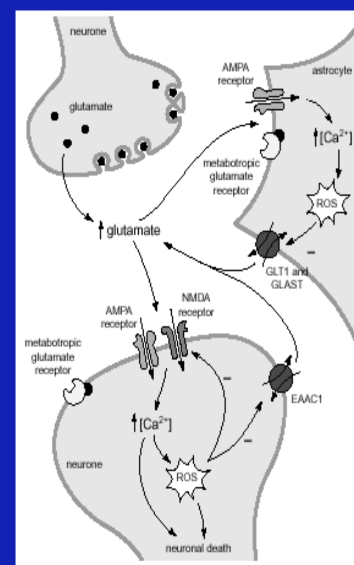
  reduced by adrenalectomy

  enhanced by corticosteroids

- **Kainic acid neurotoxicity - CA3**

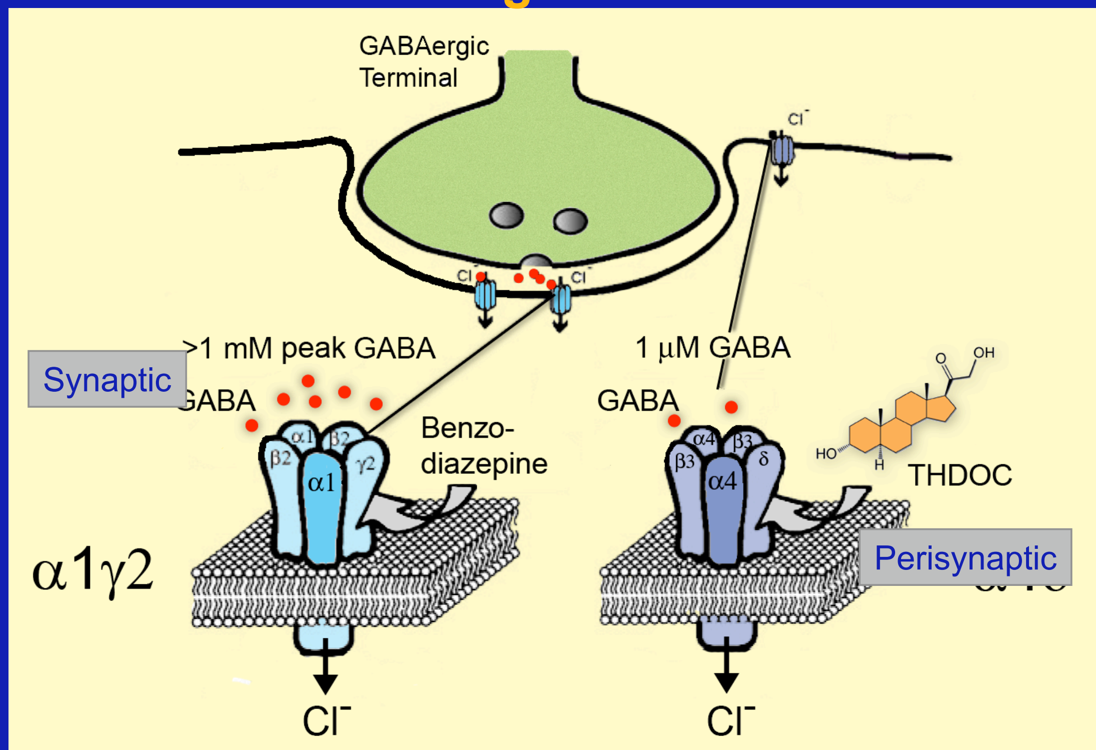
  blocked by metyrapone

  reversed by corticosteroids

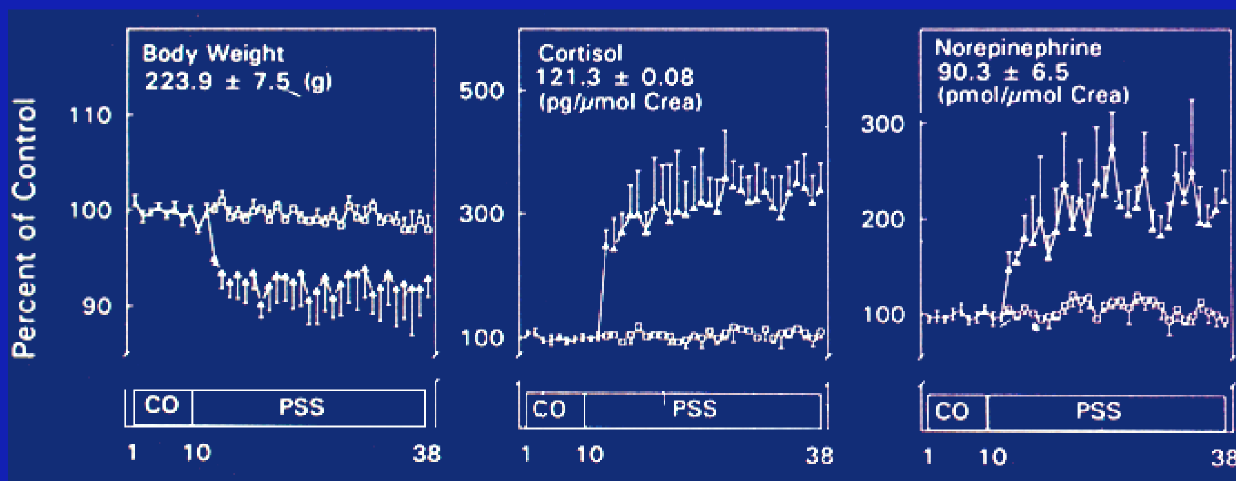


Studies by Robert Sapolsky and collaborators

Stress, seizures and the GABA system; Adrenal cortex generates THDOC

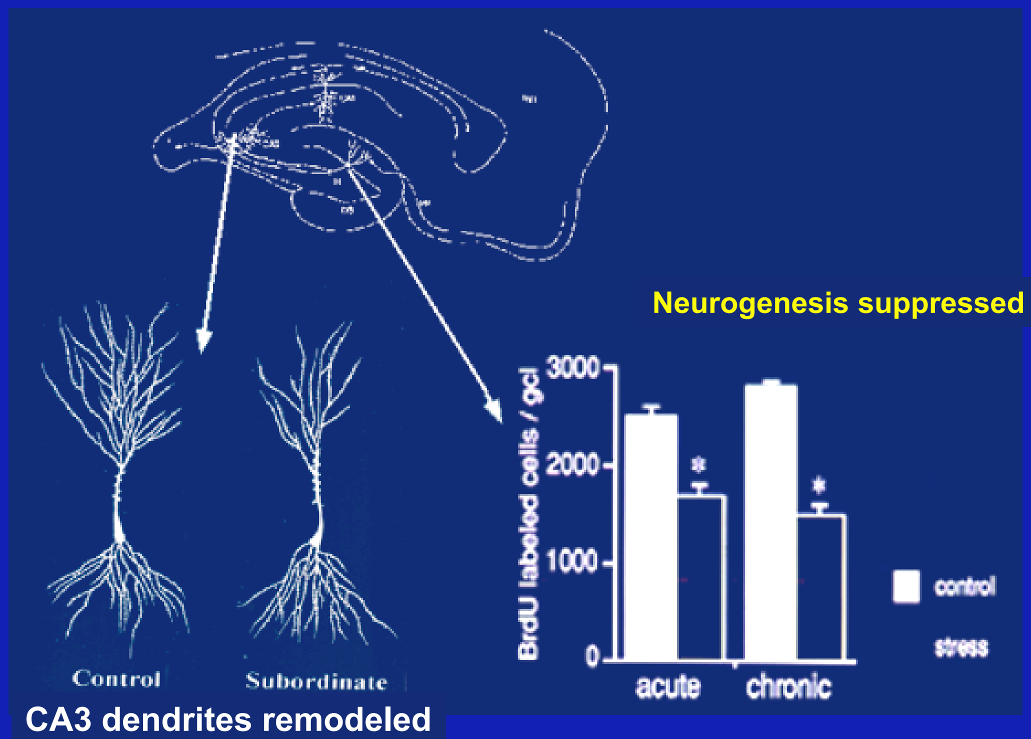


Stell et al., 2003



28 Days of Resident-Intruder Stress

Chronic Confrontation with Dominant Causes Remodeling of Hippocampus



Repeated stress: effects on behavior and structural remodeling

Resident-intruder model:
ree shrew (E. Fuchs)

Behavioral changes:

Impaired spatial learning.

Increased aggression.

Increased fear

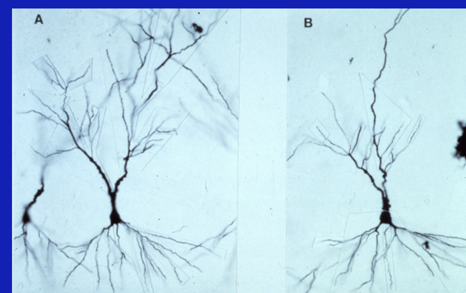
Behavioral depression
Learned helplessness

Attention set shifting impairment

Structural remodeling

Reduced DG neurogenesis and volume.
Shortened dendrites - CA3
Shortened dendrites - PFC
Expanded dendrites - OFC
Increased dendrites - BLA

Repeated stress causes CA3 pyramidal cells to show reversible dendritic shrinkage

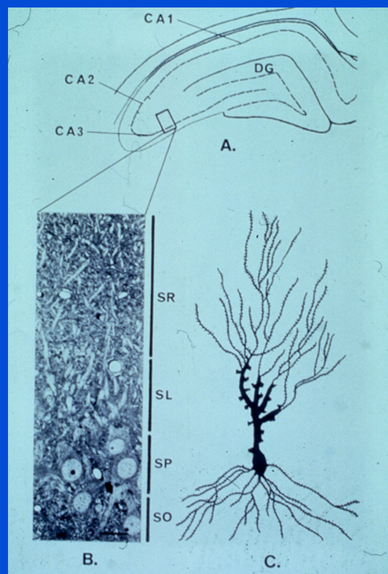


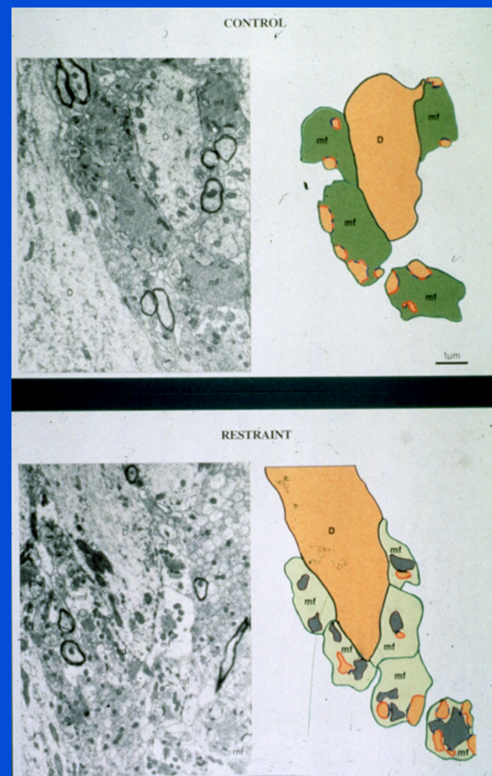
Mimicked by chronic glucocorticoid treatment
Increased extracellular glutamate after stress

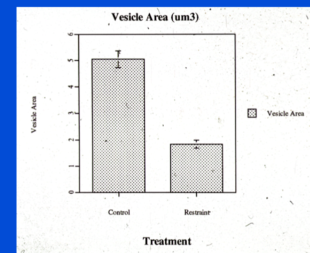
Prevented by….

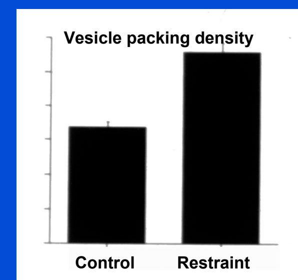
1. Blocking glucocorticoid synthesis
2. Blocking NMDA receptors
3. Lithium
4. Dilantin
5. Antidepressants
6. Benzodiazepine

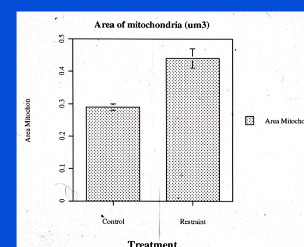
Mossy fiber terminals on CA3 neurons











Increased release of glutamate?

Depletion of synaptic vesicles by repeated stress

Participants in structural changes

Excitatatory amino acids

Adrenal steroids

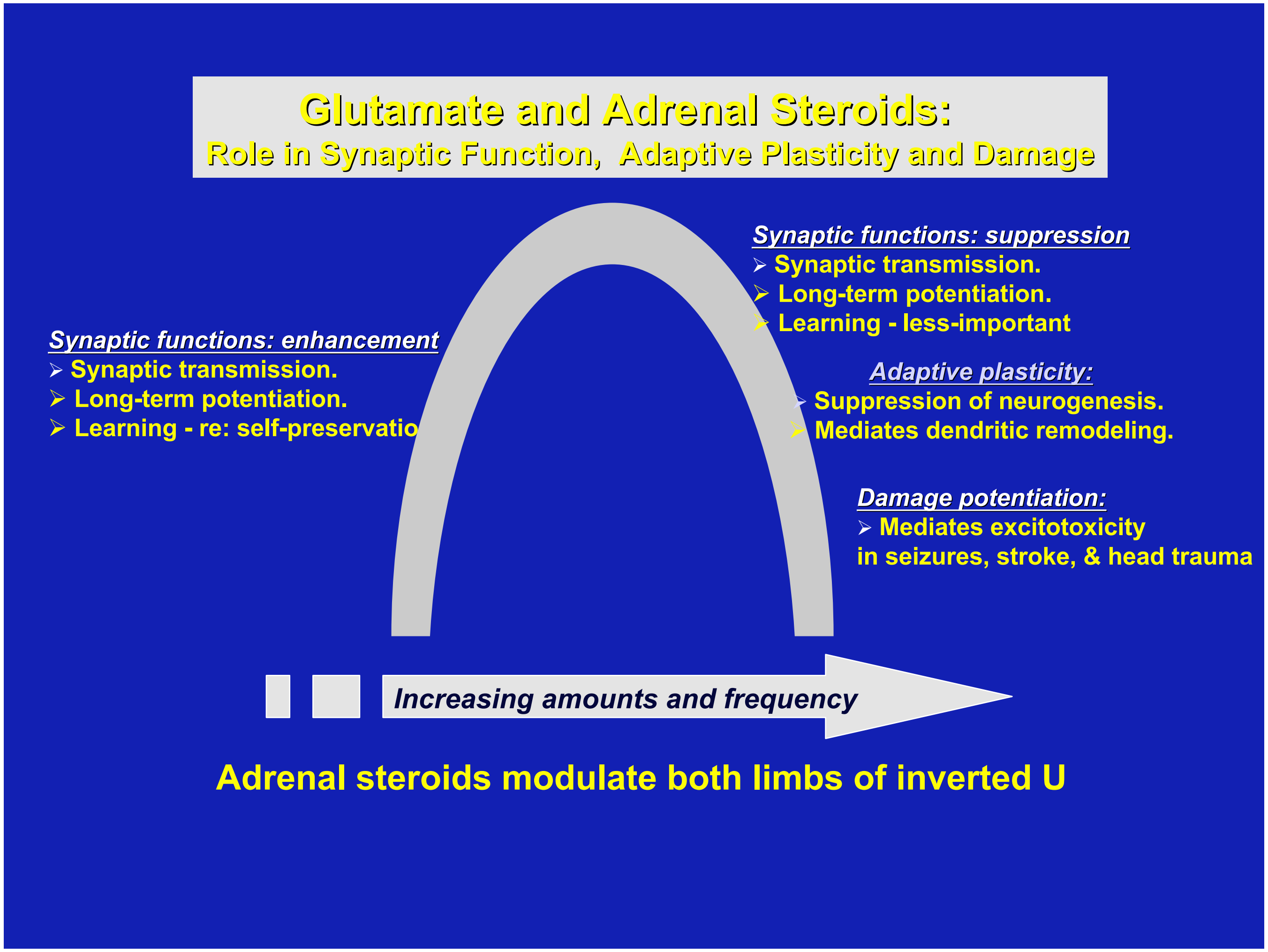
Proteases, eg, tPA

Metabolic hormones and glucose

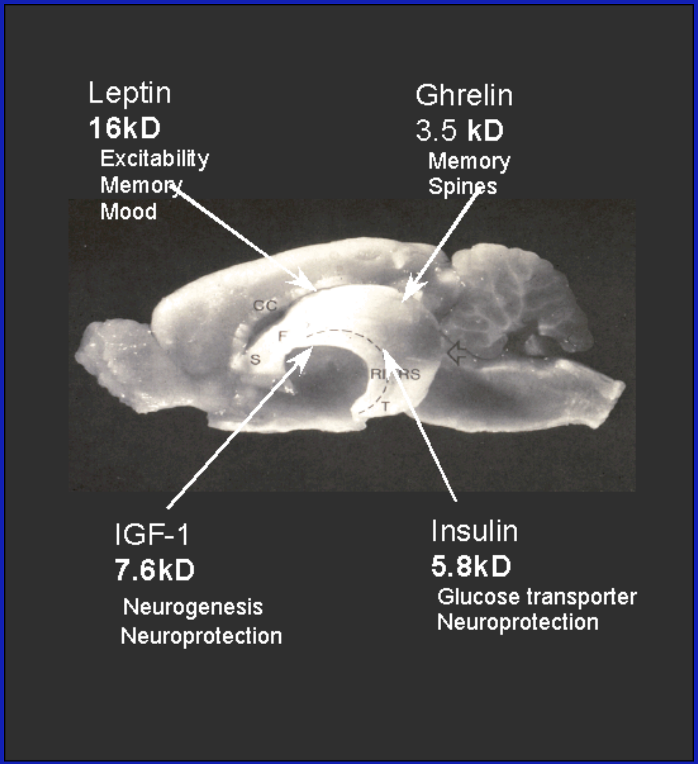
Cytokines

Extracellular factors - eg PSA-NCAM

Cytoskeleton reorganization
actin,tubulin, MAP and tau


Glutamate and Adrenal Steroids:
Role in Synaptic Function, Adaptive Plasticity and Damage
Synaptic functions: enhancement
➢ Synaptic transmission.
➢ Long-term potentiation.
➢ Learning - re: self-preservatio
Synaptic functions: suppression
➢ Synaptic transmission.
➢ Long-term potentiation.
➢ Learning - less-important
Adaptive plasticity:
➢ Suppression of neurogenesis.
➢ Mediates dendritic remodeling.
Damage potentiation:
➢ Mediates excitotoxicity
in seizures, stroke, & head trauma
Increasing amounts and frequency
Adrenal steroids modulate both limbs of inverted U

Metabolic hormones that enter and affect the brain



Perspective on the role of hippocampus:

-spatial,contextual,episodic memory
-mood
- glucose homeostasis and food intake control

Hippocampus is affected by blood-borne factors:

Glucocorticoids

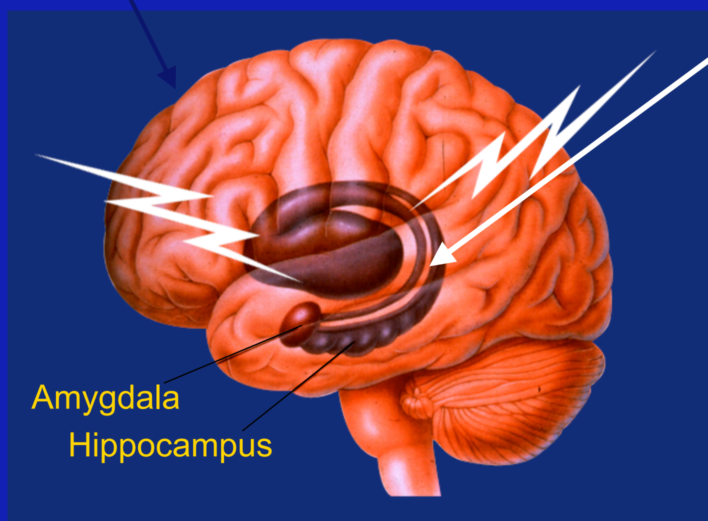
Glucose
Insulin and IGF-1

LPS and proinflammatory cytokines
Leptin
Ghrelin

Sex hormones and developmentally-regulated sex differences

The Human Brain Under Stress:
Role in cognitive function and emotion

Prefrontal cortex



Hippocampus

Contextual, episodic, spatial memory

Diabetes

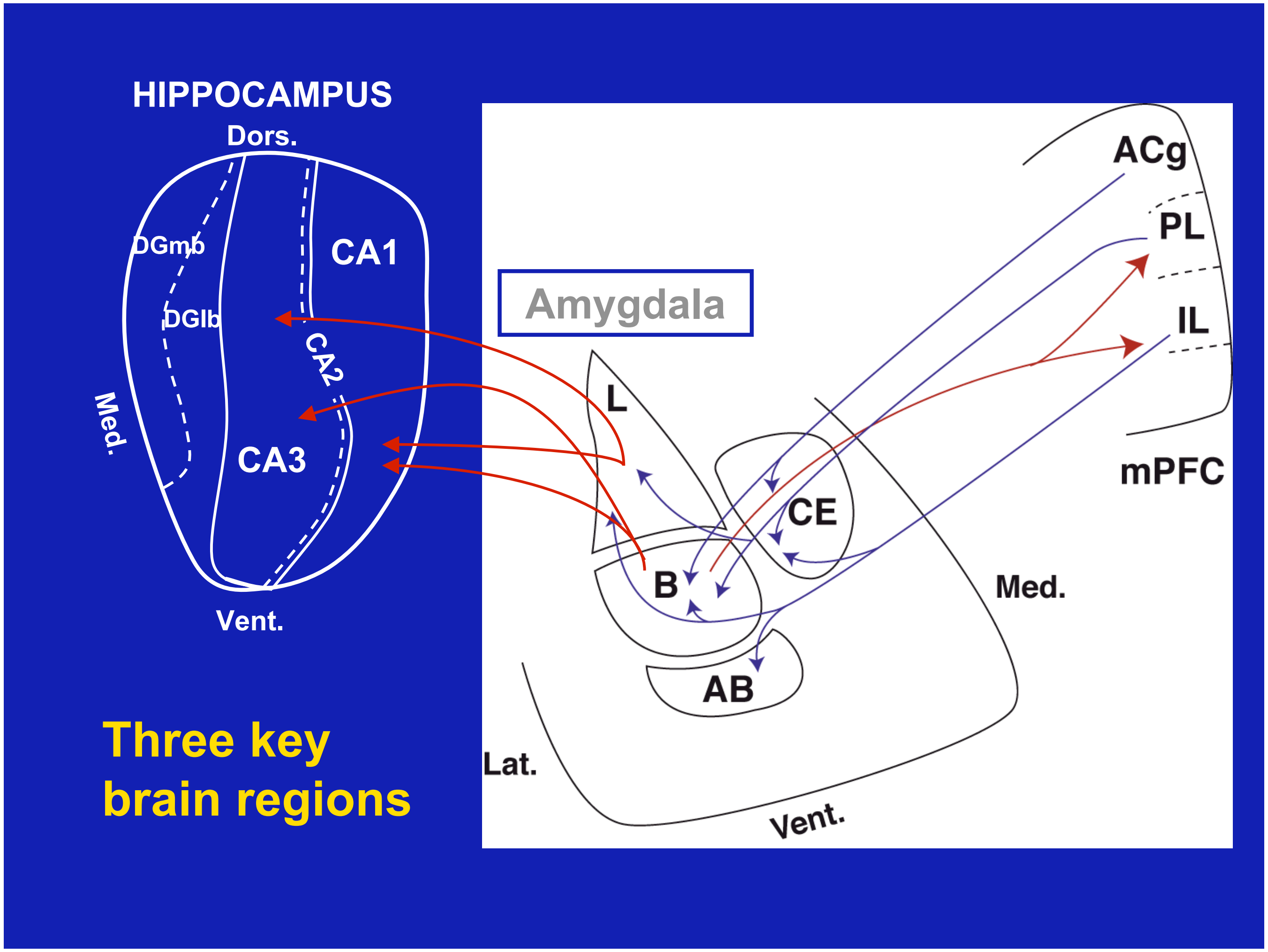
Depression

Cushing's Disease

Long-term stress

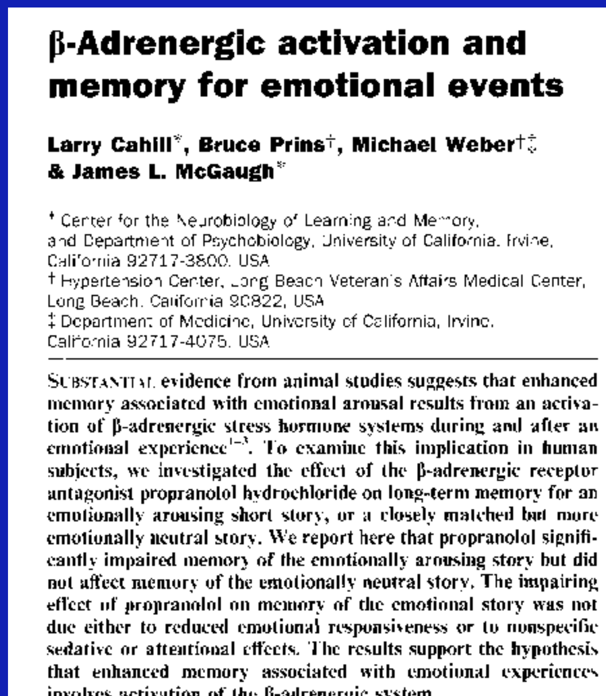
Low self-esteem

Amygdala



HIPPOCAMPUS
Dors.
DGmb
DGlb
CA1
CA2
CA3
Med.
Vent.
Amygdala
L
B
CE
AB
ACg
PL
IL
mPFC
Med.
Lat.
Vent.
Three key
brain regions

Stress-related hormones enhance memory

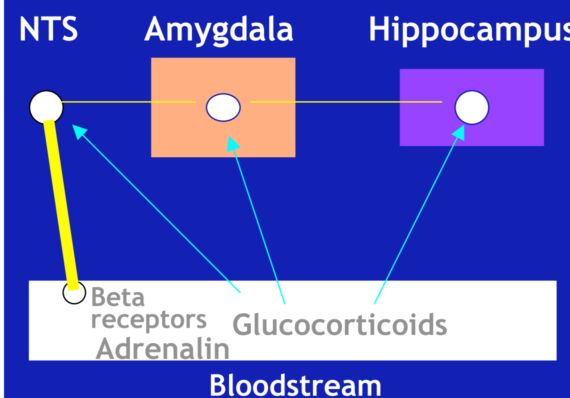


β-Adrenergic activation and memory for emotional events

Larry Cahill[*], Bruce Prins[†], Michael Weber[†‡] & James L. McGaugh[*]

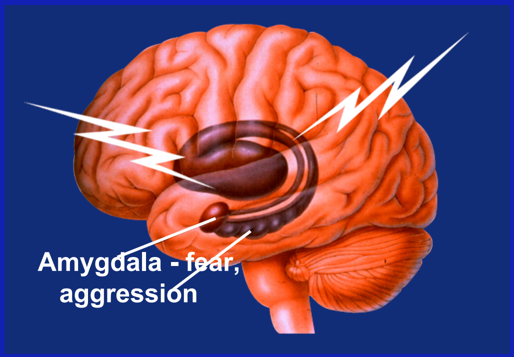
[*] Center for the Neurobiology of Learning and Memory, and Department of Psychobiology, University of California, Irvine, California 92717-3800, USA
[†] Hypertension Center, Long Beach Veteran's Affairs Medical Center, Long Beach, California 90822, USA
[‡] Department of Medicine, University of California, Irvine, California 92717-4075, USA

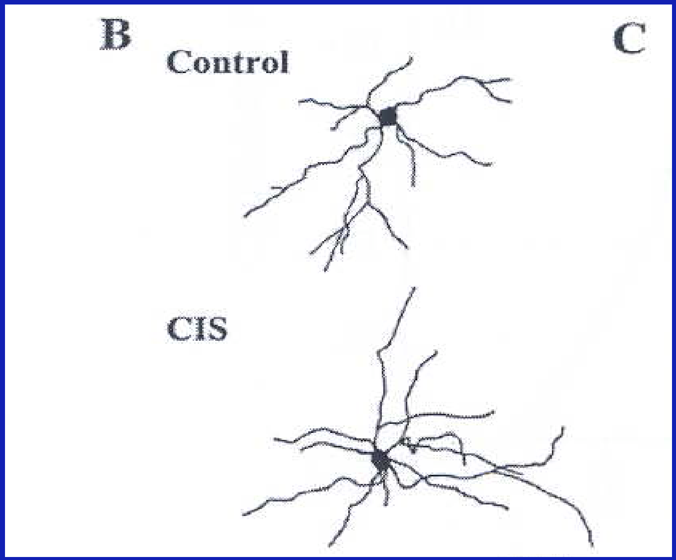
SUBSTANTIAL evidence from animal studies suggests that enhanced memory associated with emotional arousal results from an activation of β-adrenergic stress hormone systems during and after an emotional experience[1–3]. To examine this implication in human subjects, we investigated the effect of the β-adrenergic receptor antagonist propranolol hydrochloride on long-term memory for an emotionally arousing short story, or a closely matched but more emotionally neutral story. We report here that propranolol significantly impaired memory of the emotionally arousing story but did not affect memory of the emotionally neutral story. The impairing effect of propranolol on memory of the emotional story was not due either to reduced emotional responsiveness or to nonspecific sedative or attentional effects. The results support the hypothesis that enhanced memory associated with emotional experiences involves activation of the β-adrenergic system.



Roozendaal, McGaugh
Studies in rats
Passive avoidance learning

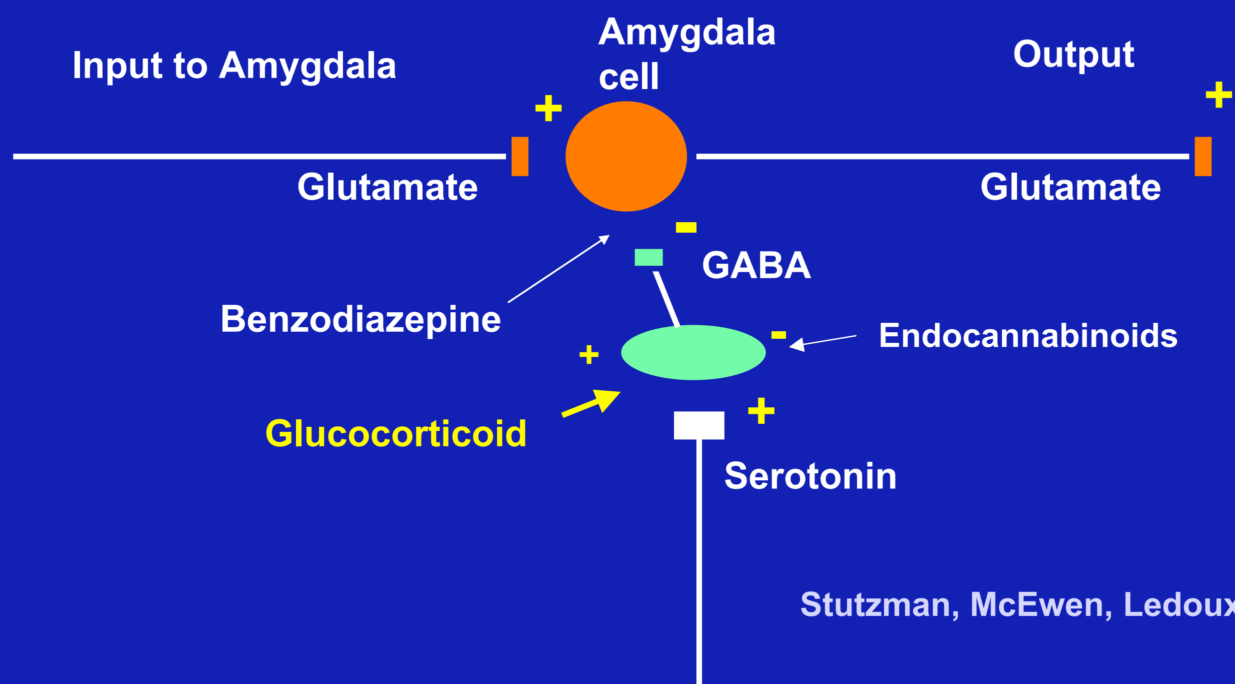
Repeated stress INCREASES dendritic arborization and spine density in the basolateral amygdala





A single immobilization:
New spines and anxiety in 10d!

Gating of Information in the Amygdala



Stutzman, McEwen, Ledoux

Non-nuclear glucocorticoid receptors: association with PSD

L. R. Johnson et al. / Neuroscience 136 (2005) 289–299 293

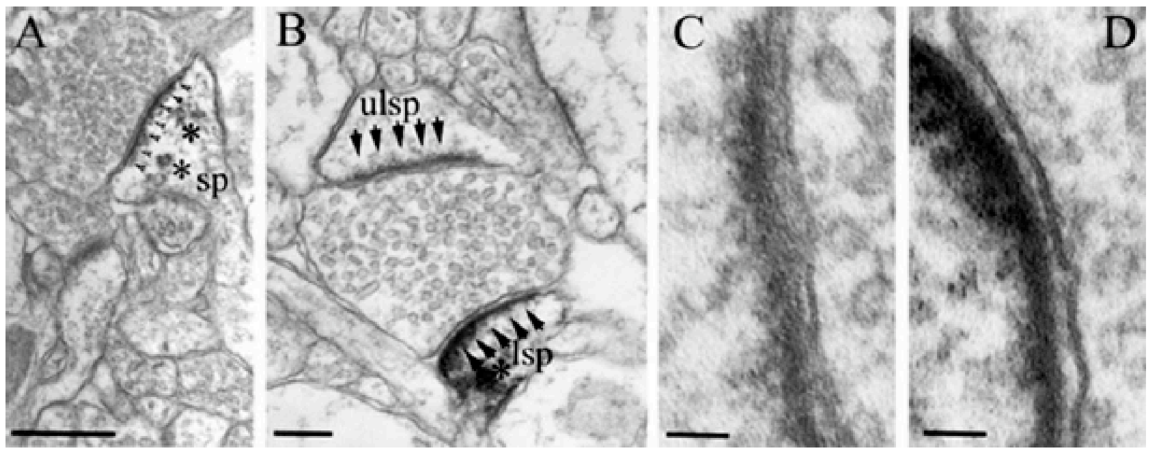
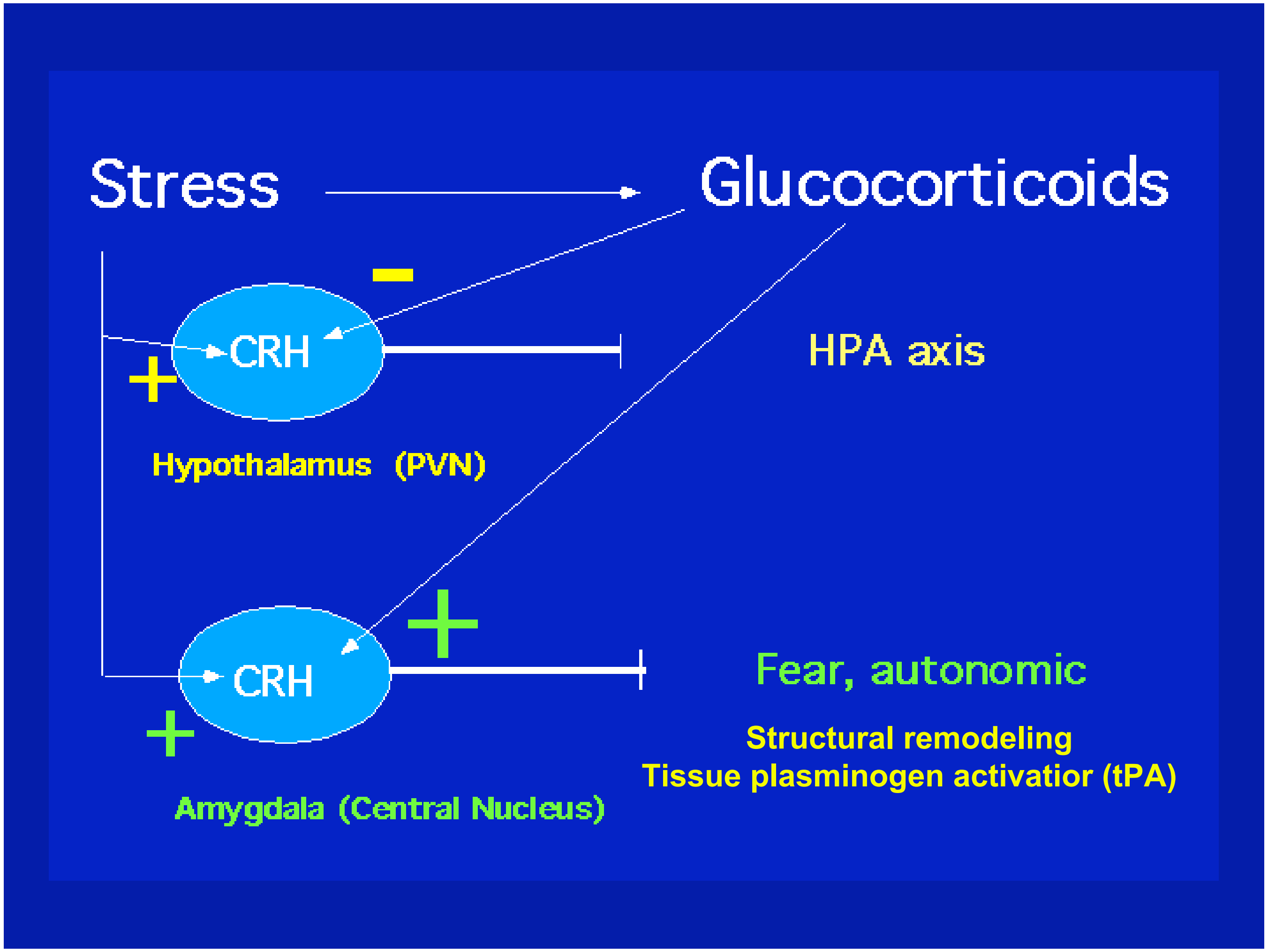
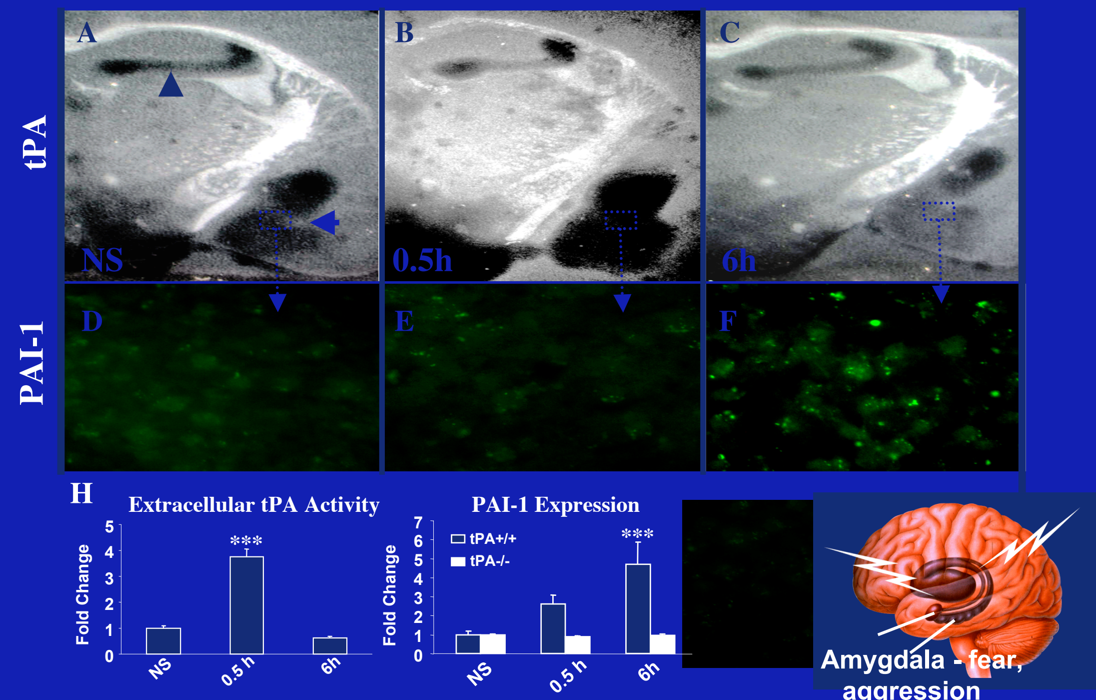


Fig. 3. GR immunolabeling of the PSD. (A) GR-ir labeling of the PSD (arrowheads) of an asymmetrical synapse located on the head of a LA spine (sp). GR-ir spine organelles are also present in the spine head (asterisk). (B) A presynaptic terminal simultaneously forms two asymmetric synapses onto spines (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


Stress
Glucocorticoids
−
CRH
+
HPA axis
Hypothalamus (PVN)
+
CRH
Fear, autonomic
+
Structural remodeling
Tissue plasminogen activatior (tPA)
Amygdala (Central Nucleus)

Mouse amygdala: acute stress activates tPA and PAI in MeA and CeA



Pawlak R, Magarinos A, Melchior J, McEwen B, Strickland S
Nature Neuroscience Feb 2003

Acute stress also increases fear and anxiety: tPA dependent

Tissue plasminogen activator:
role in amygdala fear and structural remodeling

Plasminogen (inactive zymogen → **tPA** → Plasmin (active serine protease)

CRF initiates tPA release via CRF-R1

tPA - activates PAI to turn off response

tPA - exerts plasminogen independent effects

- tPA binds to lipoprotein-related receptor (LRP)
- this enhances LTP.

tPA is essential for remodeling in medial amygdala but not in lateral amygdala, and is also essential in hippocampus

Amygdala overview

1. Adrenal steroids may both “enhance” and “contain” excitatory activity

1. Adrenal steroids participate in contextual memory

2. Acute and chronic stress - BlA neurons grow and fear is increased

3. Acute and chronic stress - MeA neurons show reduced spines

4. tPA and CRF play a role in 3 but not in 2.

<u>What we do not yet known</u>:

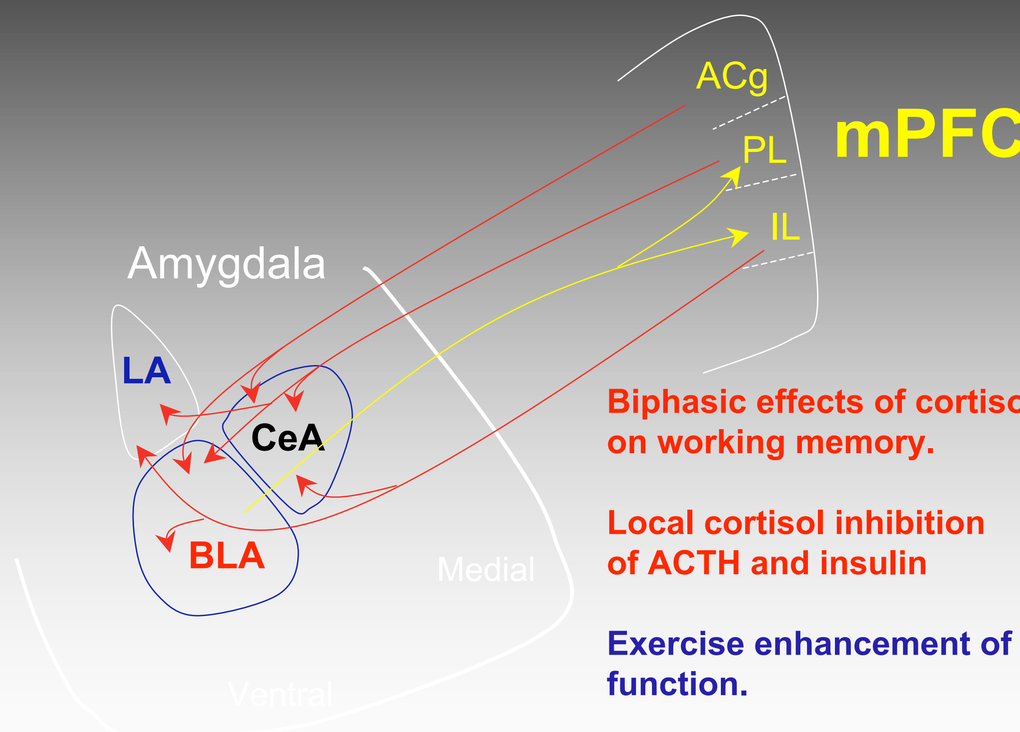
Role of adrenal steroids and EAA in structural remodeling

Implications for PTSD: Glucocorticoids protect

The Neurobiology of Stress and Adaptation

Part 2

mPFC: external influences and responses



Biphasic effects of cortisol on working memory.

Local cortisol inhibition of ACTH and insulin

Exercise enhancement of function.

Stress-remodeling and behavior

Prefrontal cortex:

processes that are or might be affected by stress

Executive function

Attention shifting - mental flexibility

Extinction of fear conditioning

Working memory

Ability to suppress negative thoughts

Learned helplessness

Parasympathetic regulation

HPA regulation

Cardiovascular fitness, cortical plasticity, and aging

Stanley J. Colcombe[*,†], Arthur F. Kramer[*,†,‡,§], Kirk I. Erickson[*,†,§], Paige Scalf[*,†,§], Edward McAuley[¶], Neal J. Cohen[*,†,§], Andrew Webb[*,‖], Gerry J. Jerome[¶], David X. Marquez[¶], and Steriani Elavsky[¶]

[*]The Beckman Institute, [†]Neuroscience Program, and Departments of [§]Psychology, [¶]Kinesiology, and [‖]Electrical and Chemical Engineering, University of Illinois at Urbana-Champaign, Urbana, IL 61801

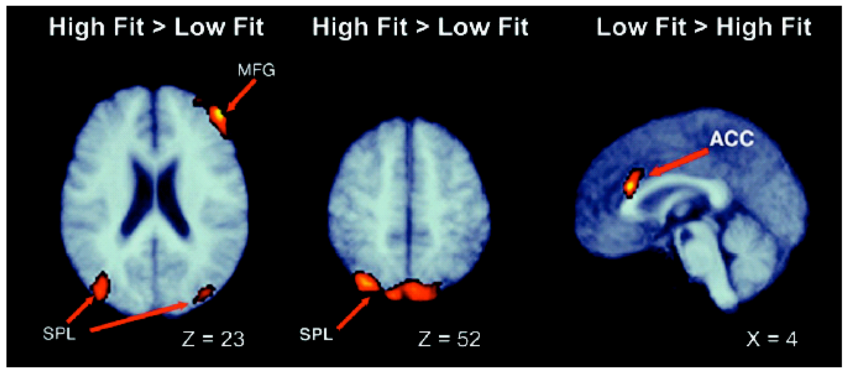


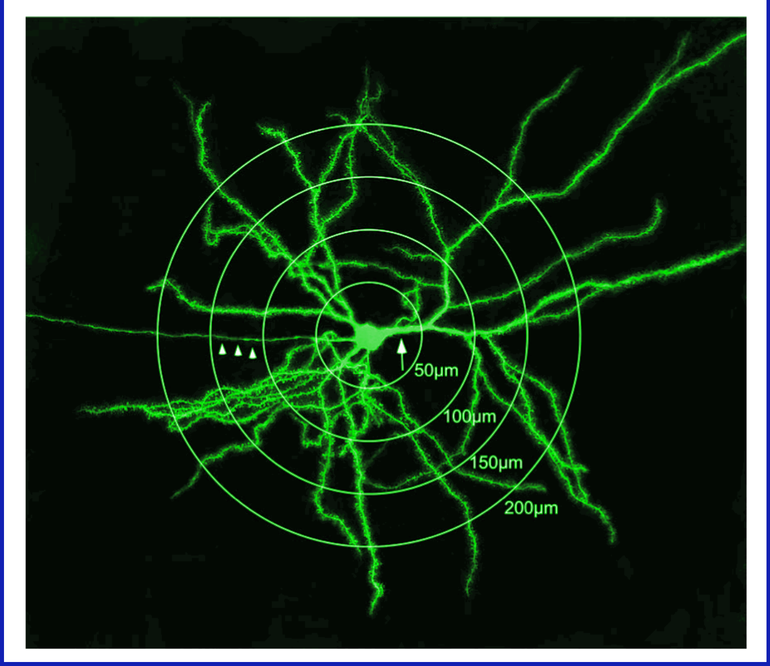
Fig. 2. Regional differences in cortical recruitment as a function of cardiovascular fitness. See Table 1 for cluster descriptions.

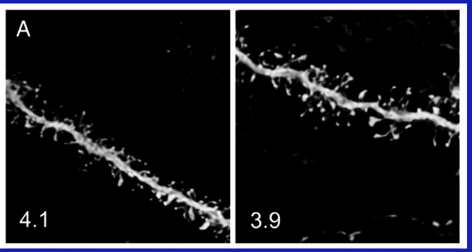
Attentional network: prefrontal and parietal cortex
Executive function: prefrontal cortex

Aerobic exercises improves executive function
Toning exercise does not

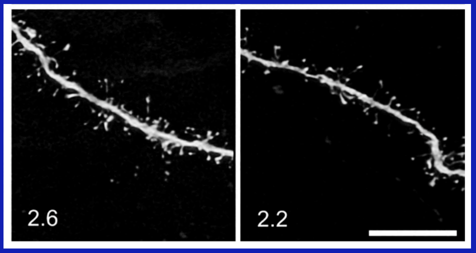
Effects of Stress on Frontal Cortical Morphology

1. 21 days of repeated restraint stress, 6 hours daily
2. Layer II/III pyramidal cells loaded with iontophoretic injections of Lucifer yellow for imaging after perfusion on day 22
1. Cells reconstructed in 3D (40x) and dendrites imaged on confocal at 100x





Spine density: controls

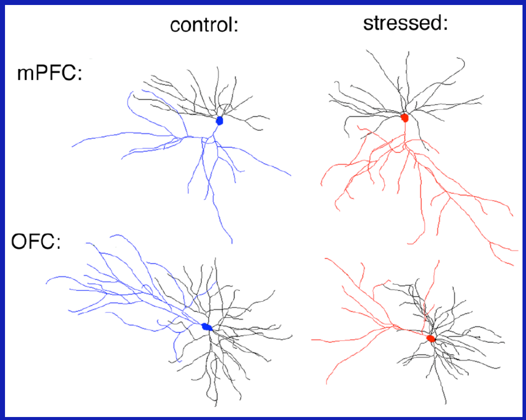


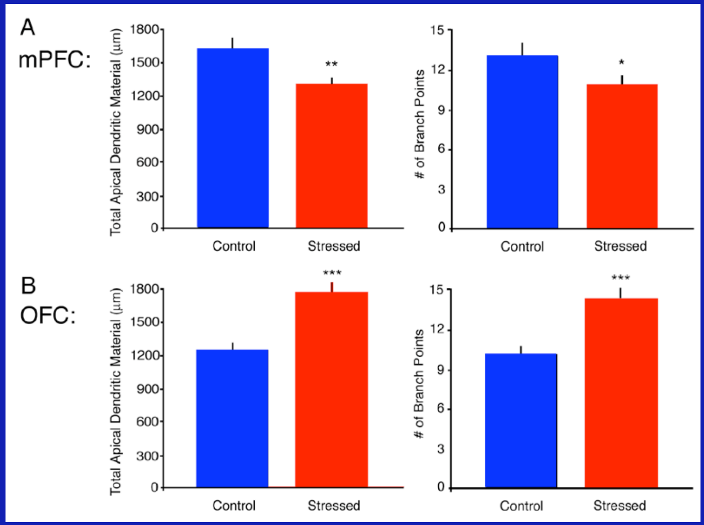
Spine density: stressed

(Radley et al, 2005)

Effects of Stress on Frontal Cortical Morphology

21d Stress induces contrasting effects in mPFC and OFC

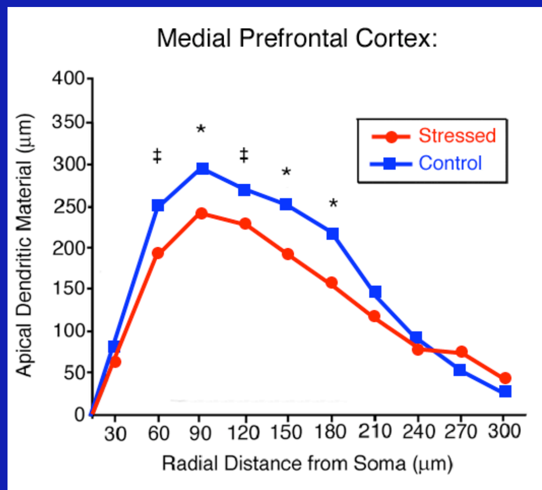


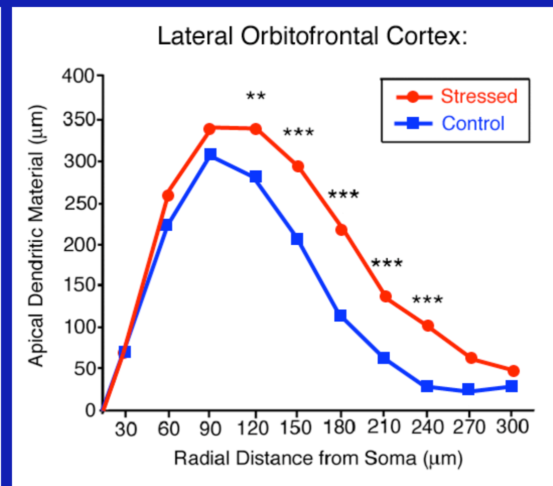


Liston et al, in preparation.

Effects of Stress on Frontal Cortical Morphology

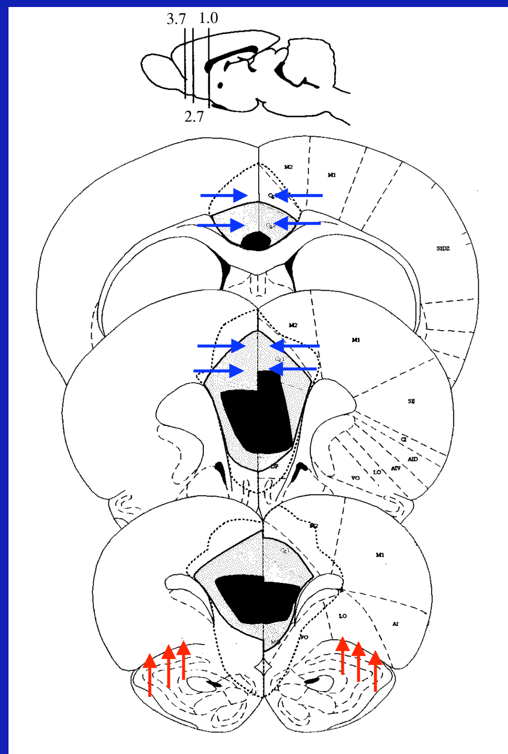
Stress induces contrasting effects in mPFC and OFC:





- In mPFC, effects are most pronounced at 60-180 µm from cell body
- In OFC, stress affects dendrites more distally: 120-240 µm from cell body

Liston et al, in preparation.



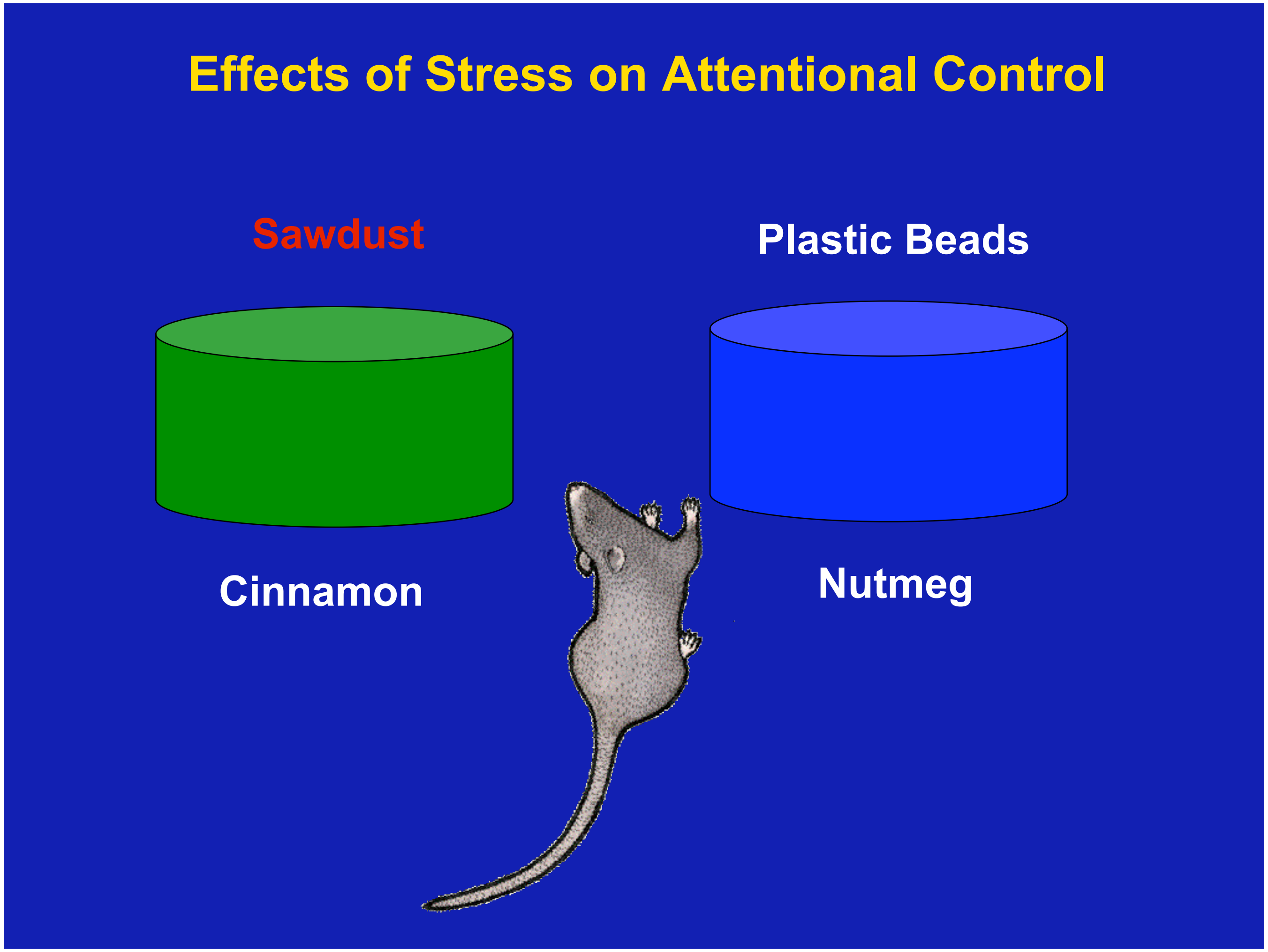
The Journal of Neuroscience, June 1, 2000, 20(11):4320–4324

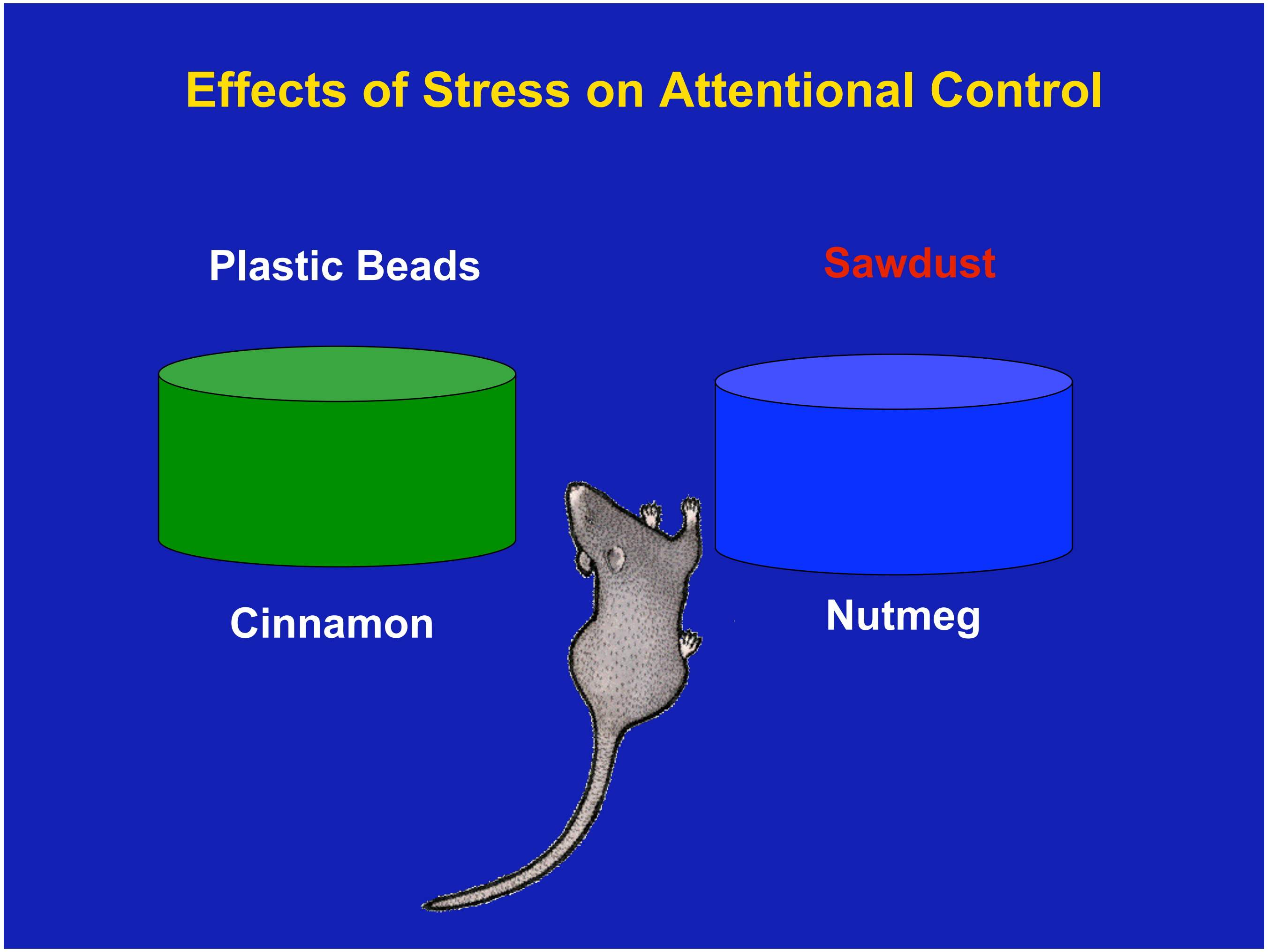
Medial Frontal Cortex Mediates Perceptual Attentional Set Shifting in the Rat

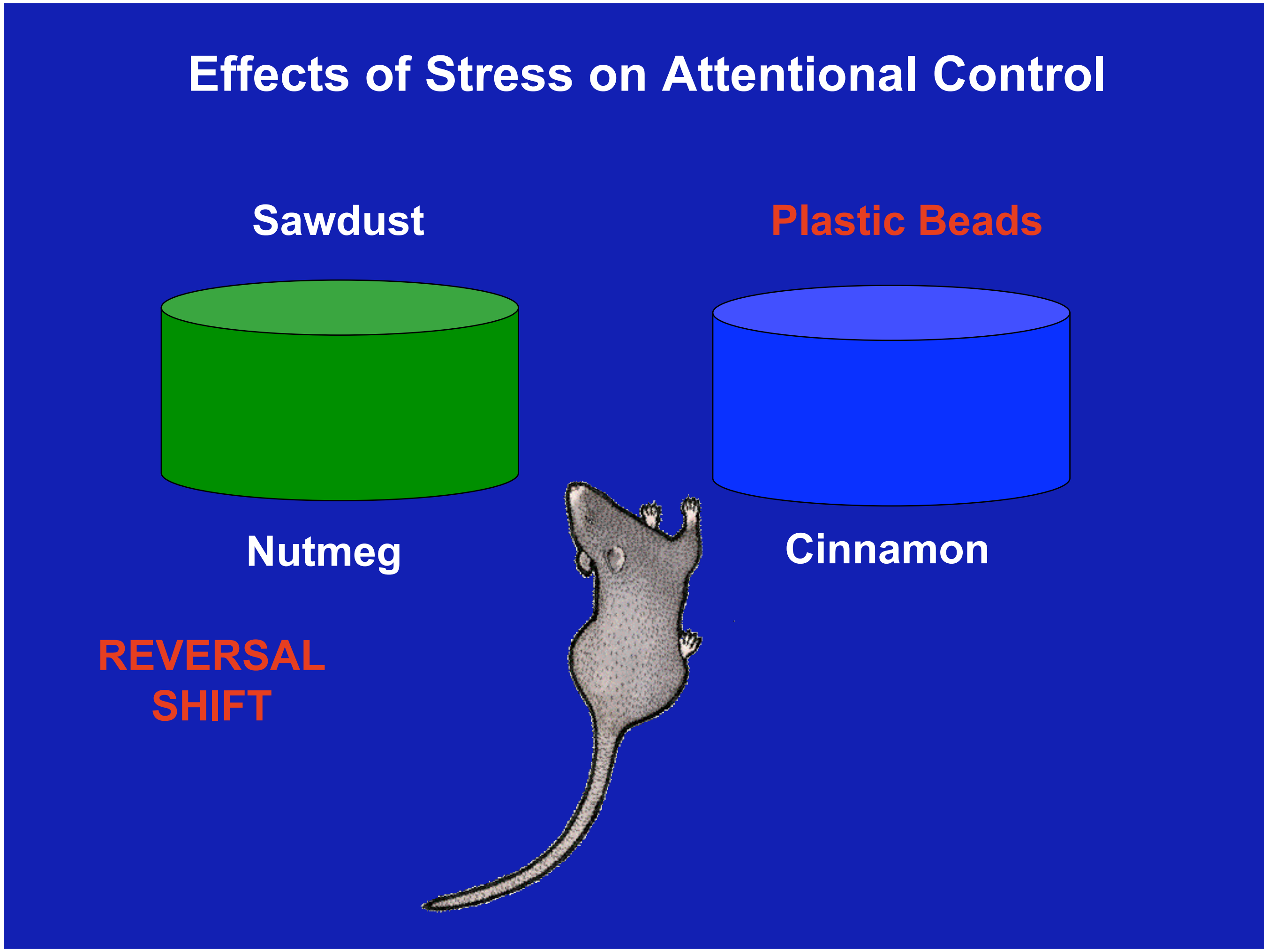
Jennifer M. Birrell and Verity J. Brown

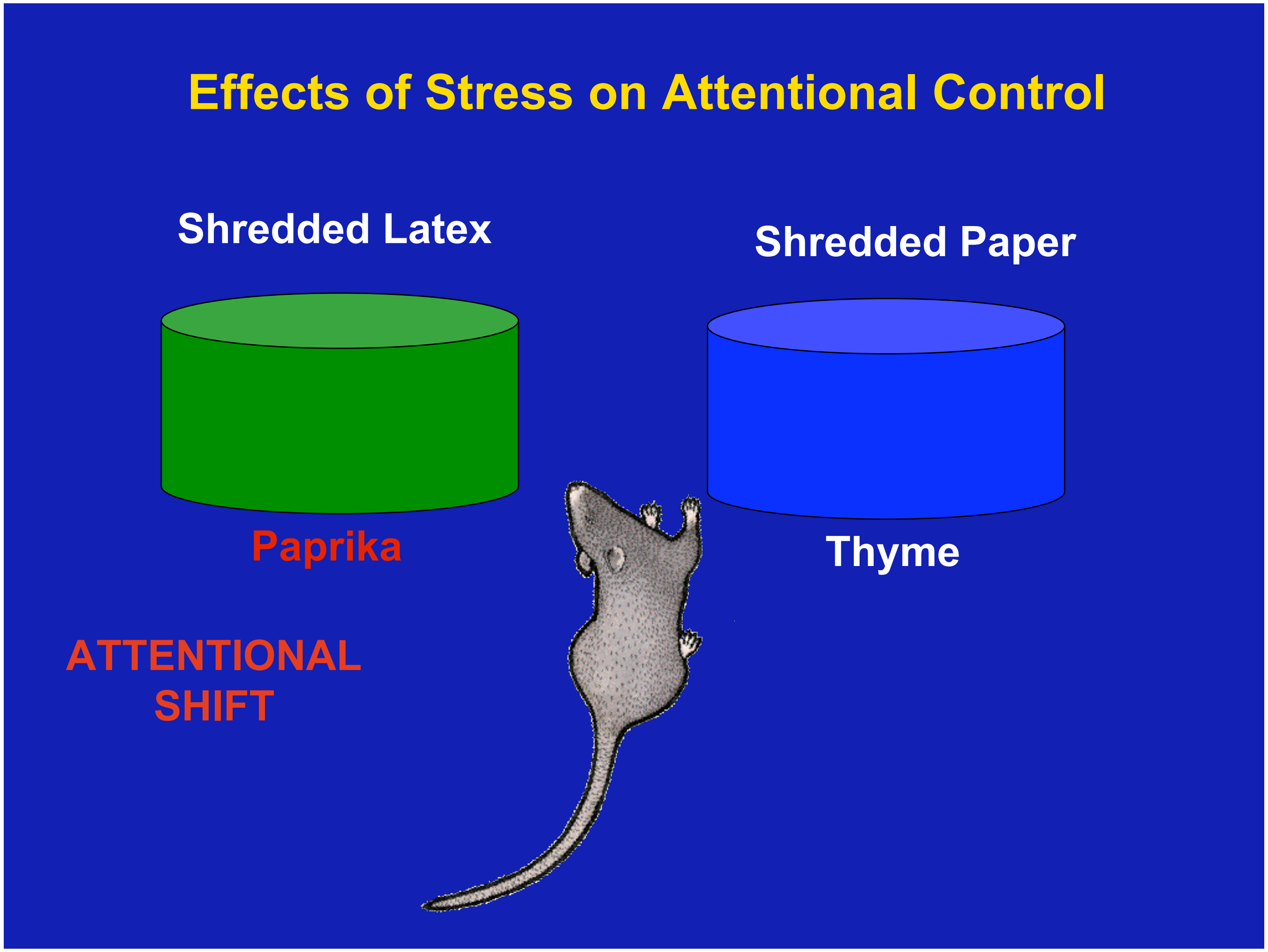
School of Psychology, University of St. Andrews, St. Andrews KY16 9JU, Scotland, United Kingdom

Layer II/III pyramidal cells were loaded in
lateral orbitofrontal cortex (red)
and the
anterior cingulate region
of medial frontal cortex (blue)

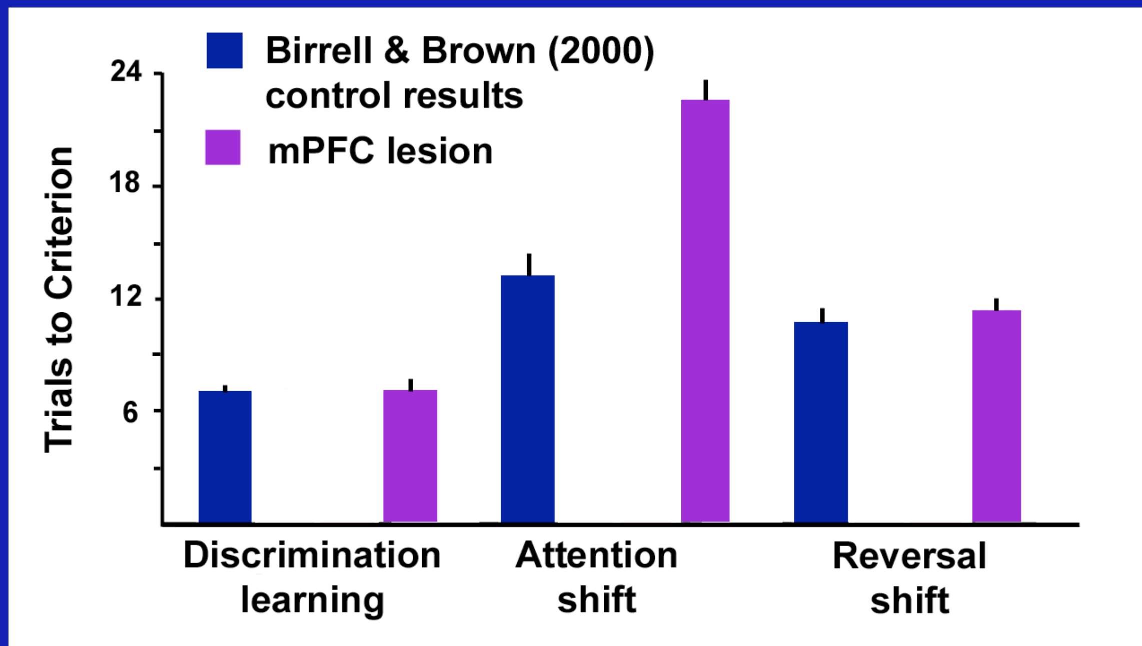

Effects of Stress on Attentional Control
Sawdust
Plastic Beads
Cinnamon
Nutmeg


Effects of Stress on Attentional Control
Plastic Beads
Sawdust
Cinnamon
Nutmeg


Effects of Stress on Attentional Control
Sawdust
Plastic Beads
Nutmeg
Cinnamon
REVERSAL
SHIFT

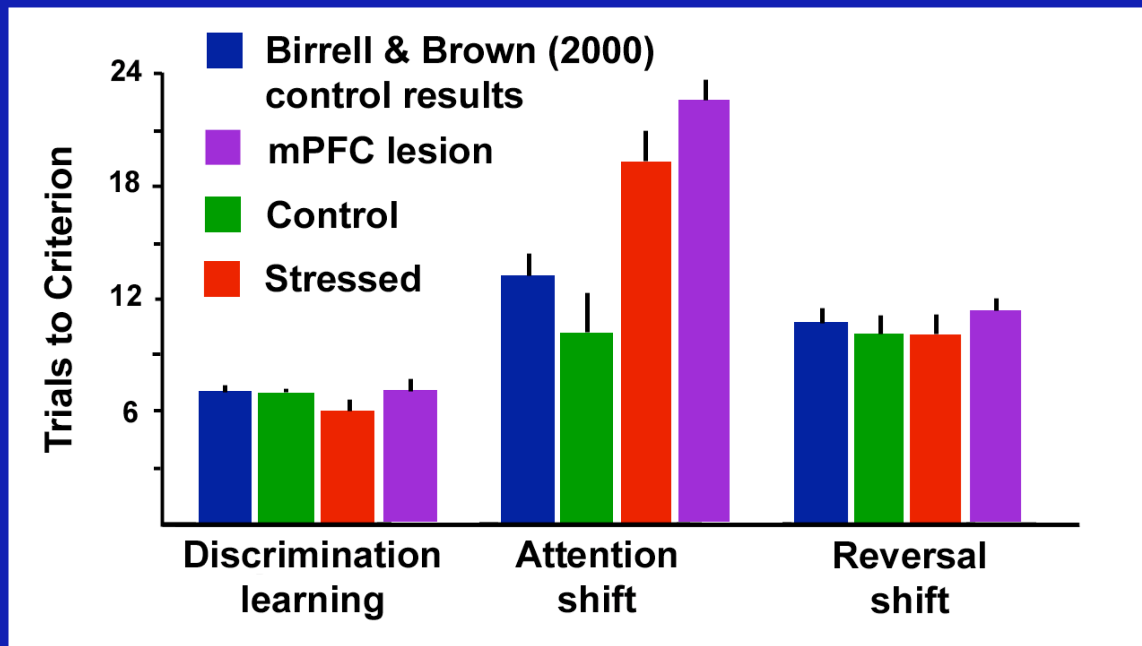

Effects of Stress on Attentional Control
Shredded Latex
Shredded Paper
Paprika
Thyme
ATTENTIONAL
SHIFT

Effects of Stress on Attentional Control



- Medial frontal cortical lesions selectively impair attention shifts

Effects of Stress on Attentional Control



- Medial frontal cortical lesions selectively impair attention shifts
- 3-week stress selectively impairs attention shifts
- Reversal shifts and discrimination learning are unimpaired

Liston et al, in preparation.

Perceived Stress Scale- 10 Item

Instructions: The questions in this scale ask you about your feelings and thoughts during the last month.
In each case, please indicate with a check how often you felt or thought a certain way.

1. In the last month, how often have you been upset because of something that happened unexpectedly?

2. In the last month, how often have you felt that you were unable to control the important things in your life?

3. In the last month, how often have you felt nervous and "stressed"?

4. In the last month, how often have you felt confident about your ability to handle your personal problems?

5. In the last month, how often have you felt that things were going your way?

6. In the last month, how often have you found that you could not cope with all the things that you had to do?

7. In the last month, how often have you been able to control irritations in your life?

8. In the last month, how often have you felt that you were on top of things?

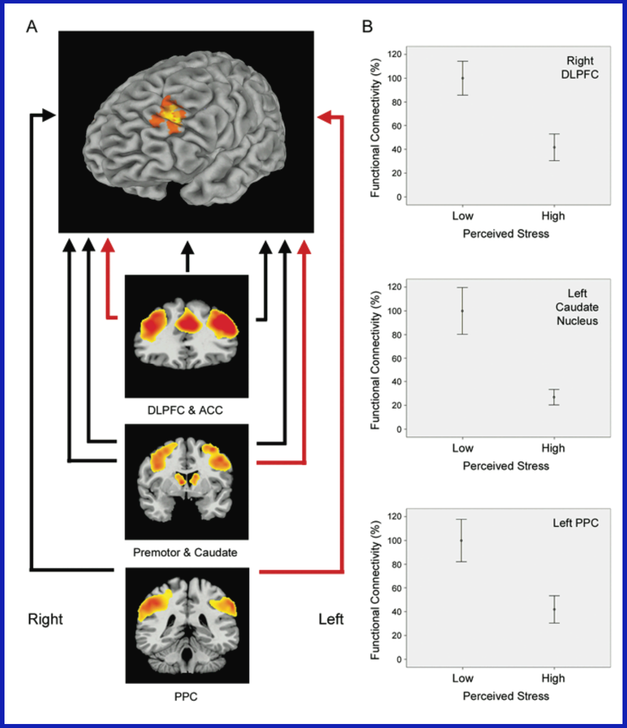
9. In the last month, how often have you been angered because of things that were outside of your control?

10. In the last month, how often have you felt difficulties wer piling up so high that you could not overcome them?

___0=never ___1=almost never ___2=sometimes ___3=fairly often ___4=very often

High perceived stress:
impaired attention set shifting and functional coupling

….but this impairment disappears after a vacation!



Conor Liston, BJ Casey Weill Medical College

On going studies and unanswered questions on prefrontal cortex: with Morrison and Hof

Spine volume decreases with chronic stress

Jason Radley

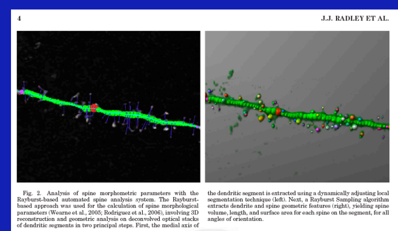

4 J.J. RADLEY ET AL.

Fig. 2. Analysis of spine morphometric parameters with the Rayburst-based automated spine analysis system. The Rayburst-based approach was used for the calculation of spine morphological parameters (Wearne et al., 2005; Rodriguez et al., 2006), involving 3D reconstruction and geometric analysis on deconvolved optical stacks of dendritic segments in two principal steps. First, the medial axis of the dendritic segment is extracted using a dynamically adjusting local segmentation technique (left). Next, a Rayburst Sampling algorithm extracts dendrite and spine geometric features (right), yielding spine volume, length, and surface area for each spine on the segment, for all angles of orientation.

Dopamine (D1) signalling is impaired; recovery is "heterotypic" Deena Goldwater, Gus Pavlides, Richard Hunter

Females show different remodeling - role of E

Rebecca Shansky

Future: role of dendritic growth of OFC

Prefrontal cortex overview

1. Increased or decreased branching of dendrites and spines with experiences.

2. Effects of stress on attention and executive function

3. Adrenal steroids have biphasic effects on working memory.

What is not yet known:

Role of adrenal steroids and EAA in remodeling.

Role of amygdala activity in remodeling

Sensivity to insulin, IGF-1, glucose, cytokines

Stress and adaptation: central role of the brain

-Protective and damaging effects of stress mediators

-Scared stiff - neural basis of fear and anxiety

- Stress hormones have beneficial effects, acting via receptors

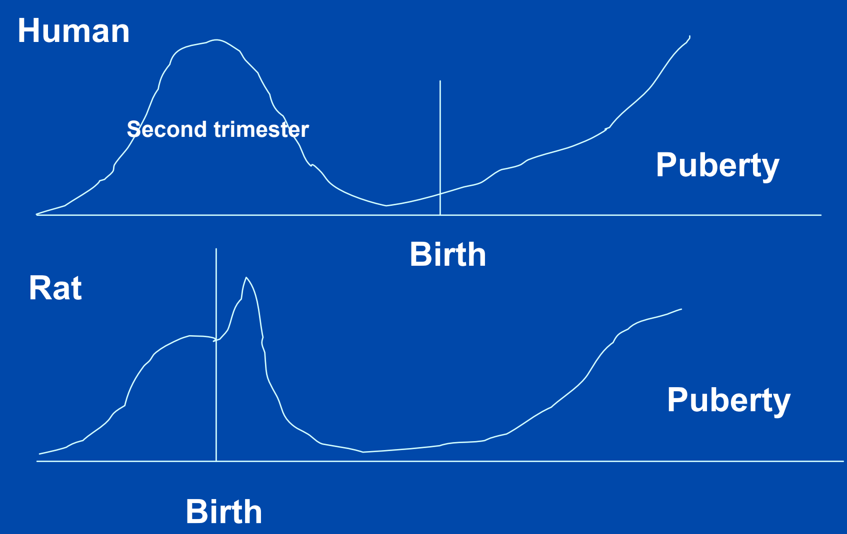
- Structural plasticity of the brain.

-Stress effects on behavior and structural plasticity
  - Hippocampus
  - Amygdala
  - Prefrontal cortex

-Sex differences in response to stress

- Importance of the mother - long-lasting effects of early experience -

Testosterone levels in human and rat male: a comparison



Genetic sex → XY → testes → testosterone

Genetic sex → XX → ovaries → estradiol

Note: estradiol levels low until puberty in female

Males and females differ in response to stress: Sex differences in stress effects on classical conditioning

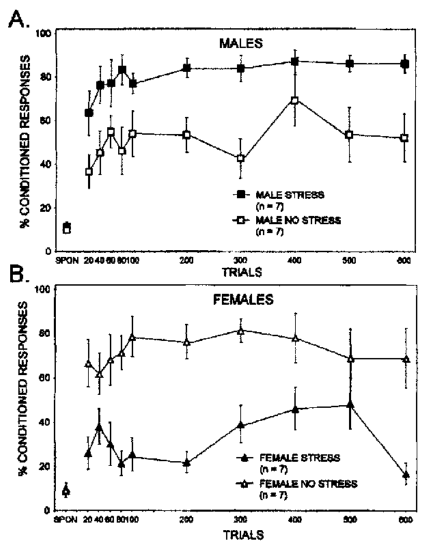


FIG. 1. Effects of sex and stress on acquisition of the conditioned eyeblink response. (*A*) In males, exposure to the stressor facilitated acquisition of the CR 24 h after stressor cessation. (*B*) In females, exposure to the same stressor impaired acquisition of the CR 24 h after stressor cessation. Unstressed females elicited more CRs than unstressed males during the first day of training (1–300 trials), but were not significantly different from each other by the second day of training (301–600 trials). Spontaneous (SPON) eyeblink activity was not affected by sex.

Wood and Shors PNAS, US 95: 4066, 1998

Stress and adaptation: central role of the brain

-Protective and damaging effects of stress mediators

-Scared stiff - neural basis of fear and anxiety

- Stress hormones have beneficial effects, acting via receptors

- Structural plasticity of the brain.

-Stress effects on behavior and structural plasticity
    - Hippocampus
    - Amygdala
    - Prefrontal cortex

-Sex differences in response to stress

- Importance of the mother - long-lasting effects of early experience -

Prenatal stress
Prolonged separation of pups from mother

Increased rate of brain aging

Birth

Increased stress hormone secretion throughout postnatal life

Postnatal handling
Maternal behavior - licking of pups

Decreased rate of brain aging

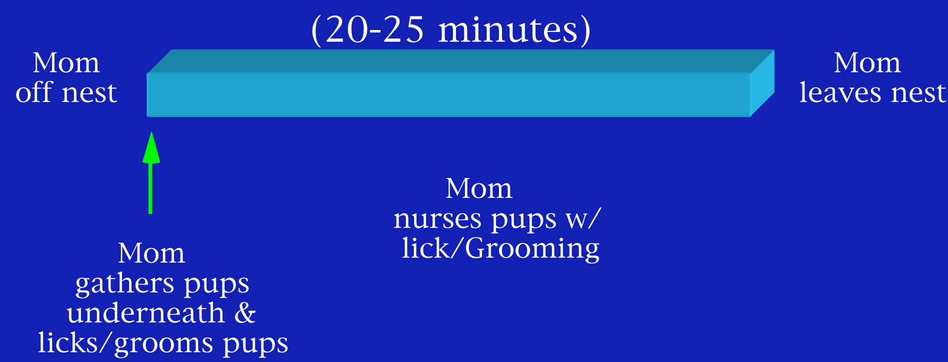
Birth

Decreased stress hormone secretion throughout postnatal life

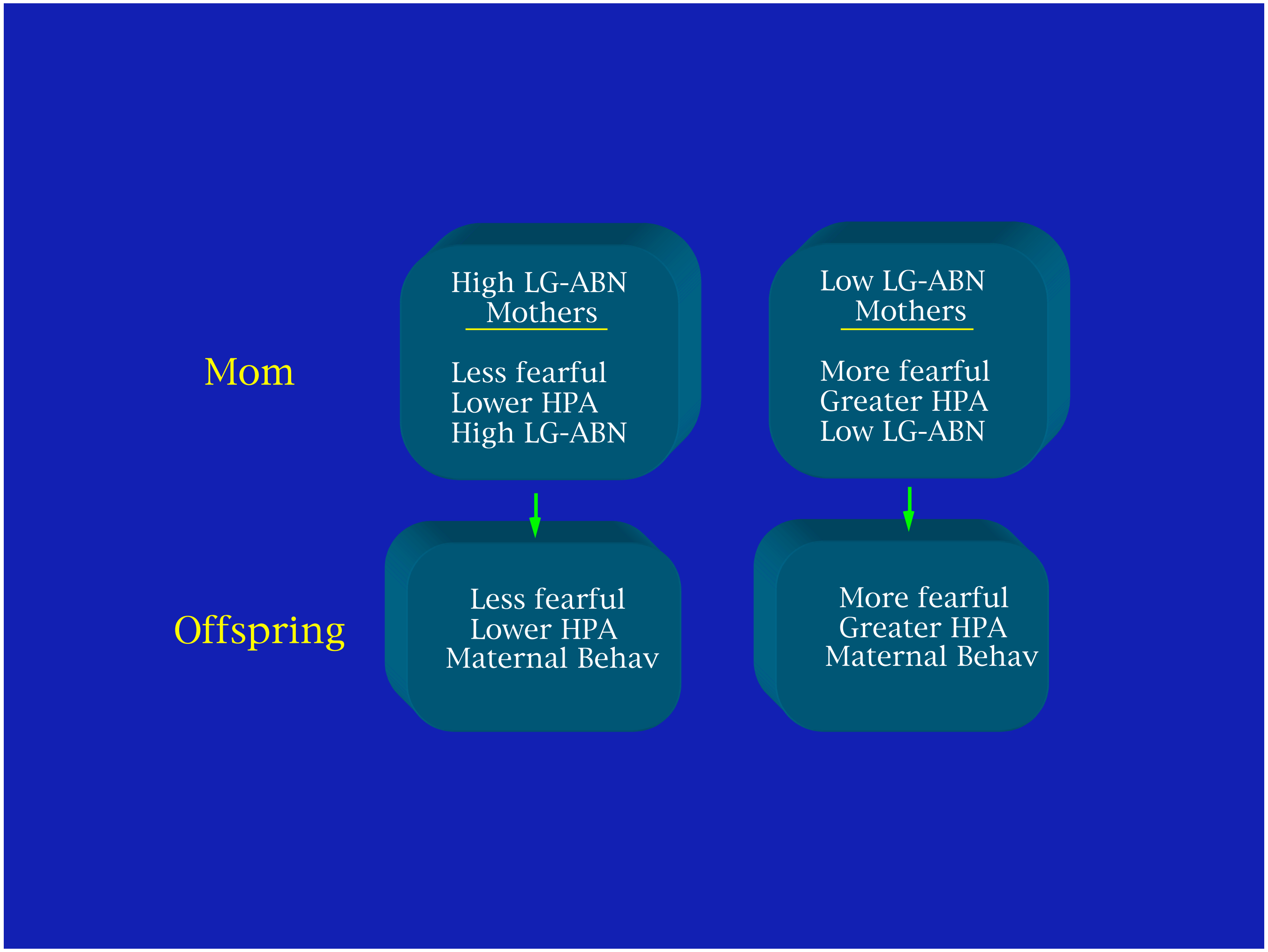
Gestation | Neonatal life | Puberty to adulthood | Senescence

Work of Levine, Denenberg, Ader, Meaney and others

Maternal Behavior in the Rat



L/G: Serves to stimulate behavioral activity (NA mediated); suckling


Mom
Offspring
High LG-ABN Mothers
Less fearful
Lower HPA
High LG-ABN
Low LG-ABN Mothers
More fearful
Greater HPA
Low LG-ABN
Less fearful
Lower HPA
Maternal Behav
More fearful
Greater HPA
Maternal Behav

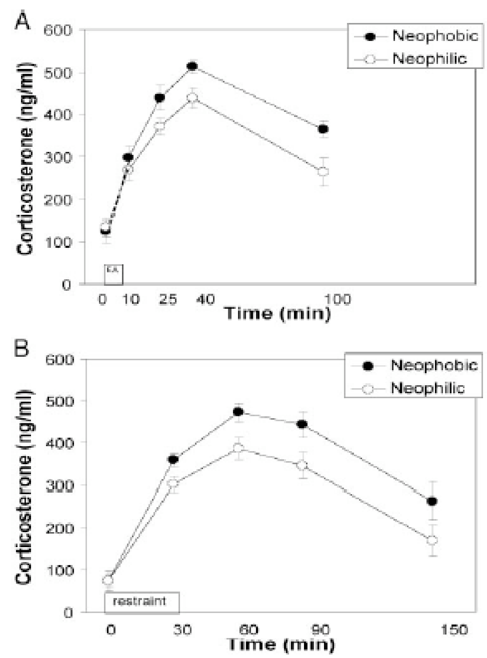


Fig. 2. (*A*) Serum corticosterone response to a 5-min exploration-arena test for neophobic (●) and neophilic (○) males at 8 mo of age. Serum corticosterone values at 0 min are from several weeks after testing. (*B*) Plasma corticosterone response to 30-min restraint in neophobic (●) and neophilic (○) males at 15 mo of age.

Cavigelli and McClintock 2003

PNAS | December 23, 2003 | vol. 100 | no. 26 | 16131–16136

Cavigelli and McClintock 2003

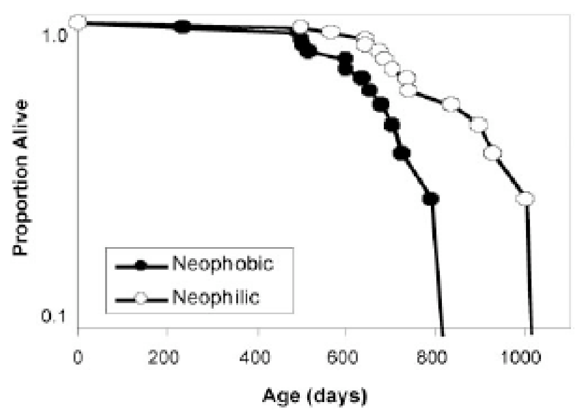
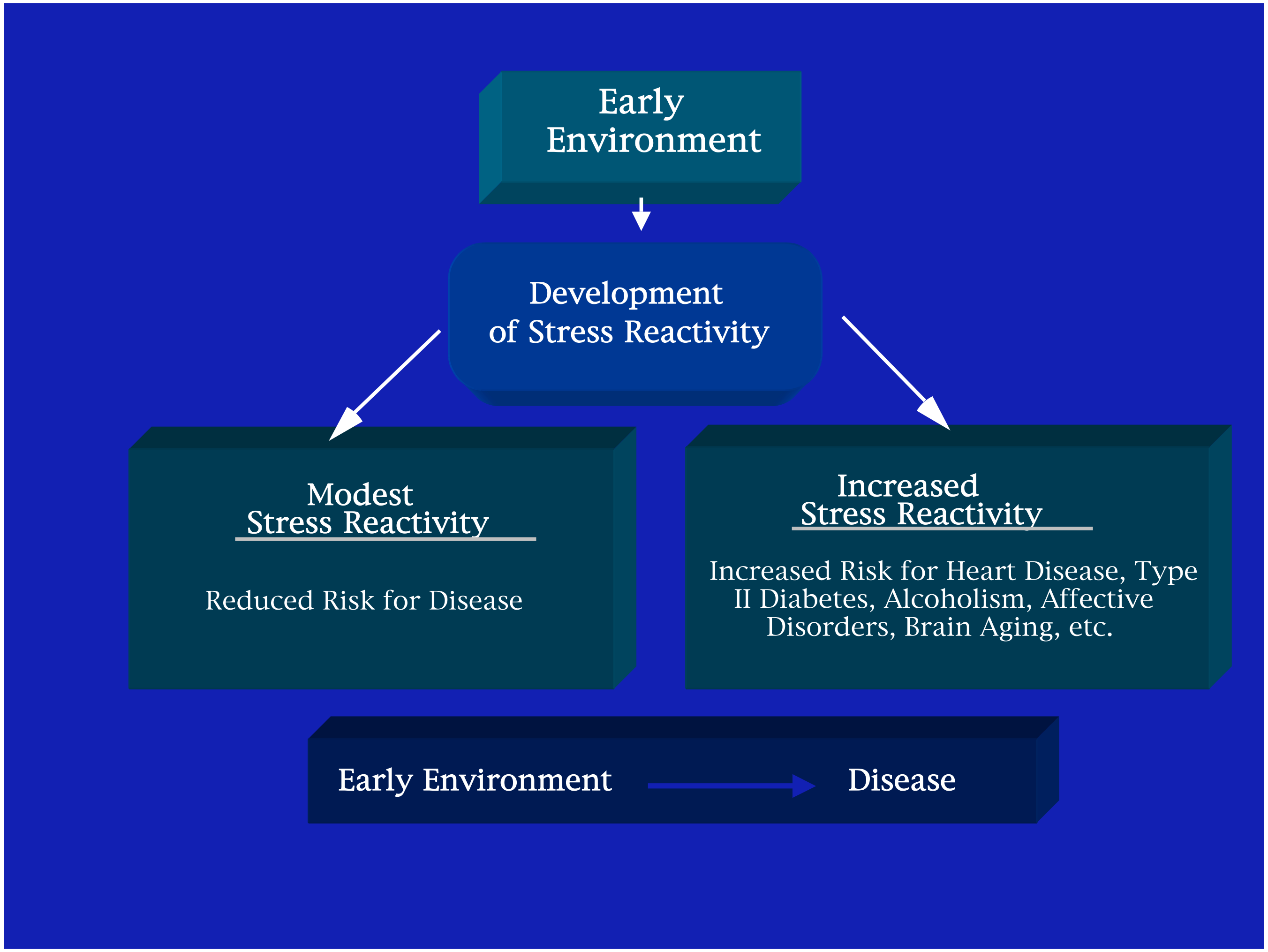
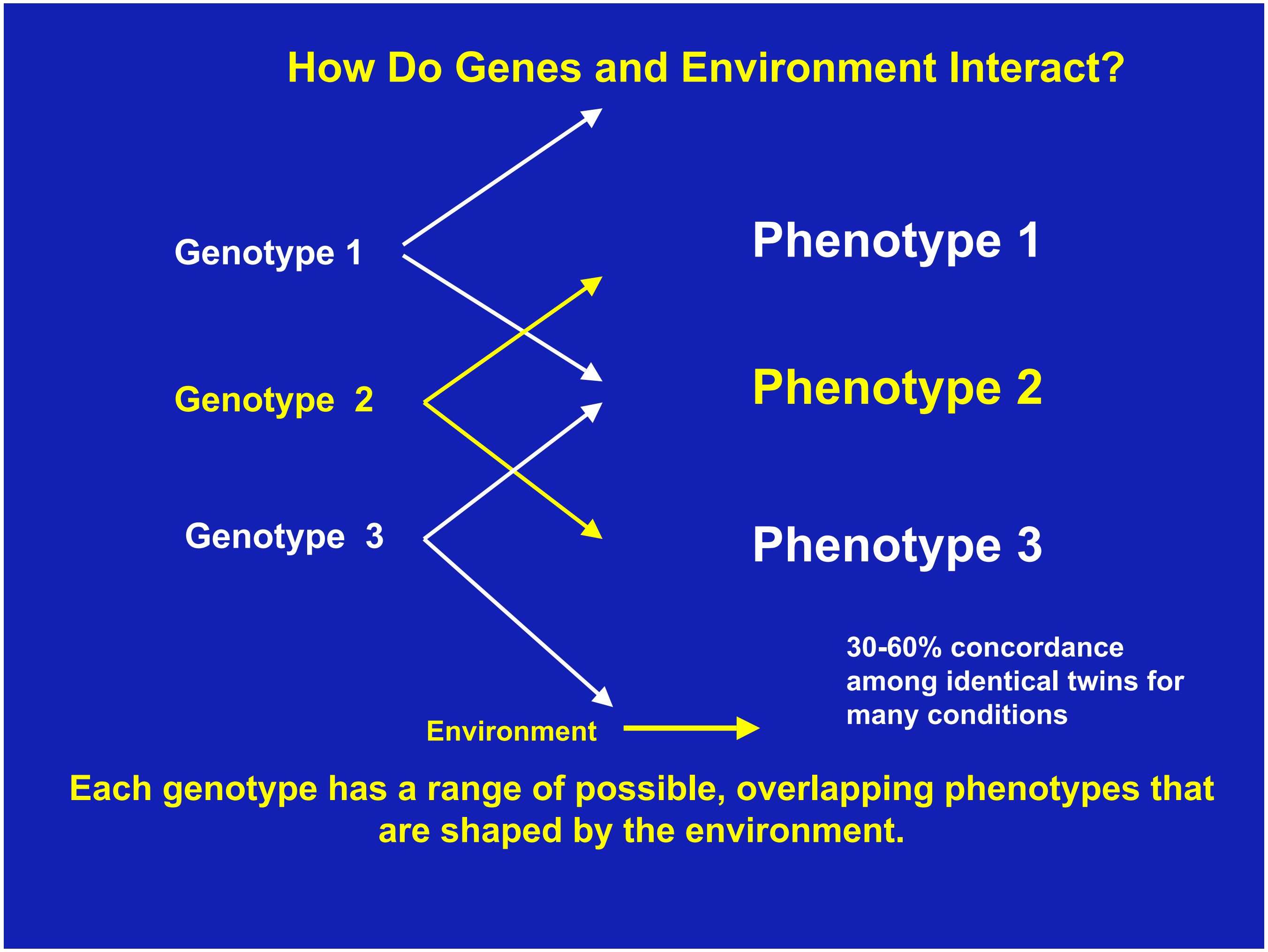


Fig. 3. Lifespan of neophobic (●) and neophilic (○) males.

PNAS | December 23, 2003 | vol. 100 | no. 26 | 16131–16136


Early Environment
Development of Stress Reactivity
Modest Stress Reactivity
Reduced Risk for Disease
Increased Stress Reactivity
Increased Risk for Heart Disease, Type II Diabetes, Alcoholism, Affective Disorders, Brain Aging, etc.
Early Environment
Disease


How Do Genes and Environment Interact?
Genotype 1
Genotype 2
Genotype 3
Phenotype 1
Phenotype 2
Phenotype 3
Environment
30-60% concordance among identical twins for many conditions
Each genotype has a range of possible, overlapping phenotypes that are shaped by the environment.

Nature-Nurture Interactions: Study in New Zealand

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

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

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.

Epigenetics

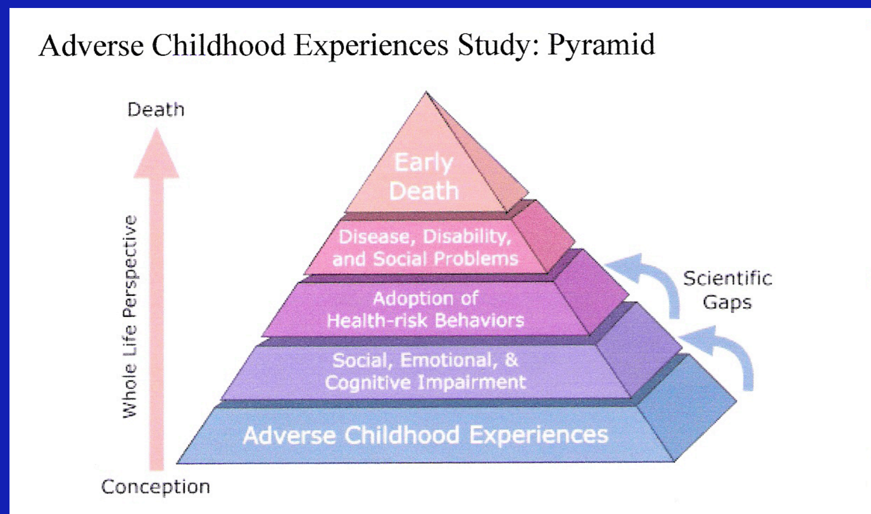
"above the genome"

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

Methylation of cytosine bases in DNA along with modifiications of histones that cause unfolding/folding of chromatin to expose or hide DNA sequences that can be read and transcribed.

Eg, Ongoing work by Michael Meaney and Moshe Szyf on maternal care effects

Epidemiology of adverse childhood experiences: Physical and emotional disorders through lifespan



Risk factors, such as smoking, alcohol abuse, and sexual behaviors as well as many common diseases were not randomly distributed in the population and tended to cluster.

Anda, Felitti and colleagues Center for Disease Control

Prospective reports of chronic life stress predict decrease grey matter volume in the hippocampus.

P.J. Gianaros et al. / NeuroImage 35 (2007) 795–803 799

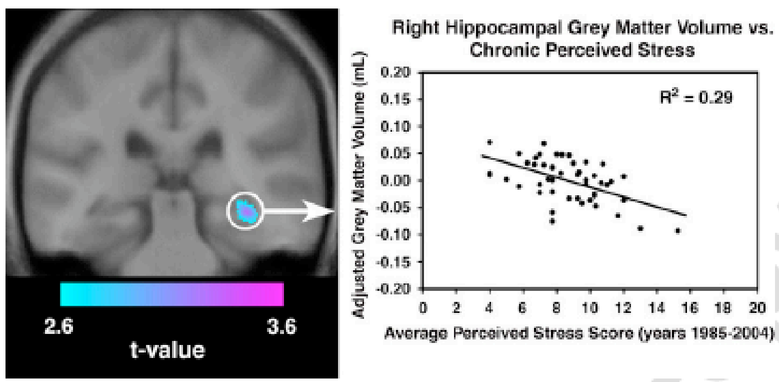


Fig. 1. Higher chronic perceived stress among 48 healthy postmenopausal women predicted decreased grey matter volume in the right hippocampus. Left panel: Profiled with color-scaled *t*-values (legend beneath the coronal image) is a cluster of right hippocampal voxels where chronic perceived stress predicted decreased grey matter volume after controlling for age and total grey matter volume in a region-of-interest analysis. Right panel: Plotted along the *y*-axis is the grey matter volume from the cluster of hippocampal voxels profiled at left; these volume estimates are adjusted for age and total grey matter volume. Plotted along the *x*-axis is the average Perceived Stress Scale score from 1985 to 2004, which was used to define chronic stress.

Hippocampal shrinkage with prolonged major depression

Hippocampal shrinkage in Cushing's - at least partially reversible

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

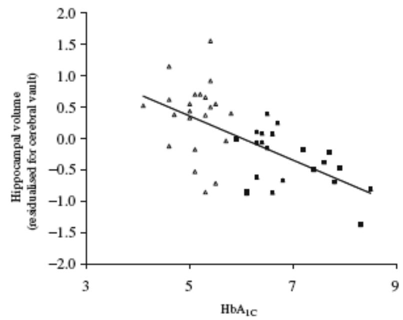
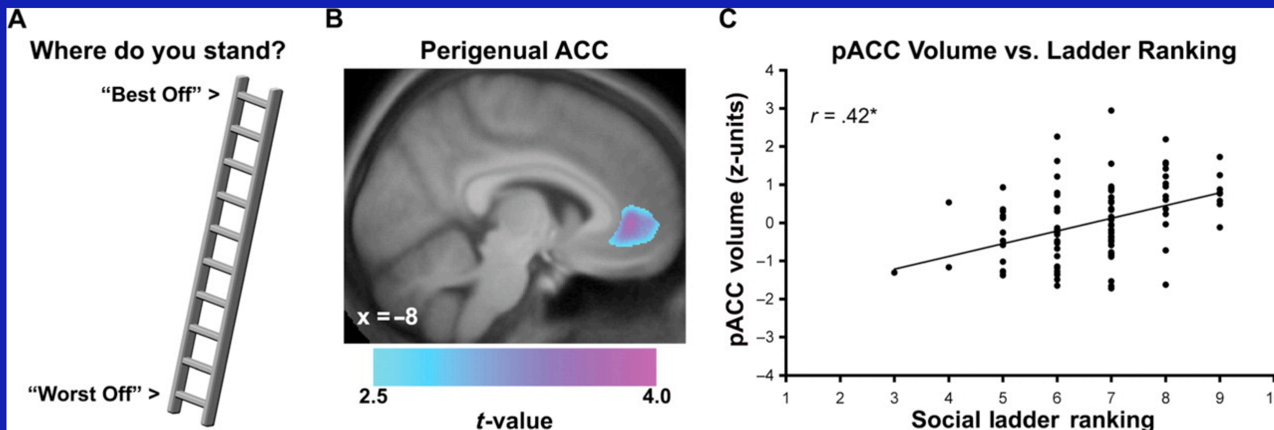


Fig. 1 Bivariate correlations of HbA_{1c} with hippocampal volume (residualised for cerebral vault size). The line shows the line of best fit for the entire study population. *Open triangles*, control subjects; *filled squares*, type 2 diabetic subjects. Descriptive characteristics of individuals with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

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

Anterior cingulate cortex: subjective SES

Lower subjective social status, as reflected by a lower self-reported ranking on a social ladder', was associated with reduced gray matter volume in the perigenual area of the anterior cingulate cortex (pACC)



Gianaros, P.J. et al. *Soc Cogn Affect Neurosci,* 2007, 0:nsm013v1-13; doi:10.1093/scan/nsm013

Social Cognitive and Affective Neuroscience

Is there a neurobiology of self esteem?

Kirschbaum et.al. <u>Psychosomatic Medicine</u> 57:468-474 (1995).

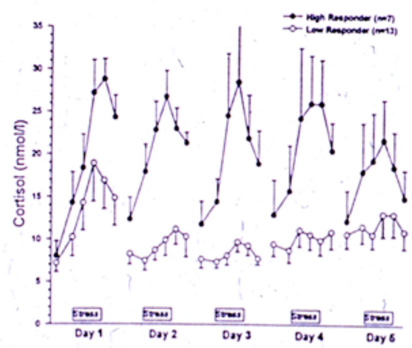


Fig. 2. Mean cortisol responses (± SE) to repeated psychological stress in high responders ($N = 7$) compared with low responders ($N = 13$). The two groups were obtained by cluster analysis of the mean cortisol response across all five stress trials. Note the scale difference in cortisol concentration compared with Figure 1.

<u>Glucocorticoid Cascade Hypothesis</u>

Vicious cycle and hippocampal shrinkage

Failure to habituate HPA response to public speaking

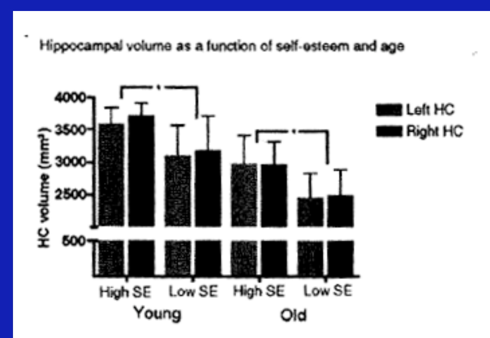
Is there a neurobiology of self esteem?

Elsevier

NeuroImage

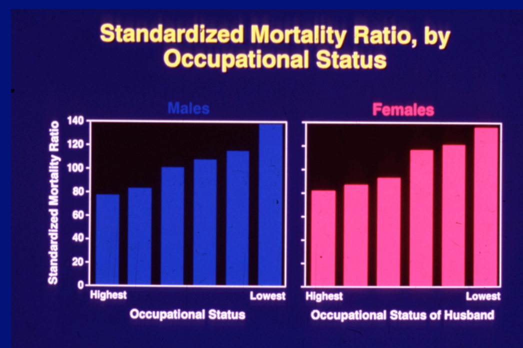
Self-esteem, locus of control, hippocampal volume, and cortisol regulation in young and old adulthood

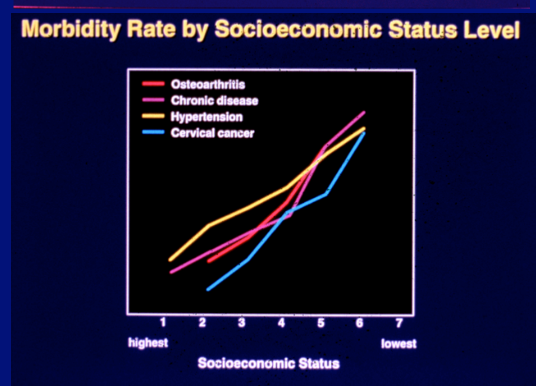
Jens C. Pruessner, Mark W. Baldwin, Katarina Dedovic, Robert Renwick, Najmeh Khalili Mahani, Catherine Lord, Michael Meaney, and Sonia Lupien



A smaller hippocampus may also mean poorer memory and depressed mood

Psychosocial Factors in Causation of Disease





How does SES get "under the skin"?

Social position
- -perceived
- -actual

Discrimination
- - perceived
- - actual

Education/resources
- -money, intellect
- -life skills

Access/use of healthcare

Lifestyle
- -diet
- -alcohol
- -smoking
- -exercise

Stressors from
- - work
- - family
- - neighborhood
- - life events

The Big Picture