EARLY BRAIN & BIOLOGICAL DEVELOPMENT A SCIENCE IN SOCIETY SYMPOSIUM

The Good, the Bad and the Damaging: Chronic Stress and the Concept of Allostatic Load

Alberta family wellness initiative
Where science meets real life

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The Stress Response

- Stress is generally defined as a real or perceived threat to an organisms well being

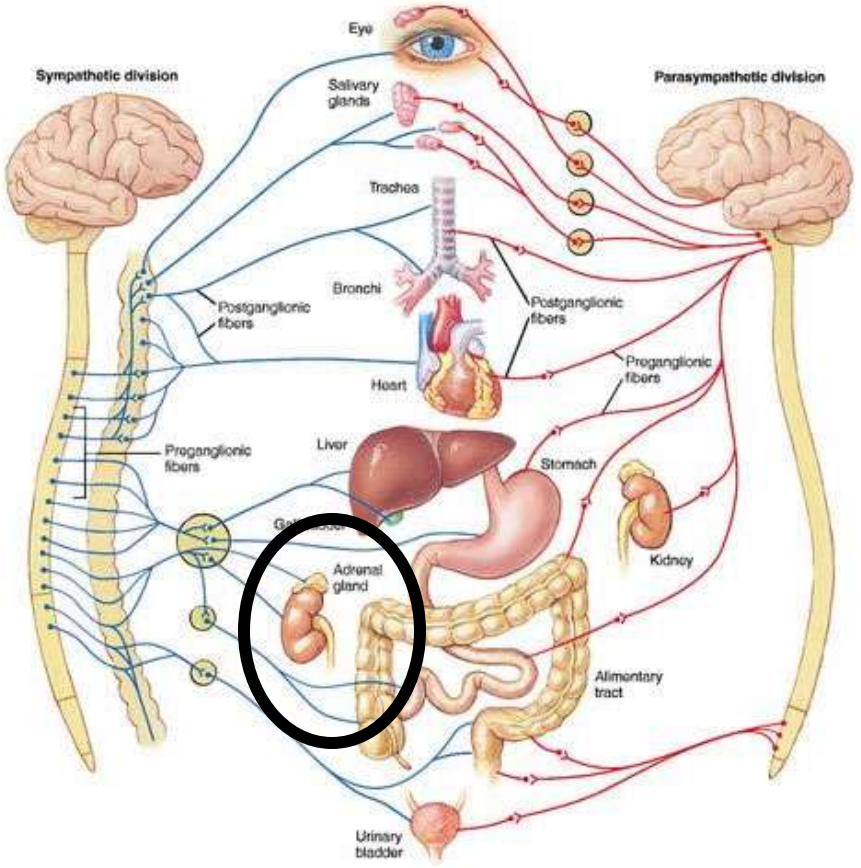
The Stress Response

- At the biological level, stress results in the activation of two pathways which increase hormonal release into the general circulation to modify biological function and optimize an organisms response to a threatening situation

The Stress Response

Autonomic response

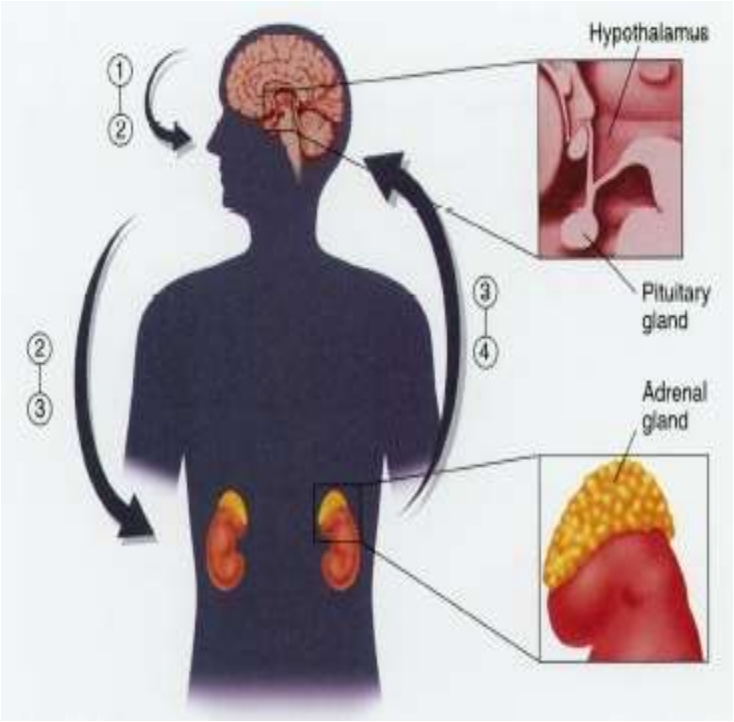
- Activation of the sympathetic nervous system results in the secretion of the hormone adrenaline into the blood from the adrenal medulla



The Stress Response

Adrenocortical response

- Stress activates the secretion of a cascade of molecules
- This originates in the hypothalamus of the brain
- Results in the secretion of glucocorticoid hormones into the circulation from the adrenal cortex



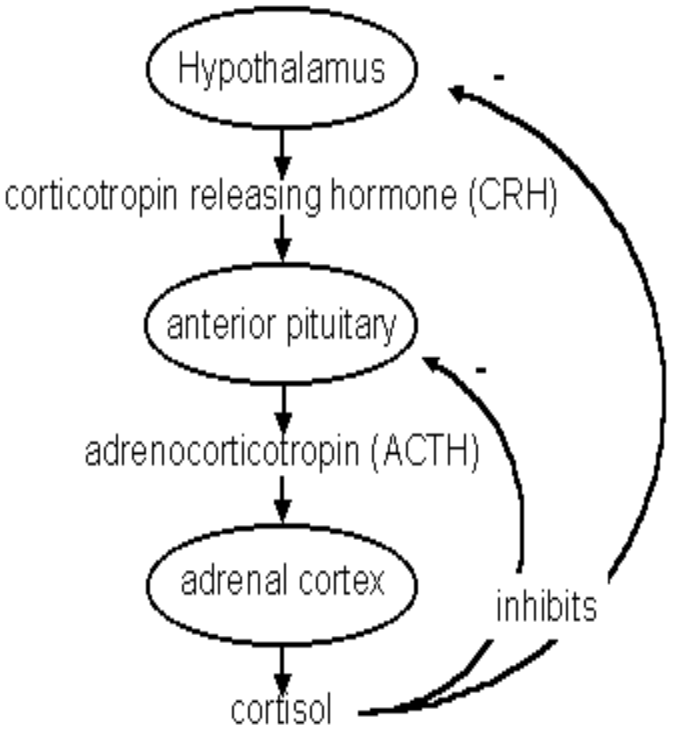
The Stress Response

- The stress response functions to:
  - Mobilize energy stores to provide fuel for muscle to engage in “fight or flight”
  - Increase heart rate and blood pressure to meet energetic demands
  - Increase vigilance to heighten awareness of our environment
  - Traffic white blood cells to prepare for wound healing
  - Enhance memory consolidation
  - Suppress higher order cognitive function and maintain simple behavioural repetoires
  - Suppress motivation for rewarding stimuli (e.g., sexual activity, food, etc.)

The Stress Response

- These biological changes prime an organism to perform optimally under adverse conditions, but are intended to be transient

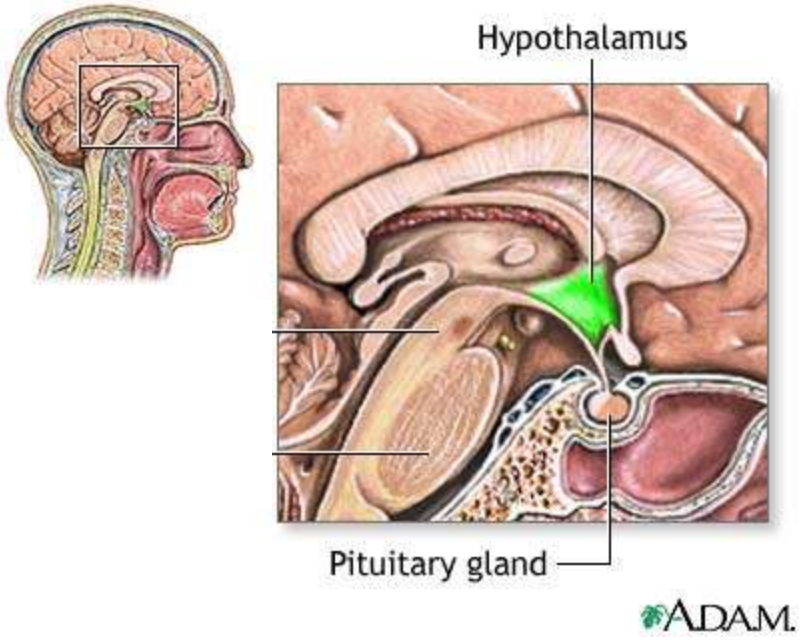
- Glucocorticoid negative feedback is “thermostat” system whereby glucocorticoids inhibit their own secretion



The Stress Response

Hypothalamus

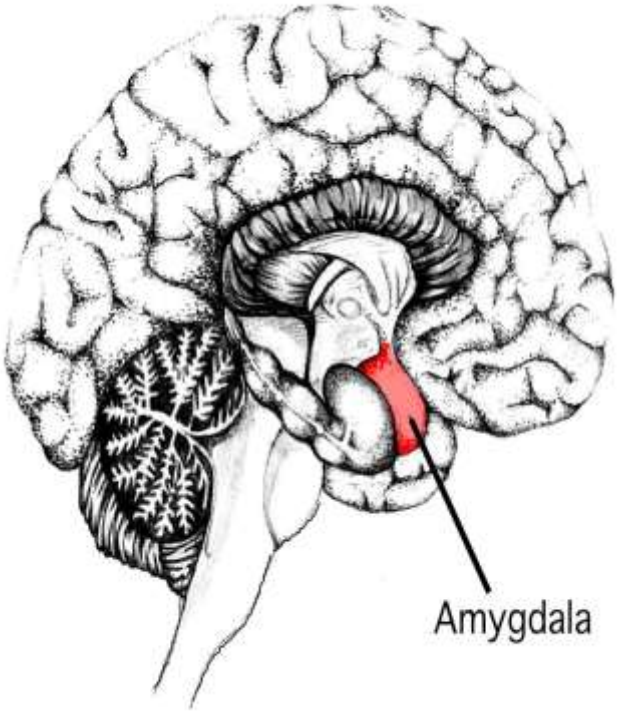
- "Master" control over the adrenocortical response to stress.
- Releases small protein molecules into the blood to result in glucocorticoid secretion from the adrenal cortex.
- Activity in this brain structure ultimately determines the activation and termination of the stress response



The Stress Response

Extrahypothalamic Brain Structures

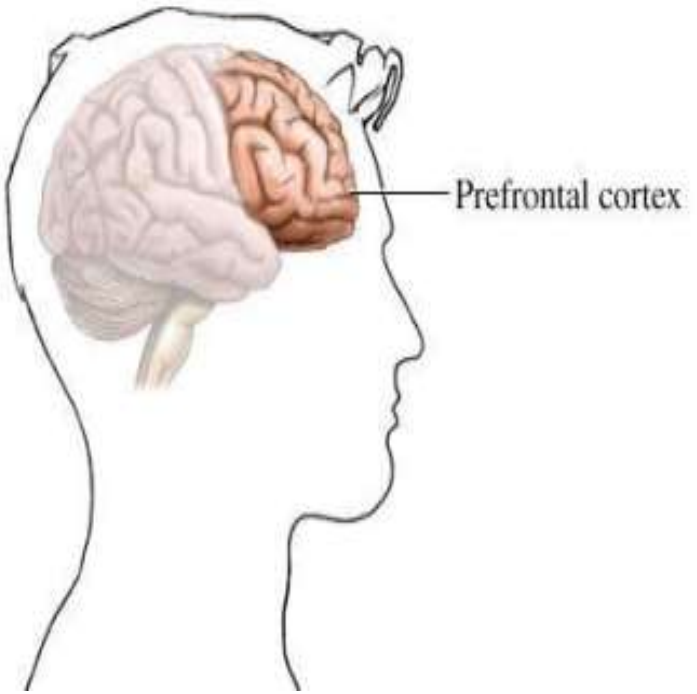
- Amygdala
  - A main site of sensory input in the brain and creates associations between stimuli and outcomes
  - Primarily involved in determining if a stimulus is threatening and generating an anxiety/fear response



The Stress Response

Extrahypothalamic Brain Structures

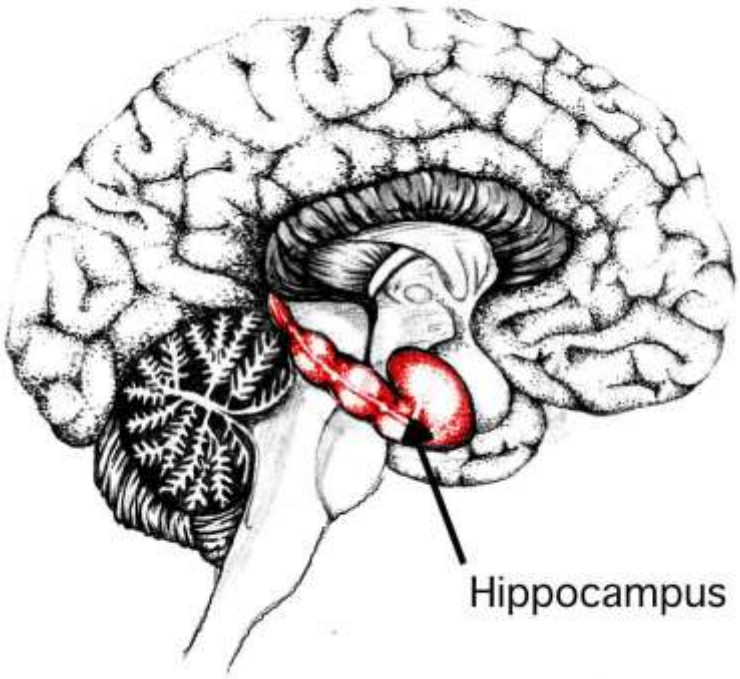
- Prefrontal Cortex
  - Involved in decision making, impulsivity and flexibility
  - Actively references previous experiences to determine if stimuli are predictive of a positive or negative response
  - Constrains activation of the amygdala and limits activation of the stress response



The Stress Response

Extrahypothalamic Brain Structures

- Hippocampus
  - Encodes contextual information
  - Involved in the consolidation of memory
  - Decreases activity in the hypothalamus and limits the duration of the stress response



The Multiple Faces of Stress

Good stress

- Controllable, short-lived and predictable
  - Solving a problem
  - Studying for a test
  - Visiting in-laws
- Helps to teach us to adapt to adverse experiences and become resilient

The Multiple Faces of Stress

Tolerable stress

- Adverse events which are inevitable and from which we cannot avoid
  - Death of a loved one
  - Moving away from home
- This form of stress is made tolerable by support such as social networks

The Multiple Faces of Stress

Toxic Stress

- This stress is produced by events which are uncontrollable, unpredictable and pervasive
  - Abusive relationships
  - Extreme poverty
  - Parental neglect
- This form of stress typically results in persistently elevated stress hormones and can exert damaging effects on the brain and body

The Multiple Faces of Stress

- All of these forms of stress engage the same biological processes, but it is the persistent nature of toxic stress which can leave a biological fingerprint of damage

The Multiple Faces of Stress

- Further, it must be considered that not every brain reacts the same.
- What is considered tolerable stress to some, may be toxic to others.
- These differences are likely dictated by the extrahypothalamic structures in the brain which process external stimuli and determine its threatening or aversive nature

Allostasis

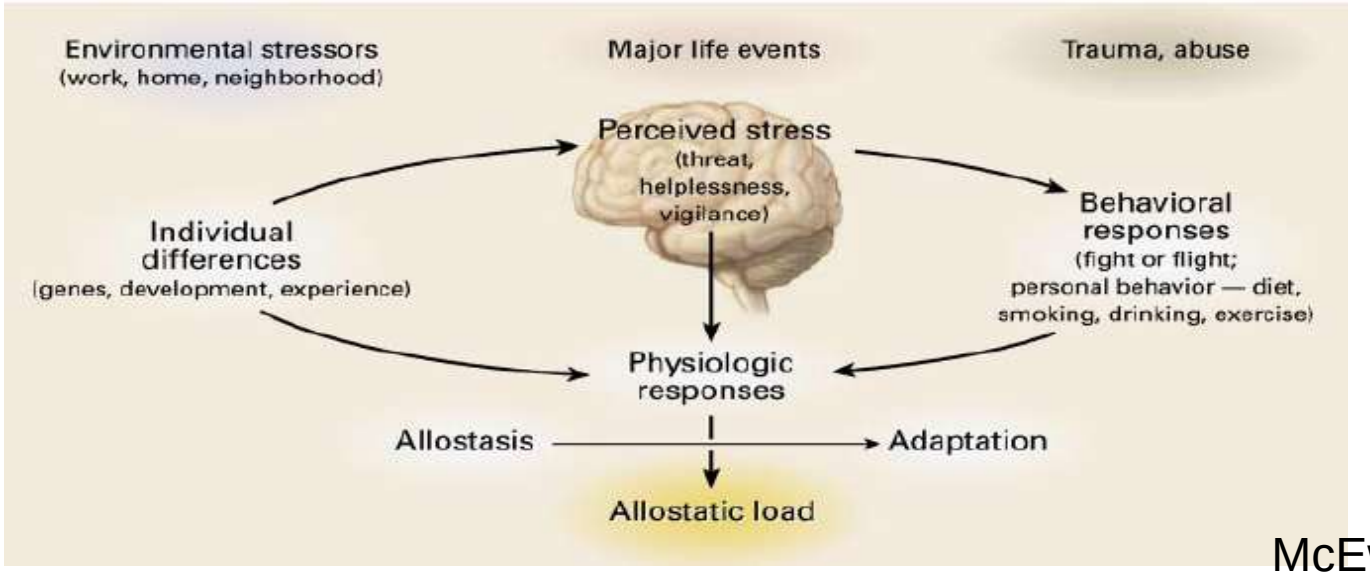
- Stability through change
- The concept of allostasis refers to a response which is launched to maintain normative function within the body and keep an organism's body in optimal conditions for the current environmental demands

Allostasis

- In the framework of stress, all of the changes evoked by stress are intended to ensure survival of the organism
- For example, increased glucose levels provides fuel for muscle tissue to cope with a fight-or-flight situation

Allostatic Load

- Allostatic load refers to the costs which are endured on the body following repeated bouts of stress
- The stress response is intended to be a short-lived process which serves to better allow an organism to escape an impending threat.
- Persistent exposure to stress can result in a breakdown of the systems which stress modulates and result in wear and tear on the body



McEwen, 1998

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Allostatic Load

Acute Stress Response

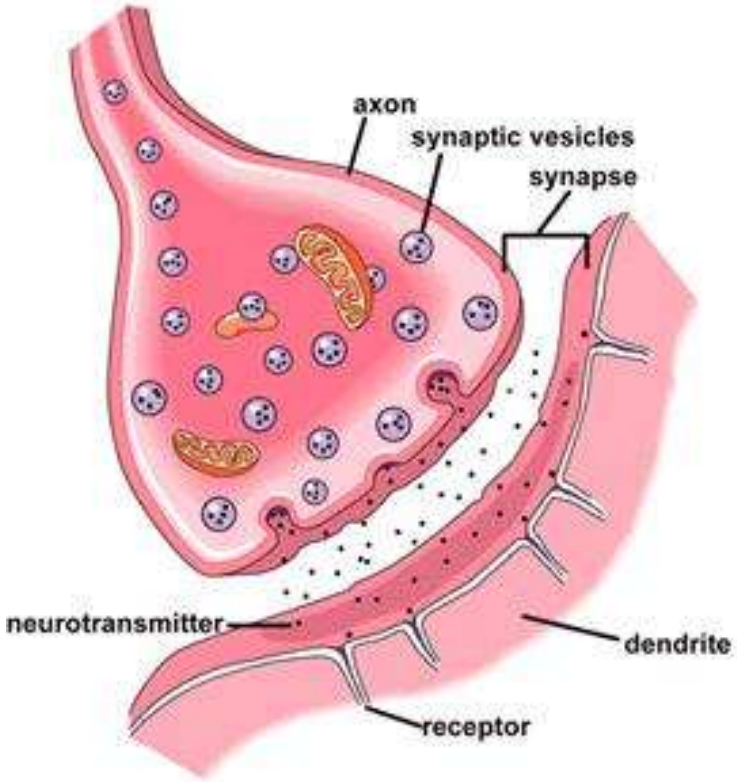
- Increase blood glucose
- Increased blood pressure
- Modulation of immune response
- Reduced motivation for rewarding stimuli
- Vigilance and arousal
- Consolidation of aversive memories

Effect of Persistent Stress

- Excessive insulin secretion, type II diabetes
- Hypertension, coronary heart disease
- Vulnerability to inflammatory diseases
- Loss of interest, depression
- Hyperarousal and anxiety disorders
- Preponderance of aversive memories

Allostatic Load and the Brain

- Brain is also a target of stress and stress hormones
- Stress hormones increase the release of excitatory neurochemicals that activate neurons

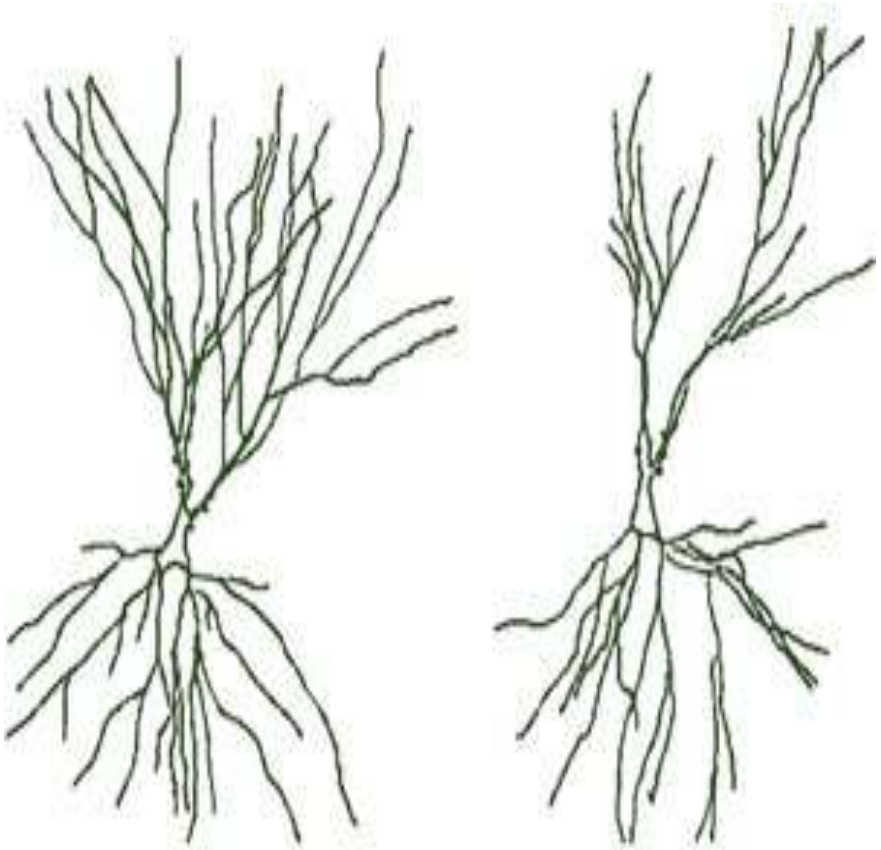


Allostatic Load and the Brain

- Chronic exposure to stress results in repetitive excitation of neurons
- This excessive level of excitation can become toxic to neurons

Allostatic Load and the Brain

- In response to this excessive excitation, neurons retract their dendrites, which represents their receptive field
- This neuronal "shrinkage" is an adaptive response to prevent over-excitation of the cell and cell death



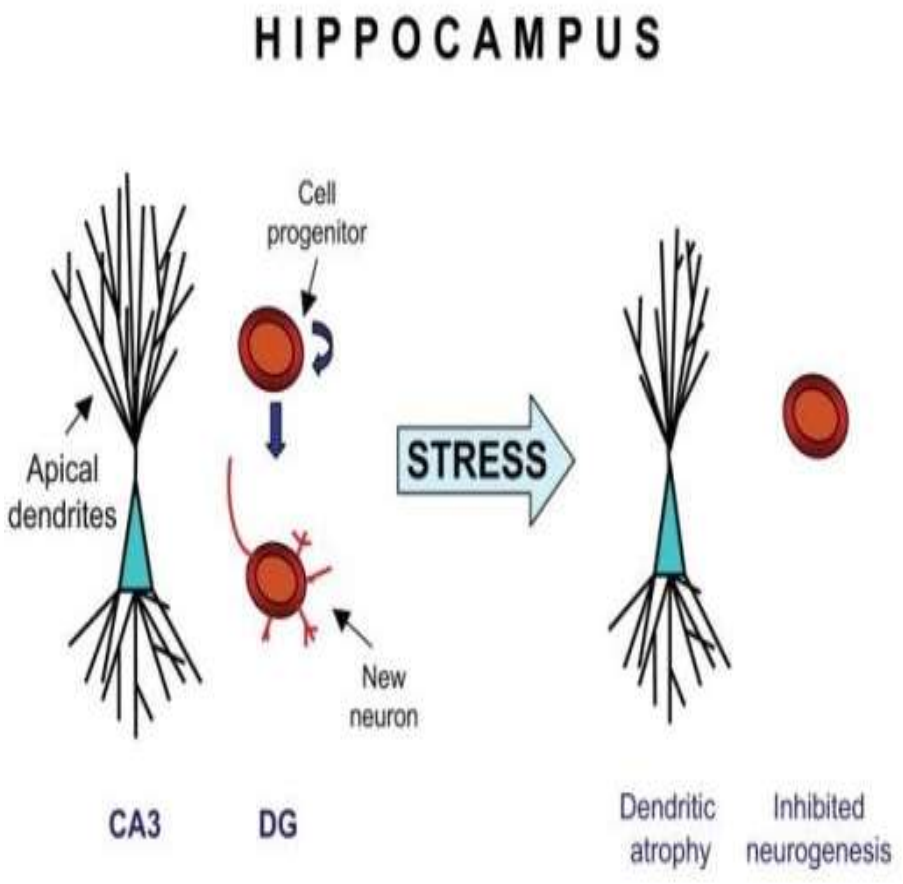
Margarinos et al., 2010

Allostatic Load and the Brain

- While this shrinking of neurons is an adaptive response, the cost is that these neurons no longer perform optimally.
- The two major brain regions where this has been documented is
  - Hippocampus
  - Prefrontal Cortex

Allostatic Load and the Brain

- One consequence of chronic stress is memory deficits
- Compromised function of the **hippocampus** is believed to subserve the adverse effects of chronic stress on memory processes



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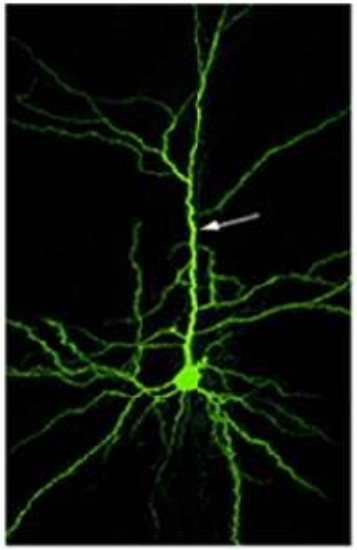
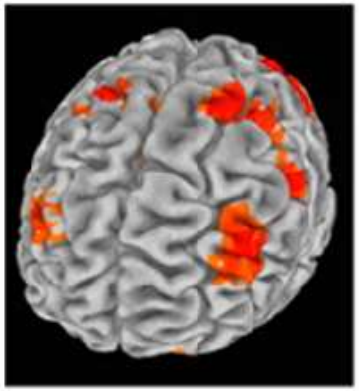
Allostatic Load and the Brain

- Compromised function of the **prefrontal cortex** is believed to subserve problems in decision making, poor impulse control and the development of bad habits following chronic stress.

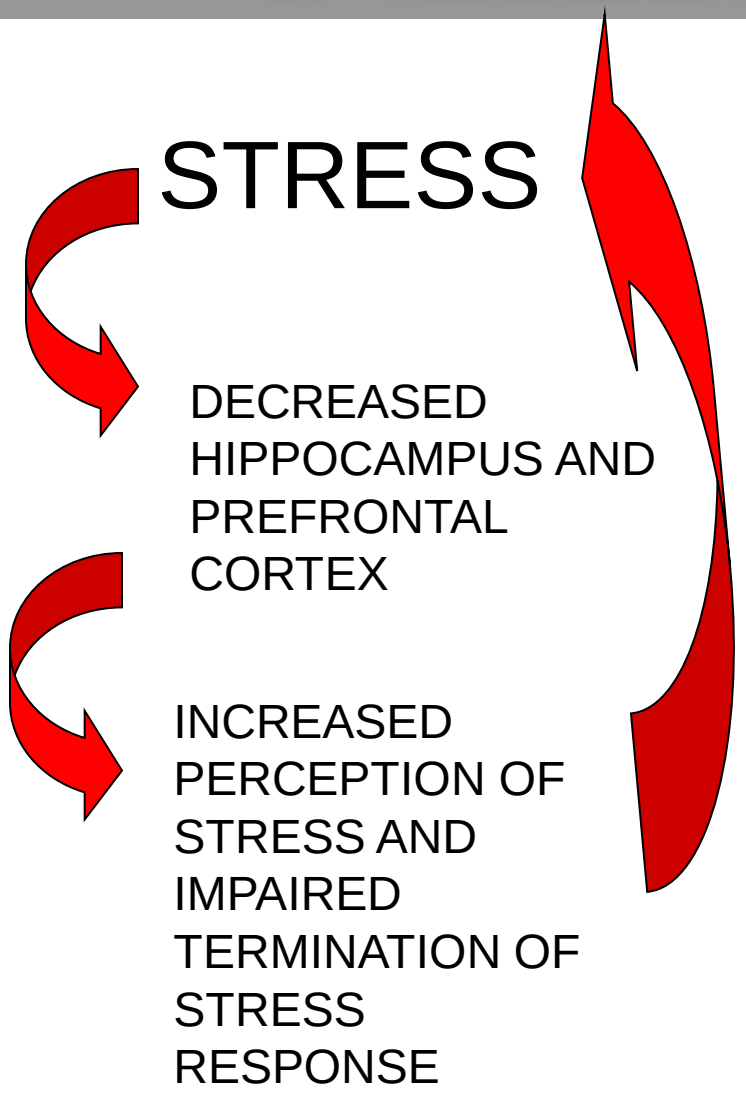




Liston et al., 2009

Allostatic Load and the Brain

- Further, both the prefrontal cortex and hippocampus are involved in stress perception and termination of the stress response.
- Impairments in these structures may lead to a vicious circle which perpetuates and exacerbate the allostatic load of chronic stress

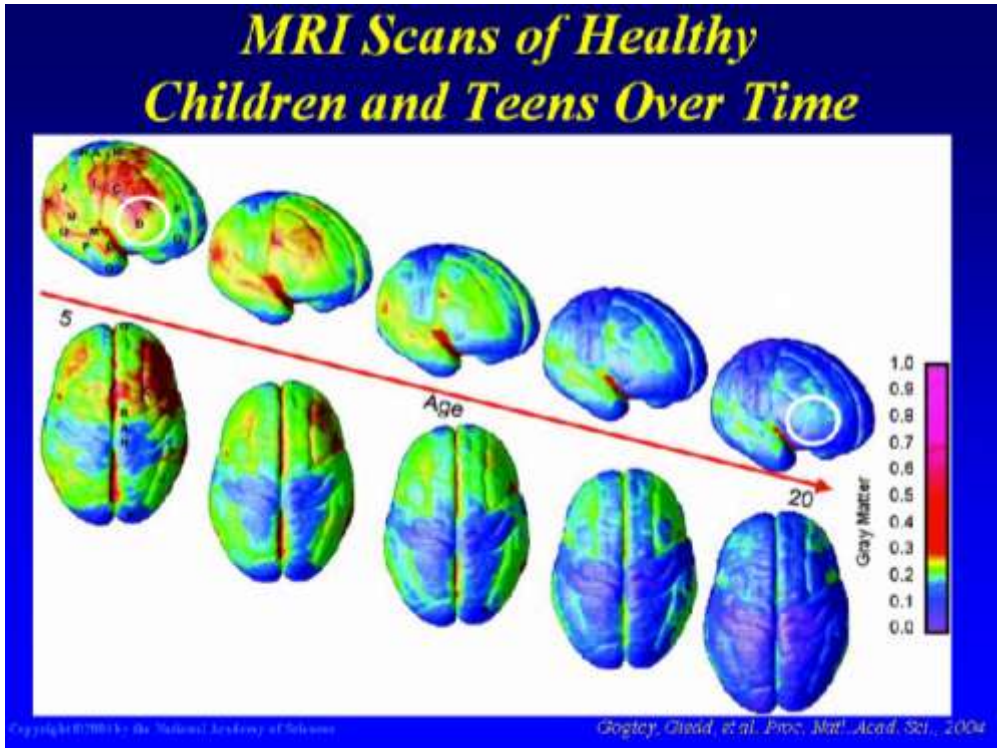


Allostatic Load and the Brain

- In the adult brain, this neuronal shrinkage is reversible following removal from the stressor
- This demonstrates that the adult brain exhibits a high degree of plasticity and can bounce back from the effects of chronic stress

Stress and Development

- The developing brain responds differently to stress
- Brain regions, such as the prefrontal cortex, have not fully developed in early life.
- Interpretation of stress is much more based on immediate needs and threats



Stress and Development

- Some of the biggest stressors during early life can stem from familial instability, lack of resources and parental support
  - Poverty
  - Maternal depression
  - Abusive relationships

Stress and Development

- Long-term studies investigating children raised in abusive or unstable family environments have found that they have an increased propensity for:
  - Mental illness
  - Inflammatory disease
  - Metabolic disorders

Stress and Development

- These persistent changes in individuals who were raised in a stressful environment suggest that early life stress may change the set point for normative function and create a pervasive state akin to allostatic load

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Stress and Development

- Animal studies have attempted to investigate the magnitude and mechanisms of these effects of early life stress
- Maternal separation is the most common model employed to investigate early life stress

Stress and Development

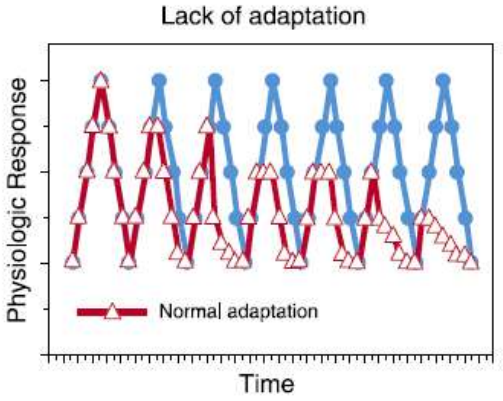
- Maternal separation in rodents results in steady-state changes in the adult brain which parallel many of the alterations produced by exposure to chronic stress
  - "Shrunken" neurons in the hippocampus
  - Reduced generation of new brain cells in the hippocampus
  - Reduced levels of growth factors in the hippocampus and prefrontal cortex

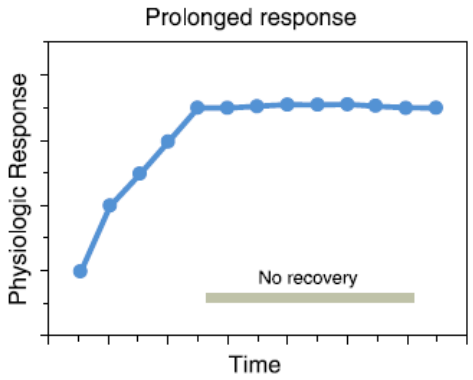
Stress and Development

- Maternal separation in rodents also produces many behavioural changes in adulthood that are akin to the effects of allostatic load
  - Increased anxiety and fear like behaviours
  - Reduced motivation for rewarding stimuli
  - Increased self administration of drugs of abuse

Stress and Development

- Maternal separation has also been found to
  - Impair adaptation to chronic stress
  - Impair plasticity of the brain to chronic stress
  - Increase reactivity to stressful stimuli





McEwen, 1998

Stress and Development

- Thus, early life stress may enhance the sensitivity of the brain to stress, thus creating a vicious cycle which promotes the effects of allostatic load and disease suceptibility.

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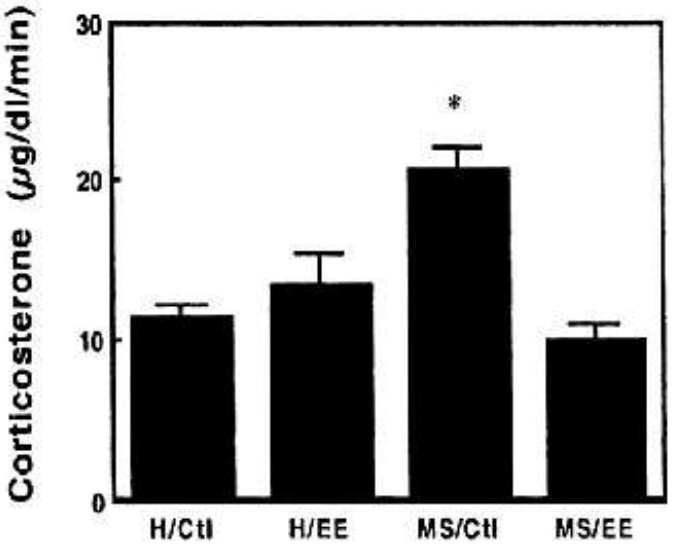
Stress and Development

- Natural variation in maternal behaviours in rodents maps onto these changes as well
- Poor maternal care to neonatal pups is associated with higher levels of stress reactivity and anxiety-like behaviors in adulthood
- High levels of maternal care to neonatal pups is associated with a stress-resilient like phenotype

Stress and Development

- Two points of interest:
  - "Stress Inoculation" - Mild forms of stress in early life may help to sculpt a stress resilient brain later in life
  - Some research has demonstrated that interventions during adolescence, such as environmental enrichment, can ameliorate the effects of early life stress



Francis et al., 2002

Summary

- Stress produces a biological response which modulates the function of most physiological systems.
- In the short term, these changes produce an optimal state of function for an organism to persevere under aversive conditions
- This adaptation to change is referred to as allostasis

Summary

- Prolonged exposure to stress results in allostatic load, or a progressive wear-and-tear on the bodily systems recruited by stress.
- This allostatic load increases suceptibility to metabolic, inflammatory, cardiovascular and mental illnesses.

Summary

- The brain is both central to the processing of stress and effected by stress and stress hormones.
- Following chronic stress, neurons in several brain areas undergo “shrinkage”, which represents an adaptive response to protect neurons from over-excitation and death.

Summary

- This “shrinkage”, however, compromises the functioning of these brain structures.
- This can result in the development of a vicious cycle that makes the brain more sensitive to stress.
- These changes may also be related to behavioural changes, such as poor decision making, impulsivity and memory deficits.

Summary

- Early life stress, particularly in the form of unstable or abusive family environments, can exert long-term effects on developing brain architecture.
- These steady-state changes which emerge in the adult brain parallel the effect of chronic stress and allostatic load.

Summary

- Early life stress may also modulate the way in which the adult brain perceives stress, thus creating a vicious cycle that renders an individual more sensitive to stressful life experiences.
- This increased stress load may increase vulnerability to a multitude of disease states.