Central Role of the Brain in Stress and Adaptation:

Allostasis and Allostatic Load

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Social environment and health
Central Role of the Brain

Non-linearity abounds!!!

Protective and Damaging Effects of Stress Mediators
Social environment and health
Part 1: Allostasis and allostatic load
Stress, allostasis and allostatic load

Many targets for 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

Cortisol

DHEA

Sympathetic

Parasympathetic

Inflammatory Cytokines

Anti-inflammatory cytokines

Oxidative Stress

CNS Function
- Cognition
- Depression
- Aging
- Diabetes
- Alzheimer’s

Metabolism
- Diabetes
- Obesity

Cardiovascular function
- Endothelial cell damage
- Atherosclerosis

Immune function
- Immune enhancement
- Immune suppression
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

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

Hippocampus

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
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

Hippocampus

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

- Leptin, 16 kD: Excitability, Memory, Mood
- Ghrelin, 3.5 kD: Memory, Spines
- IGF-1, 7.6 kD: Neurogenesis, Neuroprotection
- Insulin, 5.8 kD: Glucose transporter, Neuroprotection
A Shrinking Hippocampus?

DIABETES, MILD COGNITIVE IMPAIRMENT (MCI) and GLUCOSE INTOLERANCE

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

S. M. Gold · I. Dolechek · V. Sweat · A. Tiri · K. Rogers · H. Bruchl · W. Toil · S. Richardson · E. Javie · A. Couzii

Fig. 1 Bivariate correlations of HbA1c 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
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.
Hippocampus **INCREASES** in size with:

- Regular exercise
- Intense learning
- Anti-depressant treatment
Exercise training increases size of hippocampus and improves memory

Mitochondria in muscle: fragmentation with inactivity

**NORMAL MITOCHONDRIA**
- ATP synthesis
- \( \text{Ca}^{2+} \) signaling
- Retrograde signaling
- Cellular differentiation
- Purine synthesis

**FUSION**
- Represents mitochondrial fusion

**OVERSUPPLY**
- Represents mitochondrial oversupply

**FUSED/RETICULAR MORPHOLOGY**
- \( \uparrow \) expansion of mtDNA mutations
- \( \uparrow \) mtDNA functional complementation
- \( \downarrow \) apoptotic susceptibility
- \( \uparrow \) bioenergetic efficiency

**FRAGMENTED MORPHOLOGY**
- \( \uparrow \) accumulation of mtDNA abnormalities
- \( \downarrow \) mtDNA functional complementation
- \( \uparrow \) ROS production
- \( \uparrow \) sensitivity to apoptosis

**Respiratory deficiency**
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

**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

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

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**Synaptic functions: enhancement**
- Synaptic transmission.
- Long-term potentiation.
- Learning - re: self-preservation

**Increasing amounts and frequency**

Adrenal steroids and excitatory amino acids modulate both limbs of inverted U
Stress causes neurons to shrink or grow
....but not necessarily to die

Control

Chronic stress

Prefrontal Cortex And Hippocampus

Control

Amygdala
OFC
Brain Under Stress:
Role in cognitive function, emotion, neuroendocrine and autonomic regulation

Amygdala
Emotion, fear, anxiety,
Aggression
Turns on HPA and autonomic response
Overactivity in anxiety disorders and depression

Amygdala
Hippocampus

Control
Chronic stress – dendritic expansion
Acute stress – spine formation
Chronic stress
Increased anxiety
S. Chattarji lab
Brain Under Stress:
Role in cognitive function, emotion, neuroendocrine and autonomic regulation

Amygdala
- Emotion, fear, anxiety, Aggression
- Turns on HPA and autonomic response
- Overactivity in anxiety disorders and depression

Chronic stress – dendritic expansion
Acute stress – spine formation
Increased anxiety
Independent of Glucocorticoids, which Block stress effect

S. Chattarji lab
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)
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

Amygdala
Hippocampus

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

<table>
<thead>
<tr>
<th>Problems from the baseline data</th>
<th>Outcomes associated with the ACE score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalent diseases</td>
<td>Ischemic heart disease, cancer, chronic lung disease, skeletal fractures, sexually transmitted diseases, liver disease</td>
</tr>
<tr>
<td>Risk factors for common diseases/poor health</td>
<td>Smoking, alcohol abuse, promiscuity, obesity, illicit drug use, injection drug use, multiple somatic symptoms, poor self-rated health, high perceived risk of AIDS</td>
</tr>
<tr>
<td>Mental health</td>
<td>Depressive disorders, anxiety, hallucinations, panic reactions, sleep disturbances, memory disturbances, poor anger control</td>
</tr>
</tbody>
</table>

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<tr>
<th>Sexual and reproductive health</th>
<th>Early age at first intercourse, sexual dissatisfaction, teen pregnancy, unintended pregnancy, teen paternity, fetal death</th>
</tr>
</thead>
<tbody>
<tr>
<td>General health and social problems</td>
<td>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</td>
</tr>
</tbody>
</table>

- Heart disease, smoking, obesity
- Drug abuse, high risk for AIDS
- Depression, anxiety, anger control
- Anti-social behavior

Nature-Nurture Interactions

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.

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

Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene.

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.

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 Immunolabelling of the PSD. (A) GR-Ir labelling 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 (isp) at the PSD while the other spine PSD (upper spine) is unlabeled (ulsp). A labeled spine organelle (asterisk) is also present in the isp. (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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Stress effects involve more than glucocorticoids including molecules such as excitatory amino acids, CRF, BDNF, tPA, lipocalin-2 and endocannabinoids.

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, Benoît 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

Food restriction enhances visual cortex plasticity in adulthood

Maria Spolidoro¹, Laura Baroncelli¹, Elena Putignano², José Fernando Maya-Vetencourt¹, Alessandro Viegi² & Lamberto Maffei⁰

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: Non-genomic and genomic effects of glucocorticoids
Glucocorticoids are critical regulators of dendritic spine development and plasticity in vivo

- 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

Dendrites
Shrink and expand

Synapses
Disappear and are replaced

Neurogenesis
Continues in some brain areas

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

Recent and Current Colleagues and Collaborators

- Keith Akama
- Karen Bulloch
- Matt Hill
- Jason Gray
- Richard Hunter
- Ilia Karatsoreos
- Conor Liston
- Ana Maria Magarinos
- Melinda Miller
- Carla Nasca
- Gus Pavlides
- Kara Pham
- Jason Radley
- Rebecca Shansky
- Joanna Spencer-Segal
- Sid Strickland
- Elizabeth Waters
- B.J. Casey, Weill/Cornell
- Sumantra Chattarji, Bangalore and MIT
- Patrick Hof, Mt Sinai
- Joseph Ledoux, NYU
- Teresa Milner, Weill/Cornell
- John Morrison, Mt Sinai
- Teresa Seeman, UCLA

And to former students, postdoctoral fellows

and colleagues who have contributed so much

to this story!!!

MacArthur Research Network on Socioeconomic Status and Health

National Scientific Council on the Developing Child

Support from NIA, NIMH and NINDS