We All Experience “Stress”

But we don’t fully understand what it is . . . and how our bodies defend us.

How does all of this stress “get under our skin”?

What does it do to our brain and body? And what can we do about it?

The Brain as a Primary Organ of Stress

Perception and Response

Environmental stressors (work, home, neighborhood)

Major life events

Perceived stress (threat / stress, helplessness, vigilance)

Behavioral responses (fight or flight, personal behavior – diet, smoking, drinking, exercise)

Physiologic responses

ALLOSTASIS

Major life events

Trauma, abuse

Individual differences (genes, development, experience)

ALLOSTATIC LOAD

Arlostatic and allostatic load: What keeps us alive can also kill us!


Types of Stress

Positive Stress

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

**Toxic Stress** – lack of sense of control
- Poor social and emotional support
- Compromised brain architecture due to early life adversity
- Context-sensitive genotype makes it worse

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**Adaptation to Experiences**

“allostasis”

Allostasis, the active process that promotes adaptation, emphasizes anticipation, prediction


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**The Same Mediators that Allow Us to Adapt Also Cause Damage When Overused and Out of Balance**

Allostatic Load

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**The Brain as a Primary Organ of Stress**

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Allostasis

Allostatic load

Adaptation

Allostasis and allostatic load: What keeps us alive can also kill us!

McEwen, New England Journal of Medicine 1986

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**Conditions/Experiences that “Get Under the Skin” and Dysregulate Physiology**

HEALTH DAMAGING BEHAVIORS from being “stressed out”
- Diet: quality and quantity of food
- Lack of physical activity
- Alcohol
- Smoking

Loneliness

Circadian disruption: jet lag, shift work, sleep deprivation

Ugly, noisy, polluted neighborhood; lack of green space

ALL HAVE EFFECTS, WHETHER OR NOT CALLED “STRESS”
We Need Cortisol to Stay Alive!

**STRESS**

Many targets for cortisol

- **Acute** - enhances immunity, memory, energy replenishment, cardiovascular function
- **Chronic** - suppresses immunity, memory; promotes bone mineral loss, muscle wasting, metabolic syndrome

**We Need Cortisol to Stay Alive!**

More than Cortisol

Meditors of Allostasis and System-wide Effects

Stress-related metabolic changes contribute to multiple disorders.

Mitochondrial allostatic load

Martin Picard, Robert-Paul Juster and Bruce S. McEwen

The stress–disease cascade and mitochondrial allostatic load. Allostatic load is a pathophysiological process in which multisystem biological dysregulation caused by chronic stress synergizes with unhealthy behaviours.

**Multi-morbidity**

Number of other diseases in the Norwegian HUNT2 population (46,000)

- No other disease
- One other disease
- Two other diseases
- 3+ other diseases

Multimorbidity in the Norwegian HUNT2 population (46,000)

Tornqvist et al., 2014

**Silo Medicine**

- Fragmenting approach
  - Guideline overflow
  - "One size fits all?"
  - Uncoordinated polypharmacy

- Expert groups & "task forces"
The Brain as a Primary Organ of Stress
Perception and Response


Allostasis and allostatic load: What keeps us alive can also kill us!

Circadian Rhythm of Cortisol

Regular Oscillations in Cortisol Levels Promote Dendritic Spine Turnover

Cortisol levels

Wisdom of the Body – If oscillations stop, learning and performance suffers.

The Stressed Glutamatergic Synapse and Link to Cortisol

Chronic stress induces strong elevation of extracellular glutamate levels that is dependent on adrenal glands

Chronic stress effects on dendritic remodeling are blocked by blocking NMDA receptors, as well as blocking adrenal steroid synthesis

Hippocampus

- Contextual, episodic, spatial memory
- Mood regulation – target of depression

Stress inhibits neurogenesis

Neurogenesis recovers after chronic stress and is accelerated by physical activity
The Human Hippocampus Under Stress

- Contextual, episodic, spatial memory
- Mood regulation - target of depression

Causes of hippocampus ATROPHY:
- 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

Regular Moderate Exercise Enlarges the Hippocampus

Exercise training increases size of hippocampus and improves memory

You are never too young or too old to benefit!!!

Regular physical activity is the most important behavior that we can do to maintain brain and body health.

Stress Causes Neurons to Shrink or Grow

Control

Chronic stress

Prefrontal Cortex & Hippocampus

Impaired memory, mood, self-regulation

Amygdala

Increased anxiety and vigilance

Hippocampus size INCREASES with:
- Regular exercise
- Intense learning
- Anti-depressant treatment

Stress, Glucocorticoids and the Basolateral Amygdala

Chronic stress - expansion of dendrites; increased spine density; increased anxiety

Acute traumatic stressor
- delayed increase in spine density
- delayed increase in anxiety
- can be prevented by CORT elevation during or right after trauma

In humans

CORT elevation during or after trauma reduces PTSD symptoms

Shona Chattarji
Prefrontal cortex - stress and aging

Medial PFC neurons - dendrite shrink with chronic stress
Orbitofrontal cortex neurons – dendrite expand with chronic stress
Recovery of dendrites impaired with aging

In a study on medical students, high perceived stress
- associated with reduced cognitive flexibility
- reduced functional connectivity involving PFC.

These alterations recover - after a vacation.

Sex Hormone Action and Sex Differences in the Brain

The entire brain has receptors for sex hormones in both male and female
Many of these receptors mediate non-genomic effects on cytoskeleton, neurotransmitter
release, mitochondrial function.

Sex differences involve not only hormonal programming but also X and Y chromosomes
and mitochondrial DNA inherited from the mother

Men and women do equally well on this test....

Social Environment and Health

Environmental stressors (work, home, neighborhood)
Individual differences (genes, development, experience)

Perceived stress (threat / no threat; helplessness; vigilance)
Behavioral responses (fight or flight; personal behavior – diet, smoking, drinking, exercises)

Phylosopic responses

Alostatic load

Adaptation

Trauma, abuse

Major life events

Developmental Issues for Children

Chaos in Home
- Greater helplessness and distress, poor self-regulatory behavior
- Brain development: prefrontal cortex development is altered
- Obesity, elevated blood pressure, and cardiovascular reactivity

Adverse Childhood Experience – Abuse, Neglect, Poverty
- Increases depression, substance abuse, antisocial behavior, cardiovascular disease, obesity
- Brain structure is altered for greater vigilance and anxiety
The Human Brain Under Stress
Developmental effects on hippocampus

Hippocampus
Contextual, episodic, spatial memory

Is smaller in
- Poverty
- Low self esteem
- Risk for PTSD

The Human Brain Under Stress
Developmental effects on amygdala

Amygdala
Emotion, fear, anxiety, Aggression
Larger and more active in depression, anxiety disorders
Larger in children living with a depressed mother

The Human Brain Under Stress
Developmental effects on prefrontal cortex

Prefrontal cortex
Decision making, working memory, Self regulatory behaviors; mood, impulses
Underdeveloped with chaos of poverty, early life abuse

Looking to the Future

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

Interventions to promote resilience that "open windows of plasticity" and change brain structure and function

Regular physical activity
Increased hippocampal volume and PFC blood flow and improved executive function and memory

Mindfulness-Based Stress Reduction
Reducing anxiety decreases amygdala volume

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

Meaning and purpose (eudaimonia)
Stress Colleagues and Collaborators

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<th>Location</th>
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<td>Mt. Sinai</td>
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