Module 8: Neurobiological Sequelae of Exposure to Extreme Stress
Brain Development

Major CNS structural changes take place in development:

- Birth to 4 years
- Late childhood (6-10 years)
- Early adolescence

http://www.visembryo.com/baby/anat/brains1.gif
Acute Stress
Stressor

↓

Fight-or-flight Response
Stress Response

The array of physiological adaptations that ultimately establishes homeostasis.
Allostasis

• **Allostasis:** The functions employed to restore the body to its previous level of equilibrium.
  
  • Adaptation to Stress
  
  • Alterations
    
    • HPA Axis
    
    • Neurotransmitter Systems
    
    • ANS

McEwen, 2000, Neuropsychopharmacology, 22:1108-124
The Stress Response

The acute responses of the autonomic nervous system, HPA Axis, and CRF systems to stress are protective and promote adaptation.
Acute Stress Response

A stressor (actual or perceived) is processed by the cortex

The cortex sends a message to the amygdala

The amygdala releases corticotropin-releasing hormone (CRH), which stimulates the brain stem to activate the ANS and to stimulate the adrenal medulla to produce epinephrine

Also CRH stimulates the HPA releasing ACTH stimulating the adrenal cortex to produce: Cortisol
3-D MRI rendering of a brain with fMRI activation of the amygdala highlighted in red

Source: NIMH Clinical Brain Disorders Branch
http://www.nih.gov/news/pr/jul2002/amygdala.gif
The Acute Stress Response

Stressor

Hypothalamus

Sympathetic Nervous System

Epinephrine

Psychological arousal

Activate
- vital functions to fight or flee:
  - Heart and lungs
  - Muscles of the extremities
  - Energy mobilization
  - Brainstem mental activity

Deactivate
- Digestion
- Higher level mental processes

Adrenal Cortex

Cortisol

**Longer-lasting effects**

- Mobilization of energy (fats and glucose).
- Release of amino acids by skeletal muscle to repair damaged tissues.
- Vasoconstriction (i.e., digestive organs).
- Inhibition of inflammation and the immune response.
Adrenal Cortex releases: Cortisol

Adrenal Medulla releases: Epinephrine, Norepinephrine
The Stress Response

Release of **EPINEPHRINE**:

- Increases:
  - Heart rate
  - Blood pressure
- Increases metabolic rate:
  - ↑ serum glucose
  - ↑ free fatty acids
- Dilates:
  - Pupils
  - Bronchioles
  - Blood vessels in skeletal muscles
- Constricts blood vessels in skin and gut
The Stress Response

Release of **NOREPINEPHRINE**:  
- Majority released by *locus coeruleus*  
- Increases heart rate  
- Increases sensory vigilance  
- Increases anxiety  
- Decreases concentration
The Stress Response

Release of **CORTISOL:**

- Promotes degradation and increased delivery of amino acids
- Promotes lipolysis and increased delivery of free fatty acids and glycerol
- Raises blood glucose
- Inhibits inflammation and immune response
Childhood Stress

- Early life stress may lead to persistent sensitization of the CNS
- Related consequences:
  - Increased vulnerability to stress
  - Increased risk for depression
  - Increased risk for anxiety

Helm & Nemeroff, 2001
Early Life Stress

- Early life stress induces:
  - Hyperactivity of the CRF systems
  - Alterations in neurotransmitter systems

Helm & Nemeroff, 2001
Early Life Stress

Early life stress may affect:

1. Brain structural development
2. Sympathetic nervous system responsivity
3. HPA axis
Early Life Adversities May Initiate Allostatic Loading

- Early parental death
- Maternal deprivation
- Child maltreatment
  - Physical abuse
  - Sexual abuse
Biological Systems in Prepubertal Children with PTSD

- Elevated UFC, DA, NE, EPI,
- Smaller cerebral volumes
- Smaller corpus callosum
- No evidence of atrophy of hippocampus
- PTSS and dissociation correlated negatively with brain volume and corpus callosum

De Bellis, 1999
Stressor

Fight-or-flight Response

Chronic stress
The Paradoxical Stress Response

A sustained stress response may damage the organism and accelerate disease.
Chronic Stress

Prolonged, unrelieved exposure to a variety of stressors may cause a person to operate in physiological “full-alert” mode at all times.
Chronic Stress

Following encounter with a stressor, some persons fail to return to non-stressed functioning.
Chronic Stress

Analogy:

Fire alarm that keeps ringing even after the fire has been put out

Source: Cohen, 2003
Chronic Stress

Disease occurs when stress response systems:

- Come on too often
- Fail to habituate to stressors
- Fail to turn off the stress response
- Remain on after the stress has passed
- Wear out the ability of some organs to respond
- Cause other organs to overreact
Allostatic Load

- The price the body pays for adaptation to adverse psychosocial or physical stressors
- The result of too much stress or an inefficient operation of the stress response system
Allostatic Load

- Major life events
- Environmental stressors (home, neighborhood, work)
- Trauma
- Individual differences
- Behavioral responses
- Physiologic responses
- Allostasis
- Adaptation

McEwen, 1998
Factors Leading to Allostatic Load

- Failure to habituate to stressors
- Failure to turn off the stress response
- Inadequate hormonal stress response

McEwen, 2000
Allostatic Load and Brain Function

Normal levels of stress hormones promote attention and storage of memory.

Elevated levels of stress hormones over long periods can impair memory, promote loss of nerve cells and cause atrophy of hippocampus.

McEwen, 2002
Neurobiology of Stress

- Alterations in CRF circuitry
- Noradrenergic activity
- Serotonergic & GABA dysfunction
- Neurotoxicity
- Hippocampal Atrophy
- Cognitive and Behavioral changes
- Memory Deficits
- EXPLICIT MEMORY

Chronic Stress
Increased CORTISOL

McEwen, 2000
Allostaic Load and the Hippocampus

Chronic stress with continuing release of cortisol may lead to:

- Inhibition of neurogenesis (birth of new neurons in the mature brain)
- Suppression of plasticity (reconfiguration of the brain in response to stimuli)

McEwen, 2002
Effects of Chronic Stress on the Brain

The hippocampus has high levels of cortisol receptors, thus chronic stress impairs hippocampal function leading to:

1. Neuronal atrophy and destruction of neurons
2. Decreased short term memory
3. Poor regulation of endocrine responses to stress
Hippocampal Volume Reduction In PTSD

MRI scan of the hippocampus in a normal control & patient with PTSD secondary to childhood abuse. The hippocampus, outlined in red, is visibly smaller in PTSD. Overall 12% reduction in volume in PTSD.

J. Douglas Bremner, M.D.
Chronic Stress

Psychological Symptoms

- Anxiety
- Dysphoria
- Sleep disturbance
- Appetite change
- Psychomotor dysfunction
- Performance problems
- Interpersonal and social problems
Allostatic Effects

Failure in Allostasis

Chronic exposure to stressors with continuing release of stress hormones may lead to:

- Earlier Aging
- Depression/Anxiety Disorder
- Other Psychological Morbidities
- Immunosupression
- Cognitive Impairment
- Cardiovascular Disease
- Aggressive-Violent Behaviors
- Earlier Mortality

McEwen, 2000
Chronic Stress

- Cardiovascular Diseases
- Depression
- Obesity
- Immune Suppression
- Diabetes
- Hyperthyroidism
- Anatomical changes in the brain

Illnesses related to stress
Effects of Chronic Stress on Cardiovascular and Metabolic Function

Increased risk of:

- Coronary heart disease
- Artherosclerosis
- Myocardial infarction
- Diabetes
- Obesity
- Elevated blood pressure
Effects of Chronic Stress on the Immune System

- Decreased cellular immunity
- Immune cells migrate to different parts of the body and can worsen autoimmune and allergic conditions
- Over time, chronic stress can lead to suppression of the immune response