EARLY BRAIN & BIOLOGICAL DEVELOPMENT: A SCIENCE IN SOCIETY SYMPOSIUM

Residual Effects of Early Life Stress into Adulthood: Biological Mechanisms

Matthew Hill, Ph.D.
The Rockefeller University

June 1, 2011



Alberta family wellness initiative

Norlien Foundation

The Stress Response

Adrenocortical response

Stress activates the secretion of a cascade of molecules which prepare the body to deal with adverse conditions.

This originates in the brain, where stress causes the release of a peptide called corticotropin releasing hormone (CRH).

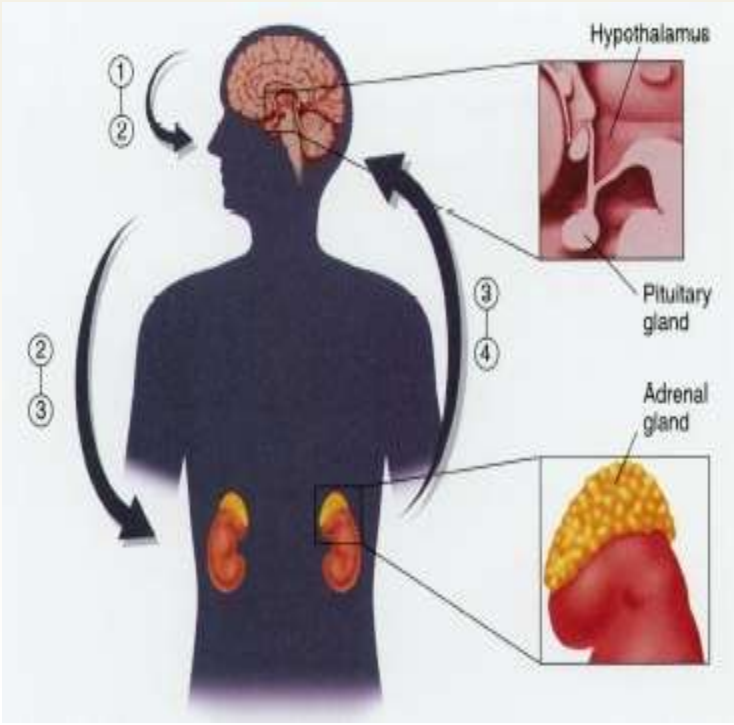
The Stress Response

Adrenocortical response

CRH performs a dual role

1) CRH released from the hypothalamus stimulates ACTH release from the pituitary into the blood which evokes glucocorticoid release from the adrenal cortex.

Glucocorticoids then mobilize energy stores to provide the body with fuel to respond to the threat at hand.



The Stress Response

Adrenocortical response

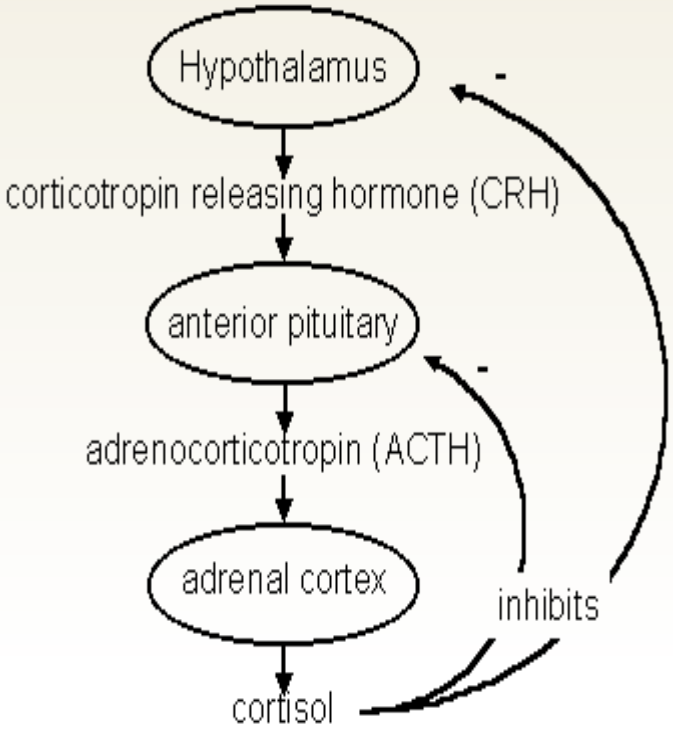
2) CRH is released in other brain circuits involved in emotional processing in response to stress and increases vigilance, anxiety and arousal.

This shift in emotional behavior and attention helps the organism to appropriately respond to any impending threats.

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

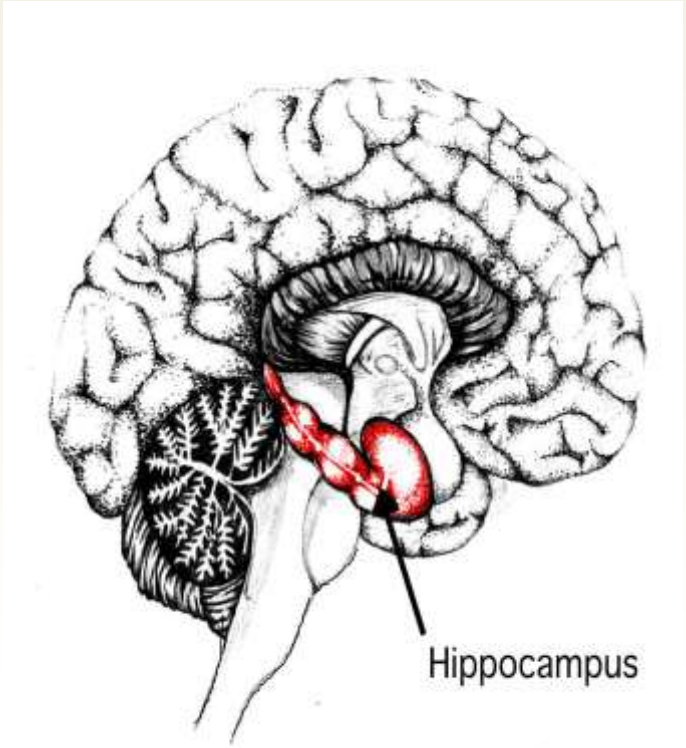


The Stress Response

Extrahypothalamic Brain Structures

Hippocampus

- Very important structure for glucocorticoid negative feedback and shutting off the stress response.
- Encodes contextual information
- Involved in the consolidation of memory

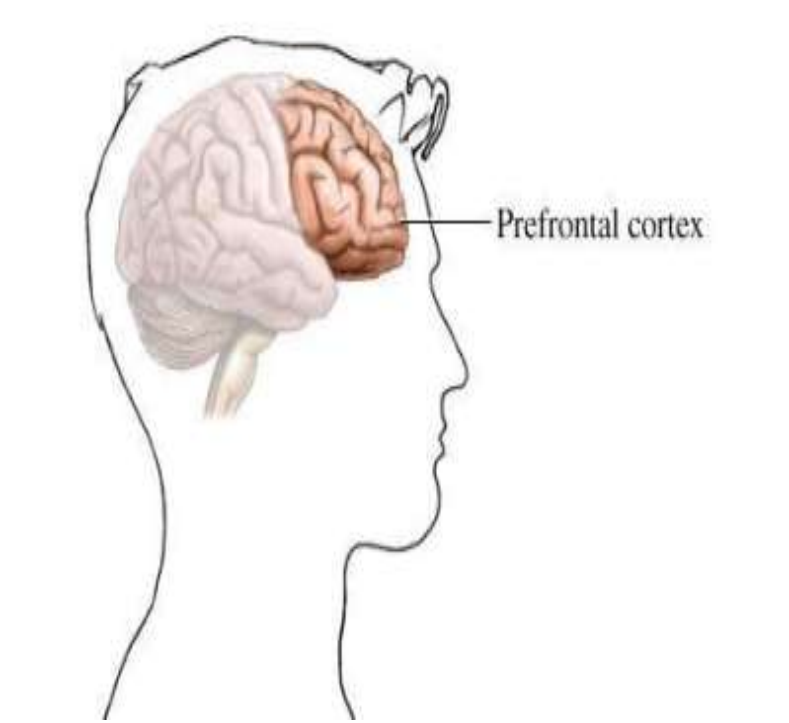


The Stress Response

Extrahypothalamic Brain Structures

Prefrontal Cortex

- Is an important site for glucocorticoid negative feedback and thus limits activation of the stress response.
- Involved in decision making, impulsivity and flexibility.
- Actively references previous experiences to determine if stimuli are predictive of a positive or negative response.

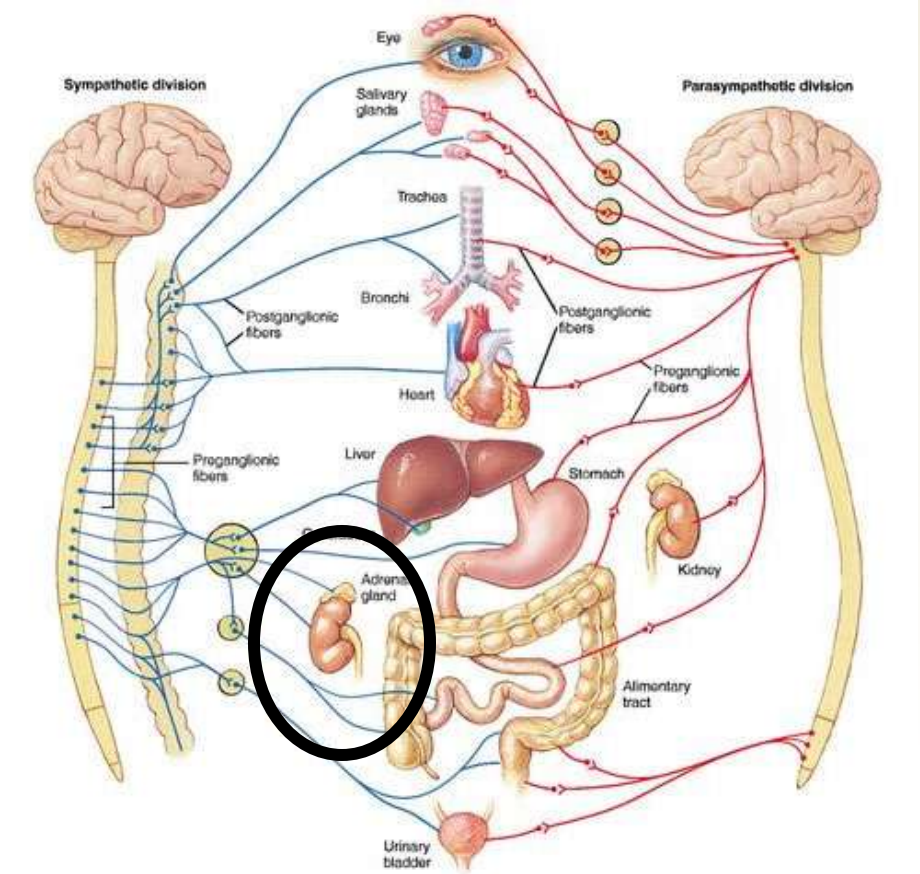


The Stress Response

Autonomic response

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

Adrenaline acts to increase blood pressure and heart rate and prepare the body for “fight or flight”.



Allostatic Load

This shift in physiological systems by stress to prepare the body for adversity is called an **allostatic response**.

The cost the body takes for the repeated activation of this system over time under conditions of chronic or persistent stress, especially of the toxic nature, is called **allostatic load**.

Allostatic load refers to the breakdown of the systems which are being engaged by stress and is related to the development of an array of cardiovascular, inflammatory mental and metabolic diseases.

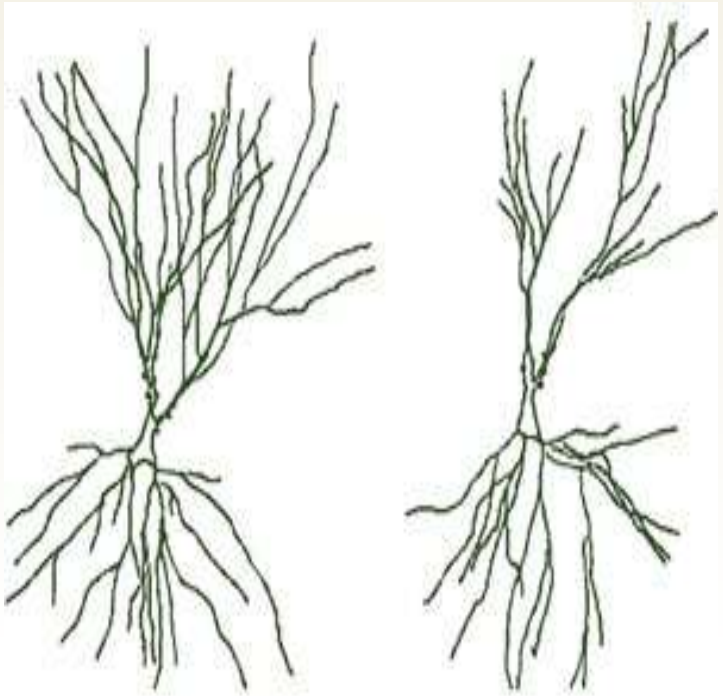
Allostatic Load

Acute Stress Response Stress	Effect of Persistent
Increase blood glucose	Excessive insulin secretion, type II diabetes
Increased blood pressure	Hypertension, coronary heart disease
Modulation of immune response	Vulnerability to inflammatory diseases
Reduced motivation for rewarding stimuli	Loss of interest, depression
Vigilance and arousal	Hyperarousal and anxiety disorders

Allostatic Load and the Brain

Within the brain, the repeated activation of circuits involved in regulating stress results in an allostatic load on the neurons in these areas.

Specifically, these neurons begin to “shrink” to prevent themselves from being overstimulated to death



BASAL CHRONIC STRESS

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.

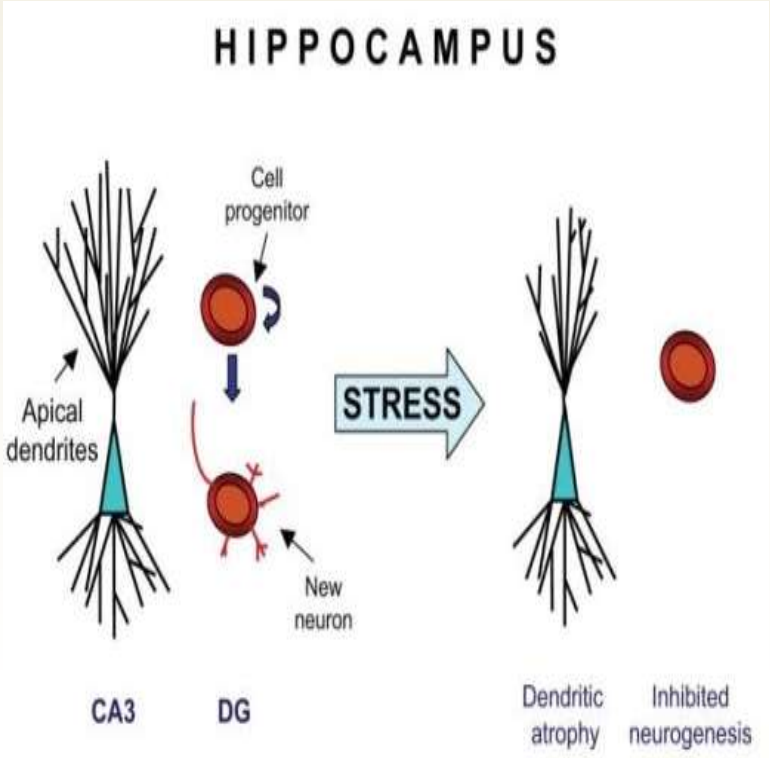
The two major brain regions where this has been documented is

- **Hippocampus**
- **Prefrontal Cortex**

Allostatic Load and the Brain

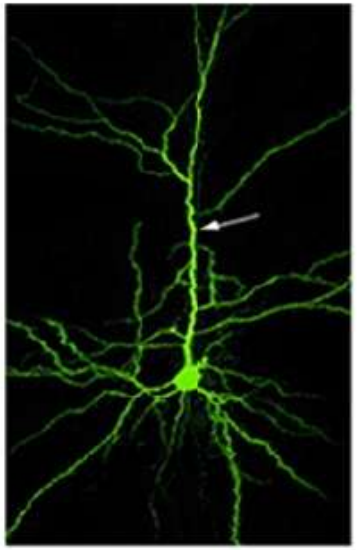
One consequence of chronic stress is memory deficits.

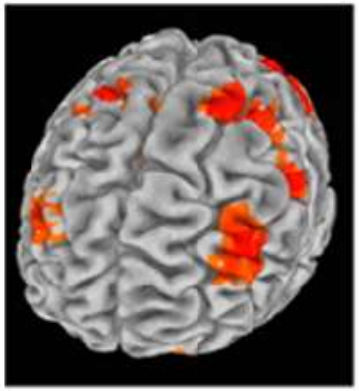
Compromised function of the **hippocampus** is believed to subserve the adverse effects of chronic stress on memory processes.



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.



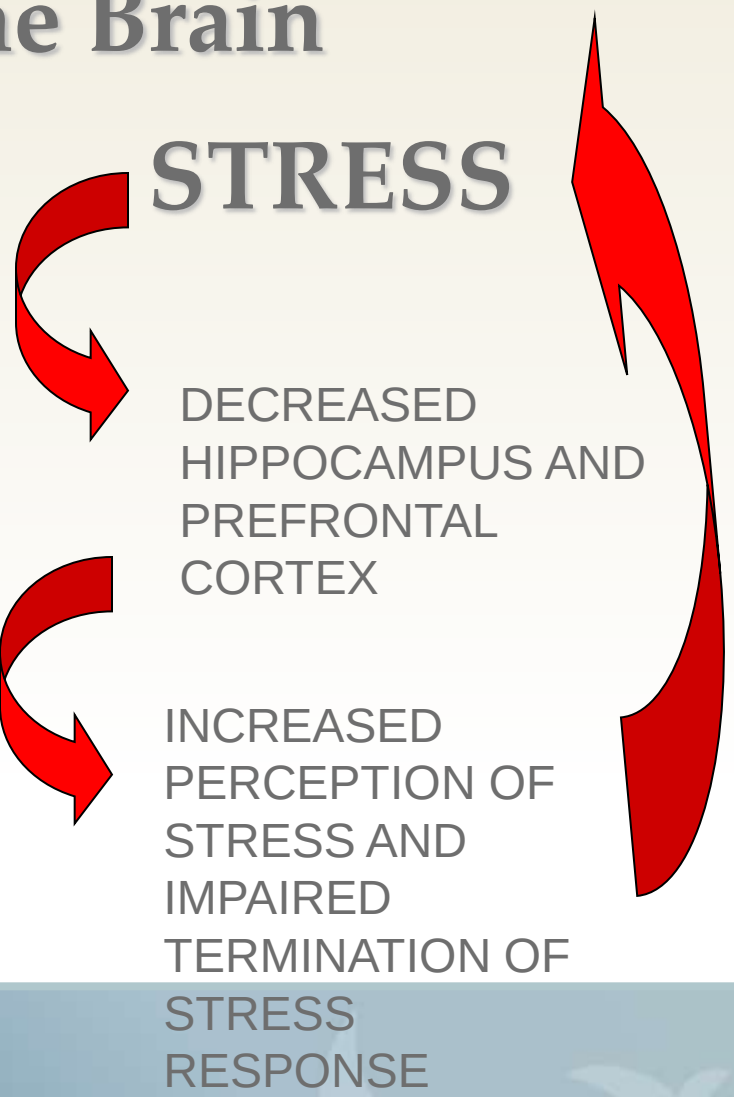


Liston et al., 2009

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

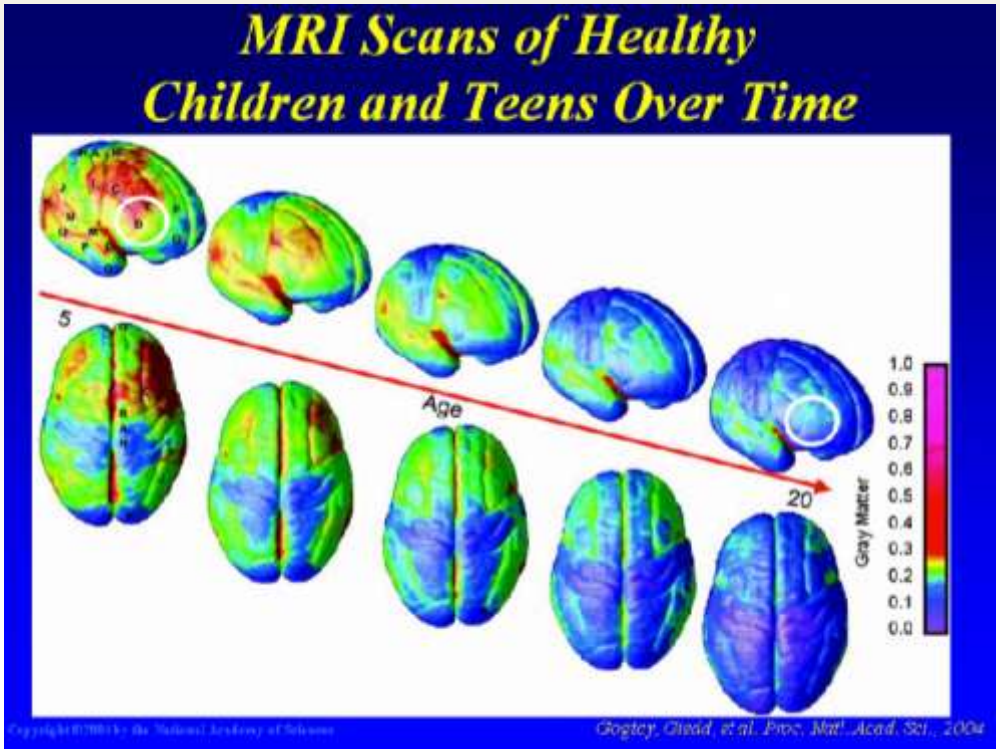
In the adult brain, this neuronal shrinkage following chronic stress is reversible following removal from the stressor.

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 stress response, however, exhibits a developmental trajectory and the long-term functioning of the stress response is often programmed during the early phases of life.

Many brain structures involved in processing stressful stimuli, particularly the prefrontal cortex, continue to develop into adolescence and form a concrete network of how our brain perceives the world.



Stress and Development

Early life stress comes in many forms, but the most toxic comes in the form of abuse, either physical, emotional or sexual.

Other pervasive forms of early life stress are parental instability or loss, social isolation and poverty.

To date, the two most comprehensive studies on the enduring effects of early life stress are:

- **Adverse Childhood Experiences study (ACE)**
- **Dunedin Multidisciplinary Health and Development Study**

ACE Studies

The ACE studies followed individuals who underwent various forms of early life stress.

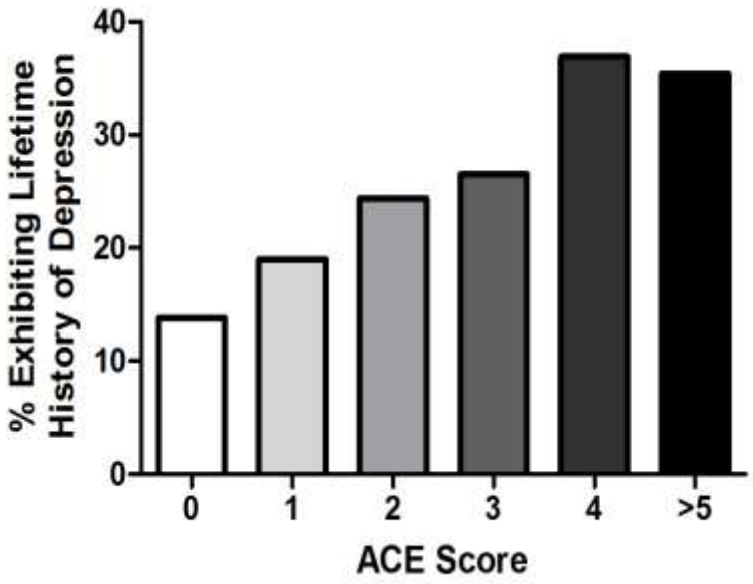
These forms of adversity were broadly categorized into two areas:

- Abuse (Physical, sexual and emotional)
- Familial dysfunction (household substance abuse, parental separation and a criminal or mentally ill family member)

ACE Studies

Depression

- Exposure to ACE's during development exhibited a significant association with the development of depression in adulthood.
- This relationship was dose responsive (more ACE's = greater incidence of depression).



Adapted from Chapman et al., 2004.

ACE Studies

Depression

- The relationship between ACE's and depression was stronger in women than in men.
- Emotional abuse as a child was the ACE most likely to predict depression in adulthood.
- Both women and men were approximately 3 times as likely to develop depression if there were exposed to emotional abuse in childhood.
- Forms of familial dysfunction in isolation were not significantly associated with depression.

ACE Studies

Other health issues arising from ACE's (4 or more ACE's; Anda et al., 2006)

- Obesity (increased 2 fold)
- Alcoholism (increased 7 fold)
- Smoking (increased 1.7 fold)
- Promiscuity (increased 3.5 fold)
- Intimate partner violence (5.5 fold)

Dunedin Studies

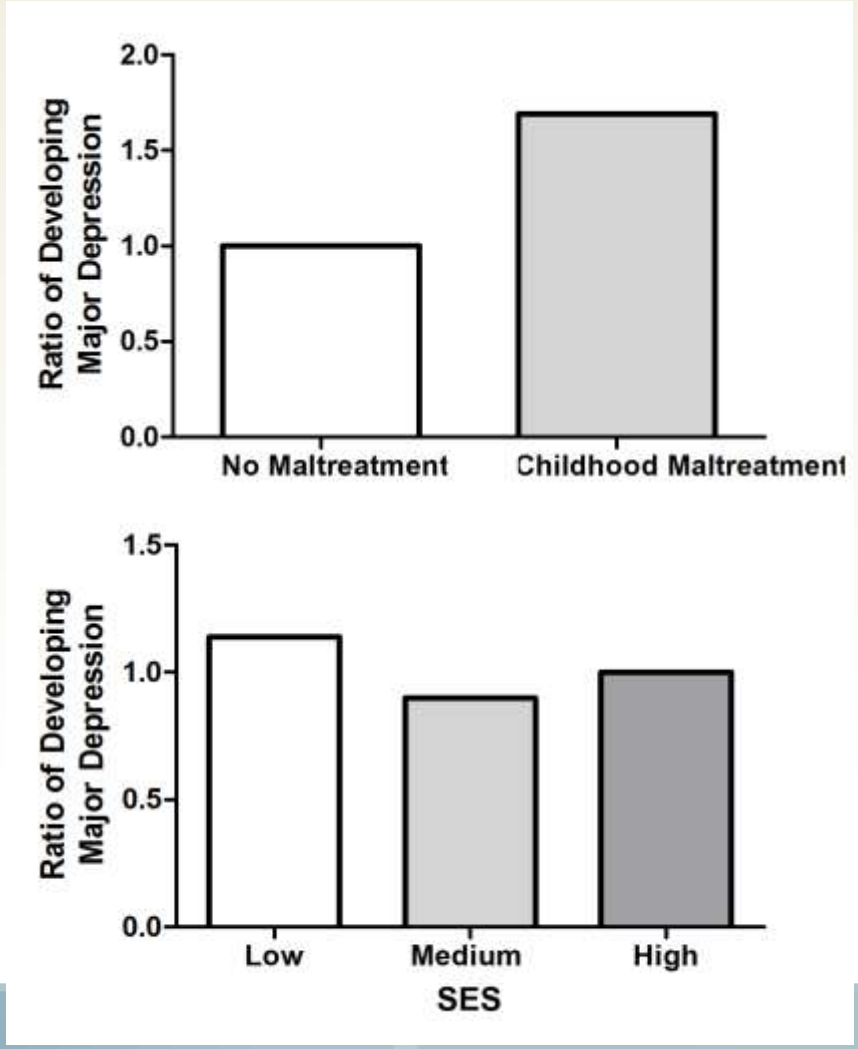
The Dunedin studies, performed in New Zealand, followed a birth cohort of over 1000 individuals over the span of their life (into their early 30's now).

This approach allowed for the examination of the emergence of different disease states in individuals from a wide variety of backgrounds and experiences.

Dunedin Studies

Depression

- Childhood maltreatment increased risk for depression 1.7 fold (Danese et al., 2009).
- Low SES in childhood did not effect rates of depression in adulthood (Poulton et al., 2002; Danese et al., 2009).



Adapted from Danese et al., 2009

Dunedin Studies

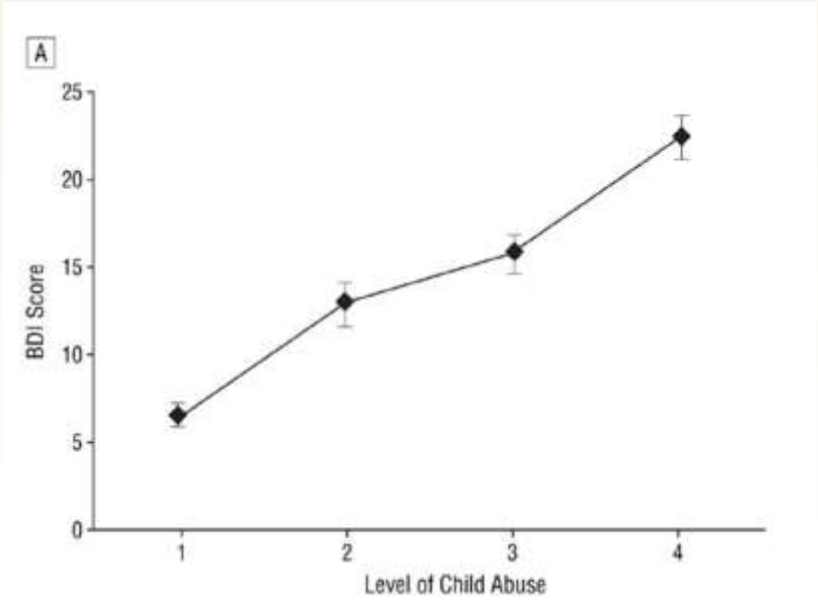
Other health issues

- Obesity was significantly related to low SES in childhood, but not maltreatment (Danese et al., 2009).
- Cardiovascular health and dental health were worse in individuals who experienced low SES in childhood (Poulton et al., 2002).
- Alcohol and tobacco use were moderately associated with low SES in childhood (Poulton et al., 2002).

Emory University Studies

Heim and Nemeroff group

- Similar to the ACE and Dunedin studies, the studies from this group have repeatedly demonstrated a strong and dose responsive association between childhood abuse and depression in adulthood (reviewed in Heim et al., 2004).



Bradley et al., 2008

Early Life Stress Studies

Major findings

- All these studies demonstrate that early life stress increases rates of depression in adulthood.
- The ACE and Dundin studies estimate that early life stress accounts for about 30% of cases of depression in adults.
- The nature of early life stress is critical, abuse is the most significantly associated with depression, while low SES is less associated with depression but highly associated with metabolic diseases.

Early Life Stress Studies

These data indicate that early life stress can increase the propensity to develop both mental and physical diseases.

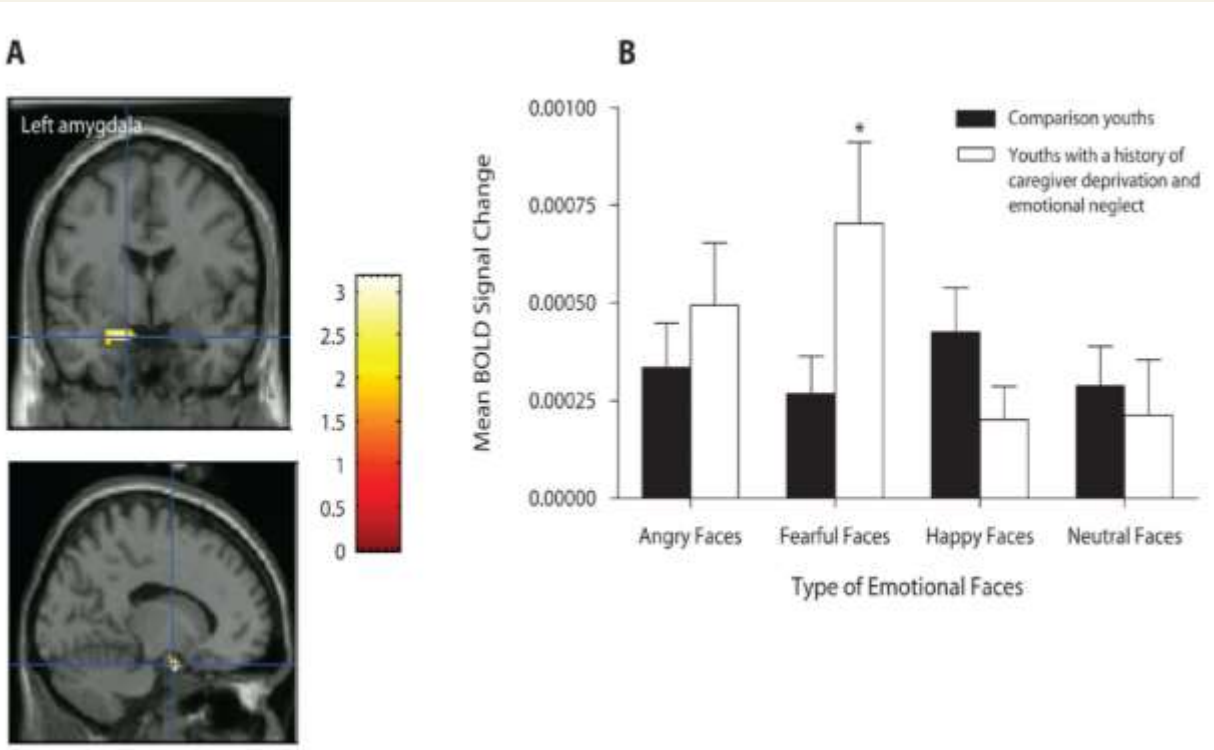
These disease states mirror the effects of allostatic load following chronic stress, suggesting that early life stress may change the set point at which the body responds to stress and create a steady state level of increased stress.

There is evidence which indicates that early life adversity increases physiological responses to stress.

Early Life Stress Studies

The ACE study revealed that individuals with a high degree of ACE's exhibit a greater than 2 fold elevation in perception of current stress than those who did not experience ACE's (Anda et al., 2006).

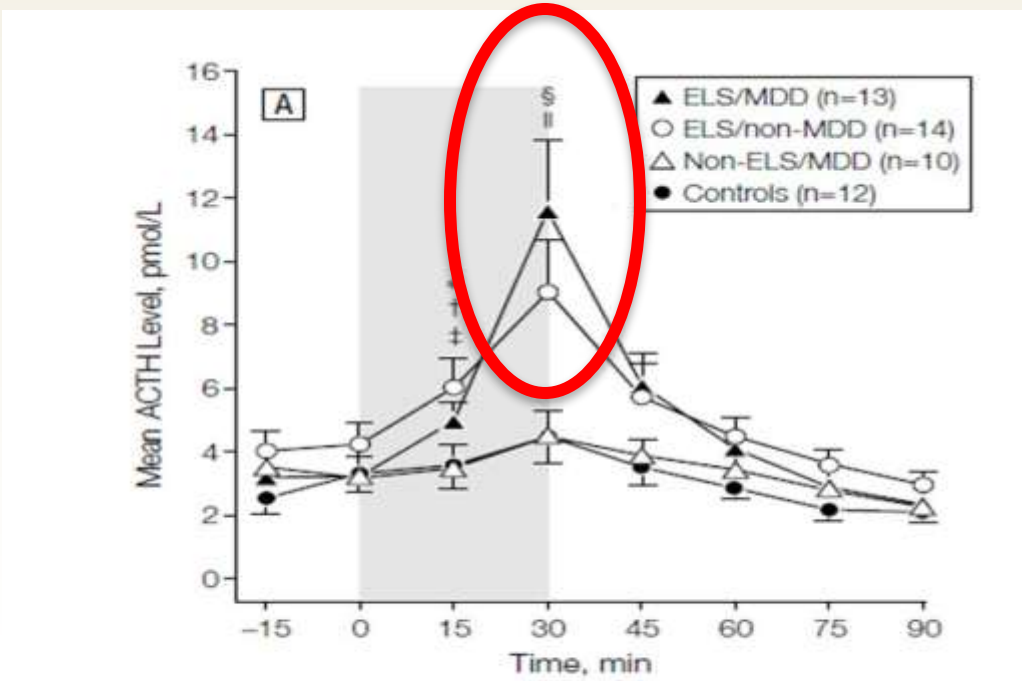
Similarly, it has also been demonstrated that individuals who experienced caregiver deprivation and emotional neglect exhibit heightened activation of neural circuits in response to fearful stimuli (Maheu et al., 2010).



Maheu et al., 2010

Early Life Stress Studies

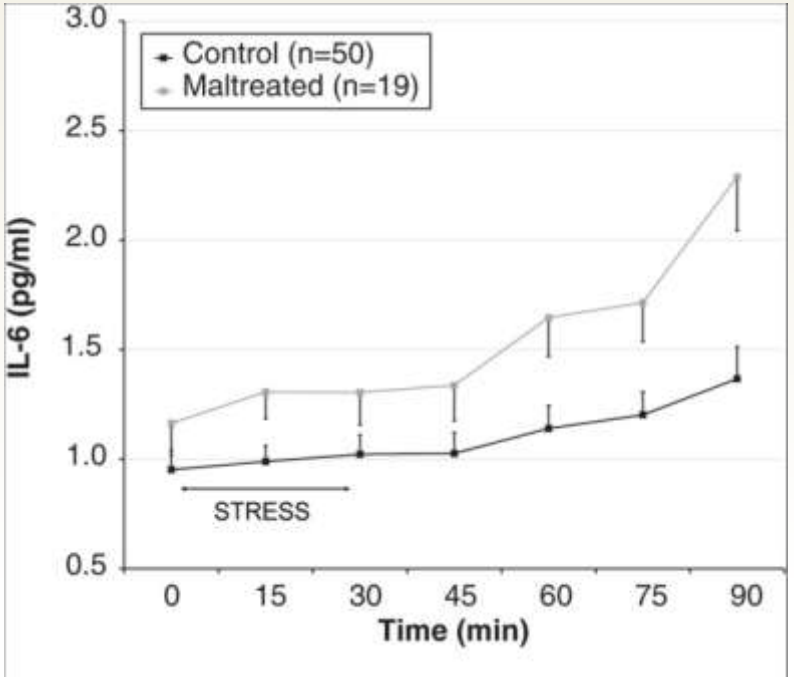
Women who were abused as children have also been found to exhibit dramatic elevations in neuroendocrine responses to social stress as adults, particularly if they are currently in an episode of depression (Heim et al., 2000).



Heim et al., 2000

Early Life Stress Studies

Individuals who experienced childhood maltreatment also exhibit an increased inflammatory response to acute social stress exposure (Carpenter et al., 2010)

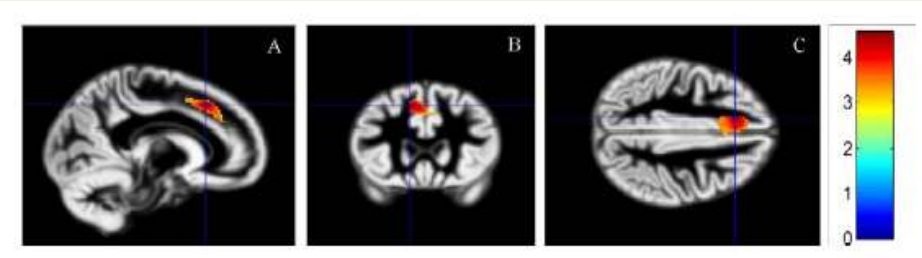


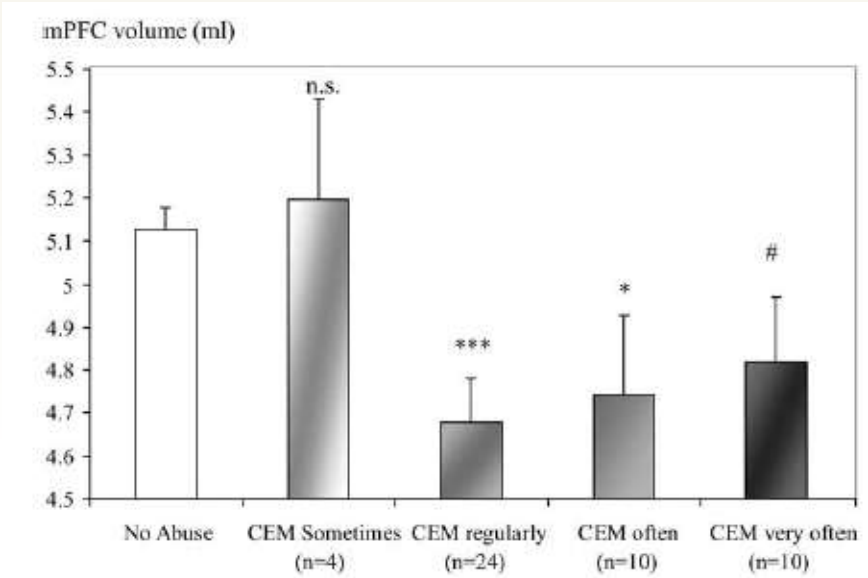
Carpenter et al., 2010

Early Life Stress Studies

Early life stress is associated with reduced volume of the hippocampus and prefrontal cortex.

The reduced volume of these structures may contribute to sensitization of the stress response due the loss of their inhibitory role.





Van Harmelen et al., 2010

Early Life Stress Studies

These studies demonstrate a sensitization of the stress axis at multiple levels following early life stress.

This phenomenon over time appears to result in a cumulative allostatic load effect which increases propensity for disease.

But how does early life stress get under the skin of people to sculpt the brain and body to respond to stress so sensitively later in life???

Early Life Stress Studies

Concept of Glucocorticoid Resistance

Evidence suggests that early life stress results in a state of glucocorticoid resistance.

Glucocorticoid resistance is defined by an impairment in actions of glucocorticoids.

Glucocorticoid resistance is the major theory of how early life stress produces long lasting effects on mental and physical health.

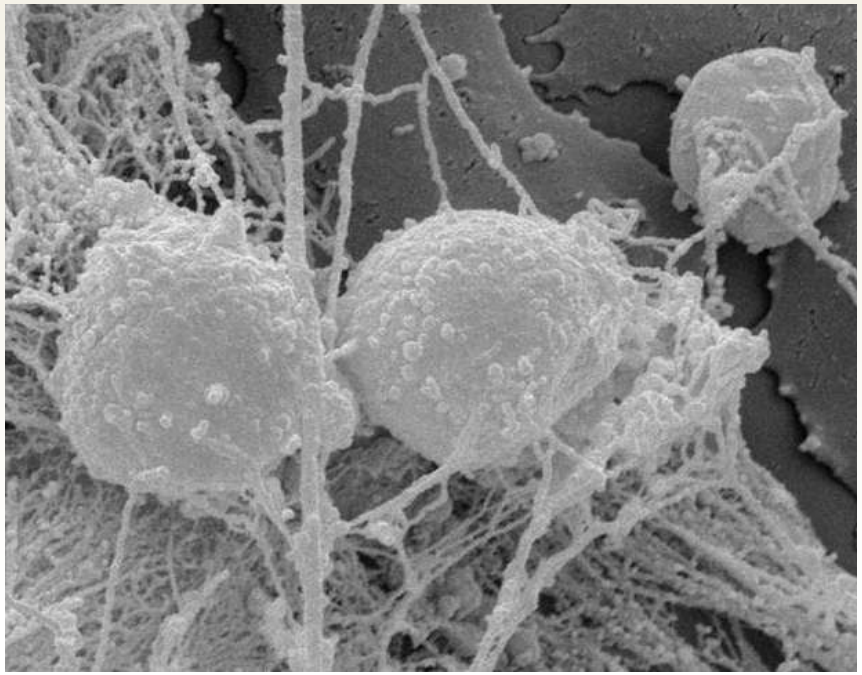
The regulation of inflammatory pathways and CRH by glucocorticoids is key to the effects of glucocorticoid resistance.

Glucocorticoids and Inflammation

Glucocorticoids act on white blood cells to reduce inflammatory molecules.

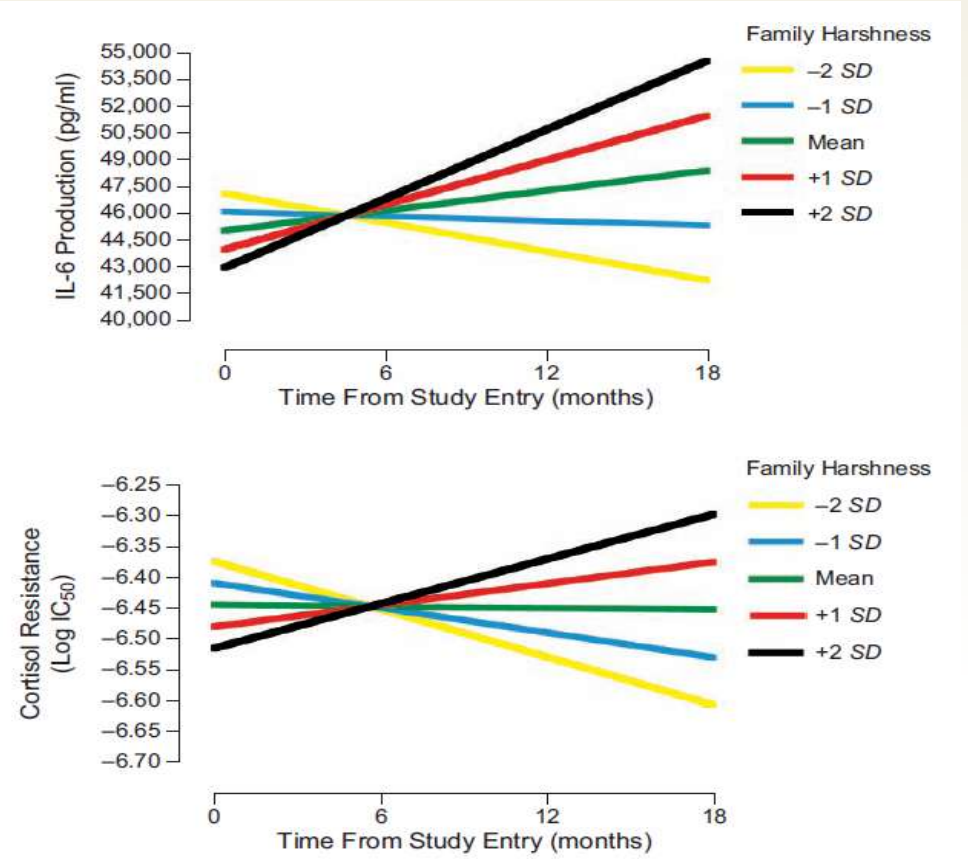
This helps to limit inflammatory responses induced by stress.

Resistance to the actions of glucocorticoids on white blood cells results in an increase in systemic levels of inflammation.



Glucocorticoids and Inflammation

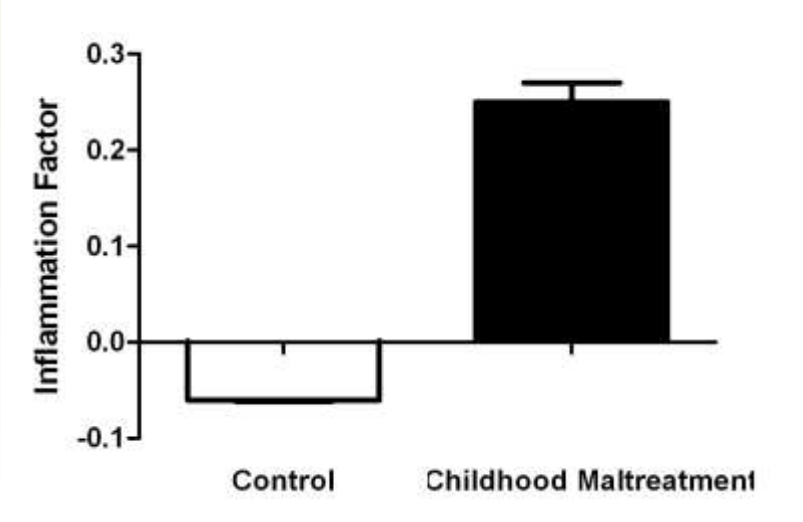
Individuals who experienced early life adversity have been found to exhibit resistance to the anti-inflammatory actions of glucocorticoids.



Miller and Chen, 2010

Glucocorticoids and Inflammation

This phenomenon correlates with the documented increase in inflammatory markers in the circulation, as well as the increased prevalence of inflammatory diseases (e.g., asthma, autoimmune diseases), that have been identified in individuals exposed to childhood maltreatment.

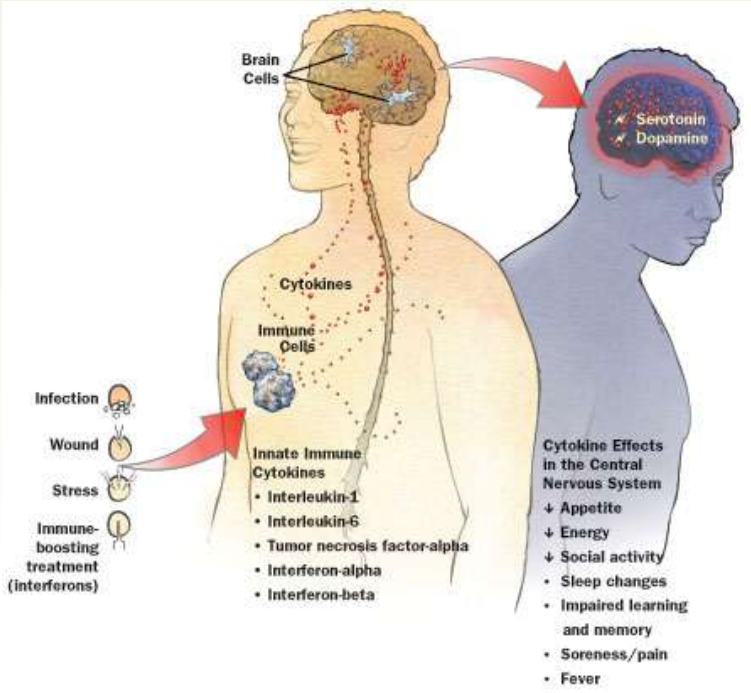


Adapted from Danese et al., 2008

Glucocorticoids and Inflammation

Furthermore, persistent inflammation has also been linked to the development of major depression.

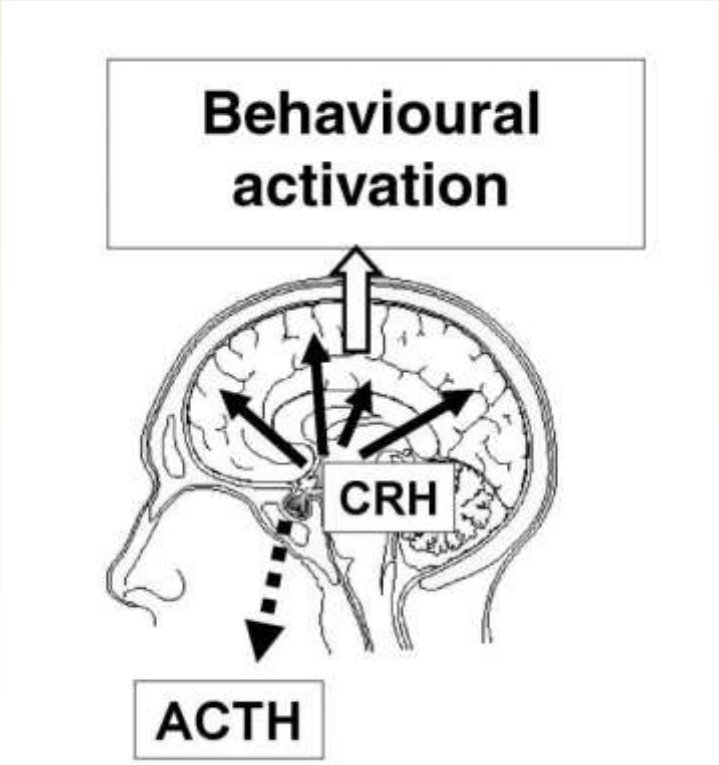
As such, heightened systemic inflammation due to glucocorticoid resistance could contribute to changes in physical and mental health following early life adversity.



Glucocorticoid Feedback and CRH Sensitization

CRH release in the hypothalamus evokes glucocorticoid release in the circulation.

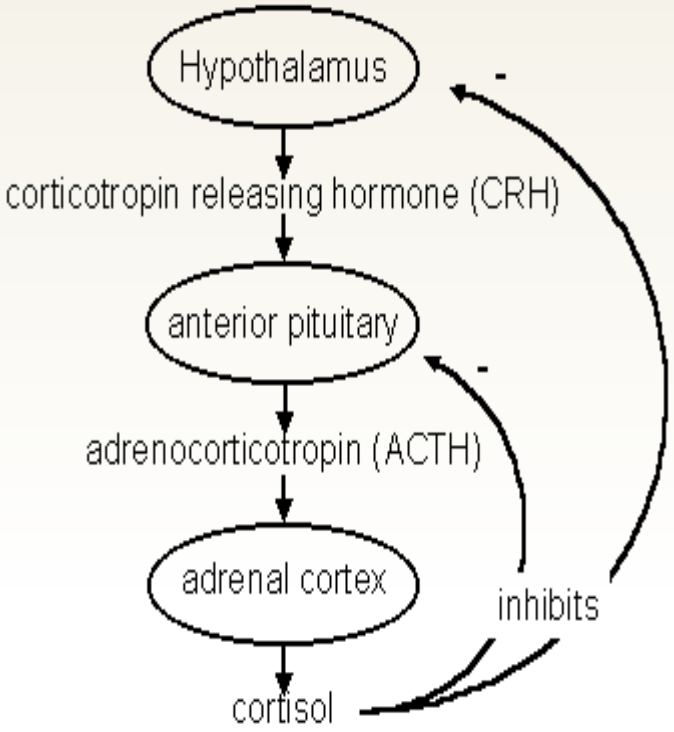
CRH release also occurs in other brain regions involved in emotional processing and can induce behavioral changes akin to depression and anxiety disorders.



Glucocorticoid Feedback and CRH Sensitization

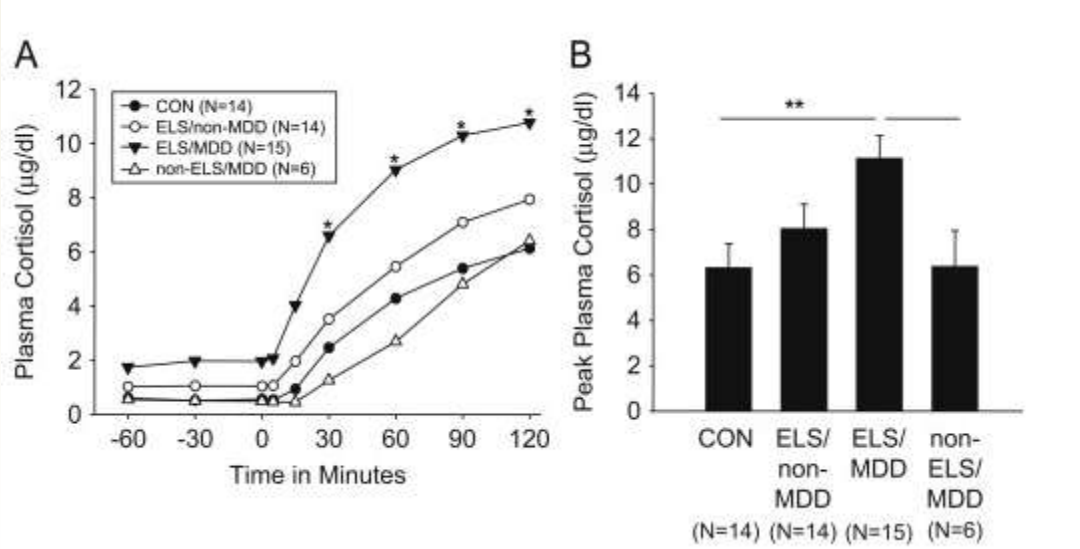
Glucocorticoid feedback acts to suppress levels of CRH and limit the actions of CRH.

Resistance to glucocorticoids results in a persistent elevation in CRH and consequential changes in emotional behavior and stress perception.



Glucocorticoid Feedback and CRH Sensitization

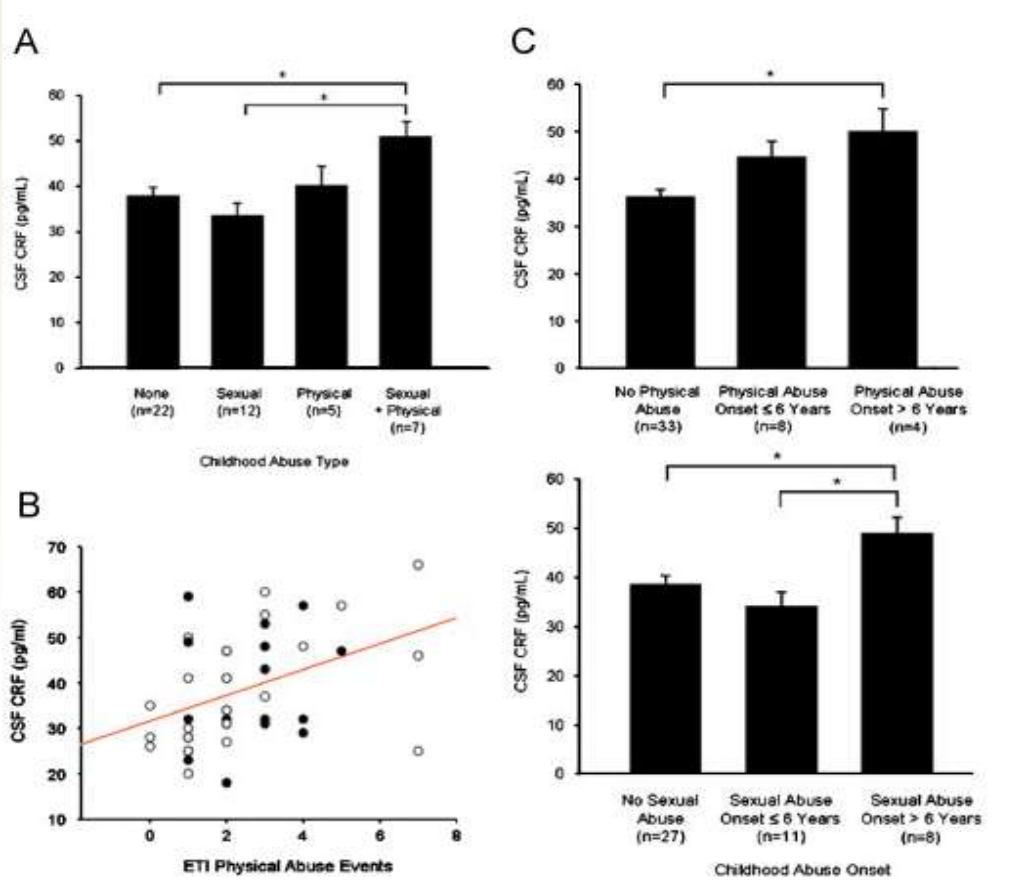
Individuals who experienced child abuse early in life have been found to exhibit facilitated cortisol responses to CRH stimulation as adults indicating a sensitization of the CRH system (Heim et al., 2008).



Heim et al., 2008

Glucocorticoid Feedback and CRH Sensitization

Individuals who experienced physical or sexual abuse early in life have been found to exhibit increased levels of CRH as adults (Heim et al., 2008).



Heim et al., 2008

Glucocorticoid Feedback and CRH Sensitization

This increase in CRH signaling is due to impaired glucocorticoid feedback, as individuals who experienced childhood abuse have also been demonstrated to exhibit impaired feedback inhibition of cortisol secretion following glucocorticoid administration (Heim et al., 2008).

Glucocorticoid Resistance and Early Life Stress

These data demonstrate that glucocorticoid resistance is present in individuals who experienced early life stress.

This glucocorticoid resistance results in an increase in both systemic inflammation and CRH signaling within the brain.

This increase in inflammation and CRH sensitize stress systems and produces a state of allostatic load, which in turn increases the propensity to develop both mental and physical illnesses.

Glucocorticoid Resistance and Early Life Stress

Thus, early life stress produces changes in adults which mirror the effects of chronic stress and allostatic load.

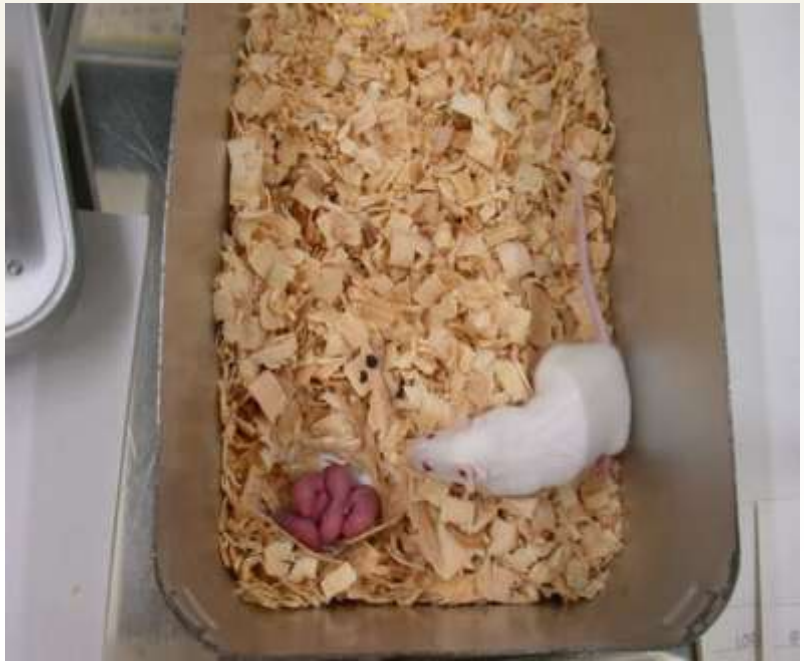
In adults, however, the effects of allostatic load dissipate following the removal of the stressor, but the effects of early life stress are persistent far beyond the period of exposure to the stressor.

How is it possible that exposure to stress over a confined developmental window exert such long lasting, detrimental and persistent changes into adulthood?

Animal Models of Early Life Stress

Animal studies are used to understand the biological ramifications of early life stress.

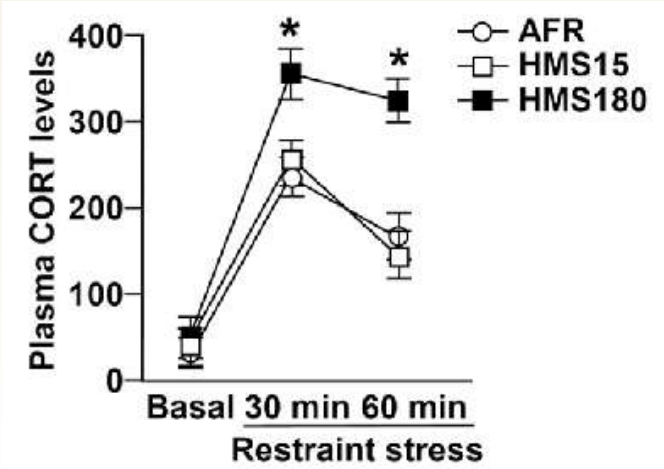
Maternal separation is the most common model employed to investigate early life stress in rodents.



Animal Models of Early Life Stress

Maternal separation produces a behavioral phenotype that parallels the effects of early life stress in humans

-hypersensitivity to stress
-increased vulnerability to depressive and anxious behavioral indices following stress
-increased voluntary alcohol consumption
-increased risk taking behavior



Uchida et al., 2010

Animal Models of Early Life Stress

Maternal separation also produces all of the biological effects which have been documented in humans following early life stress

- neuronal “shrinkage” in the hippocampus and prefrontal cortex
- impaired glucocorticoid negative feedback and glucocorticoid resistance
- hyperactivity of CRH signaling systems
- heightened inflammatory status

Animal Models of Early Life Stress

Since the maternal separation model replicates all of the behavioral and biological effects of early life stress in humans this model has been very valuable in examining the mechanisms by which early life stress produces such sustained effects into adulthood.

Animal Models of Early Life Stress

Early life stress produces glucocorticoid resistance through an epigenetic regulation of the glucocorticoid receptor.

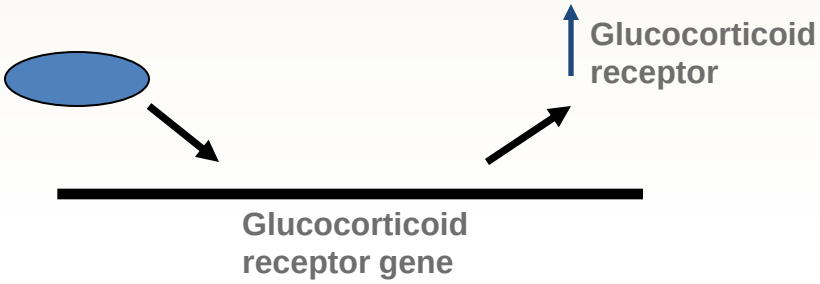
Epigenetic = beyond the genes in your DNA.

Chemical markers can be put onto genes in DNA that increase or decrease the amount of that gene that is made into a functional protein.

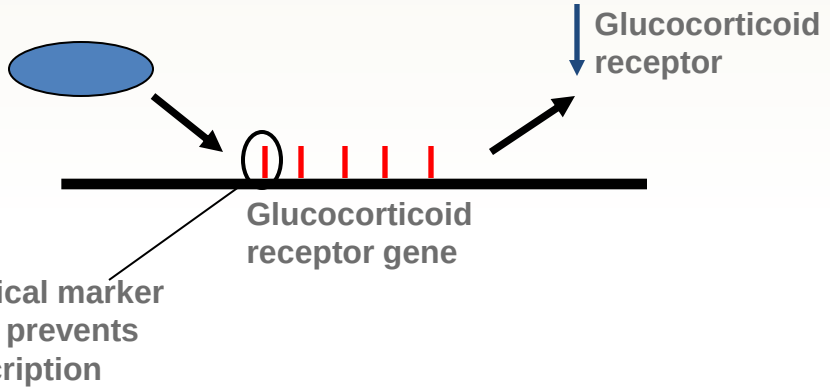
Animal Models of Early Life Stress

Maternal separation results in the addition of chemical markers to the glucocorticoid receptor gene which decreases the amount of receptor which is made.

Standard Developmental Conditions



Early Life Stress



Animal Models of Early Life Stress

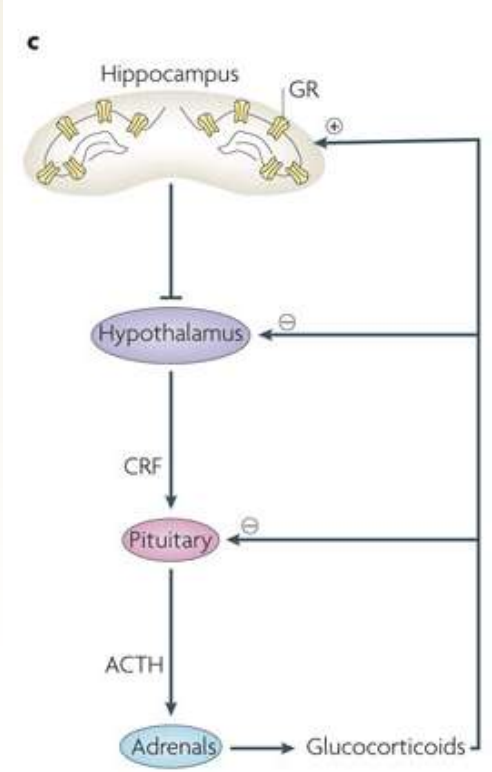
These data indicate that early life stress can modulate the expression of the glucocorticoid gene throughout life.

This repression of the glucocorticoid receptor produces a state of glucocorticoid resistance which then impairs glucocorticoid feedback, sensitizes CRH signaling and increases inflammatory processes.

Animal Models of Early Life Stress

This suppression of the glucocorticoid receptor gene results in lower levels of glucocorticoid receptor within the hippocampus of adult rats (Meaney et al., 1996).

This reduction in glucocorticoid receptors in the hippocampus is directly related to impairments in glucocorticoid feedback inhibtion and increased CRH signaling.

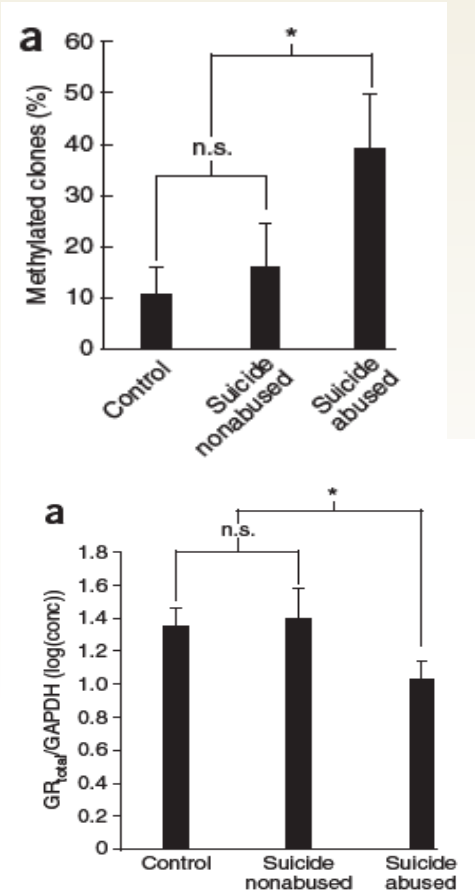


Hackman et al., 2010

Animal Models of Early Life Stress

This model of glucocorticoid receptor gene repression translates to human populations with early life stress.

Child abuse is associated with increased chemical markers of gene suppression on the glucocorticoid receptor and reduced levels of glucocorticoid receptors in the hippocampus of suicide victims (McGowan et al., 2009).

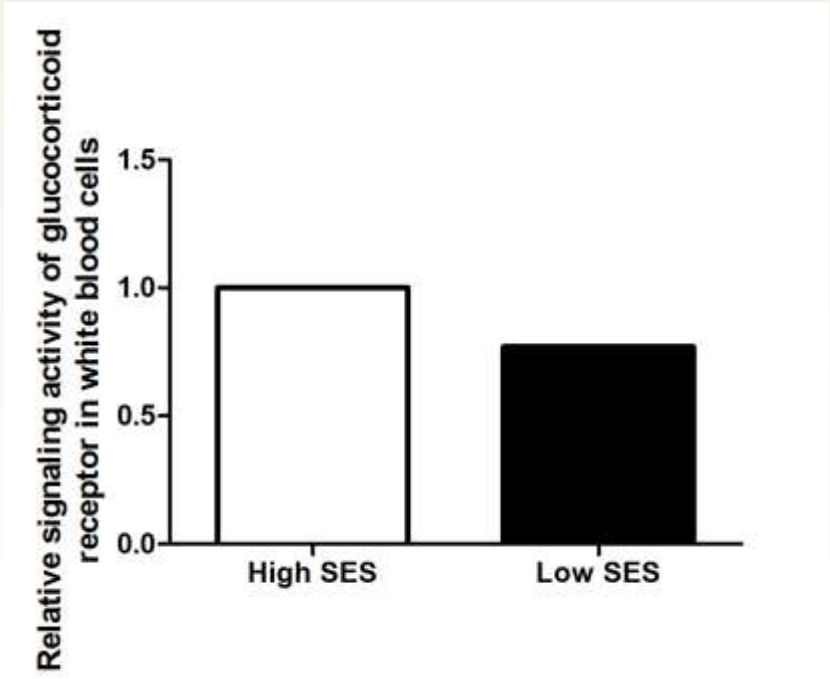


McGowan et al., 2009

Animal Models of Early Life Stress

Similarly children who grew up in poverty or who experienced abuse as a child exhibit reduced levels of glucocortcoid receptors in white blood cells (Miller et al., 2009; Heim et al., 2008).

This lower level of glucocorticoid receptors in these cells produces glucocorticoid resistance to inflammation (Miller et al., 2009).



Adapted from Miller et al., 2009

Biological Model of the Effects of Early Life Stress

Taken together, these data create the following model of how early life stress produces a state of allostatic load in adulthood that is conducive to the development of mental and physical illnesses.

Biological Model of the Effects of Early Life Stress

Adverse experiences (such as child abuse or maltreatment) early in life cause an experience-dependent increase in chemical markers on the glucocorticoid receptor gene which suppress its production.

This reduction in glucocorticoid receptors results in the development of glucocorticoid resistance which heightens sensitivity to stress, impairs glucocortioicd feedback, produces sensitization of CRH signaling and increases inflammatory pathways.

This shift in biological functioning of the stress axis creates a state of suceptibility to mental illnesses, particularly depression, as well as other health conditions, such as obesity and cardiovascular disease.

Biological Model of the Effects of Early Life Stress

The allostatic load incurred by this increased sensitivity to stress results in alterations in the structure and function of brain regions, such as the prefrontal cortex and hippocampus.

The impairments in prefrontal cortical and hippocampal function further disinhibit the stress axis and perpetuate this syndrome.

Furthermore, impairments in prefrontal cortical functioning can contribute increase risk taking and impulsive behaviors such as smoking, alcoholism and promiscuity.

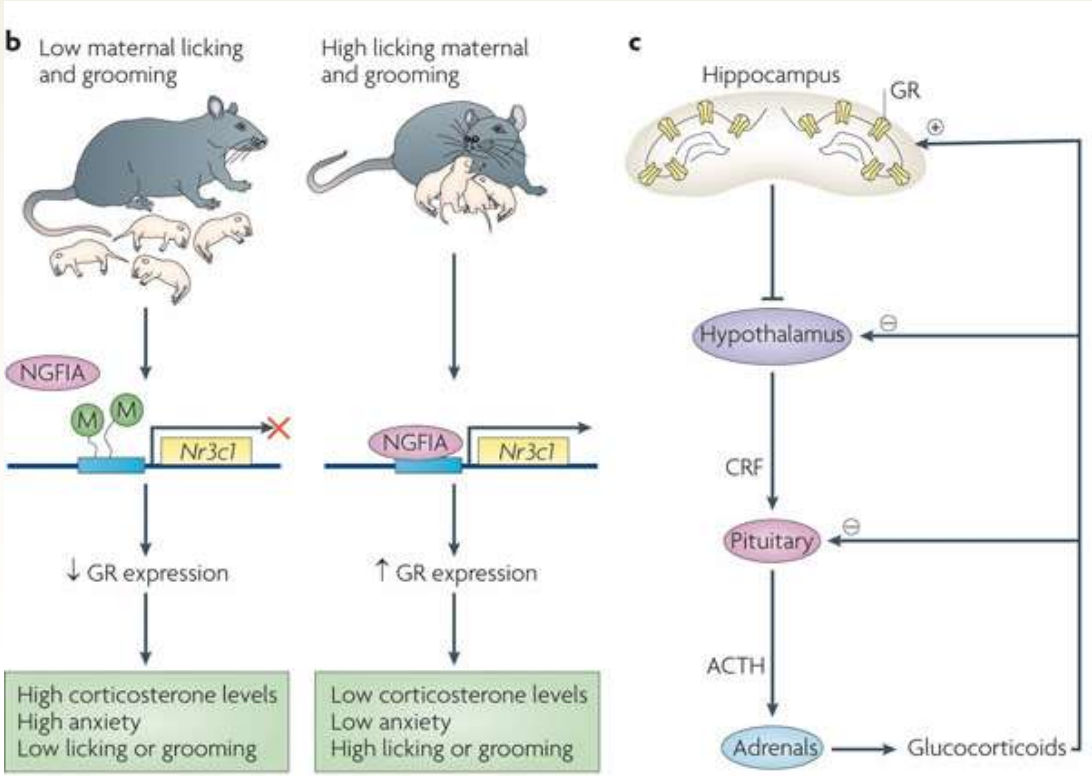
The Influence of Parental Care

A silver lining of these studies have been that they have also demonstrated that good parental care can counter these effects and produce resilience to stress later in life.

The Influence of Parental Care

Animal Studies

High levels of maternal care to rodents results in increased glucocorticoid receptor expression in the hippocampus, reductions in hormonal responses to stress and resilience against the development of anxious and fearful behavioral traits (Diorio and Meaney, 2007).

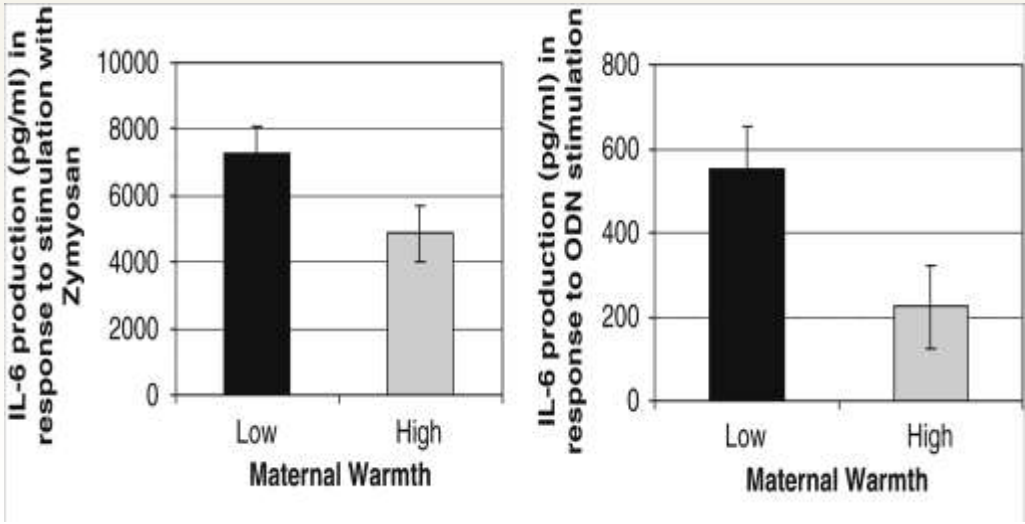


Hackman et al., 2010

The Influence of Parental Care

Human Studies

Individuals who score high on the parental bonding inventory (high levels of parental warmth) exhibit lower levels of inflammatory status as adults and counter the adverse effects of early life adversity (Chen et al., 2010).



Chen et al., 2010

The Influence of Parental Care

Thus, positive parental care early in life can produce a biological phenotype that is akin to stress resilience later in life through opposite changes in the glucocorticoid and inflammatory pathways that are found to be altered following early life stress.

The primary interpretation of these data is that the environmental conditions of early life “prime” an organism for how it will develop into adulthood.

The Influence of Parental Care

Early life adversity primes an organism to develop into a “defensive” phenotype characterized by (Zhang et al., 2004):

- persistent levels of vigilance and anxiety to the environment to scan for threats and respond appropriately
- increased levels of inflammatory markers which will allow for rapid immune responses to injuries due to attacks
- reduced prefrontal cortical processing to promote instinctive behavioral responding (e.g., fight or flight)

This phenotype is adaptive for survival in an adverse environment and is aimed to ensure reproductive success, not longevity.

Summary

The stress response is designed to provide the body with adequate biological needs to respond to a threat.

This adaptive response is called an allostatic response and is necessary for survival.

Exposure to persistent, toxic stress can result in allostatic load, which is the breakdown of systems engaged by stress.

Allostatic load is conducive to the development of mental and physical illnesses and is the cost paid by the body for attempting to maintain survival in the face of persistent adversity.

Summary

The ACE and Dunedin studies have clearly demonstrated that early life stress is associated with many health problems later in life, particularly depression, inflammatory diseases and metabolic conditions.

This suggests that early life stress appears to produce a constant state of increased stress sensitivity and allostatic load in adulthood.

This shift in the biological processes of the stress system appears to be due to the development of glucocorticoid resistance, which results in impairments in glucocorticoid feedback, sensitization of CRH signaling and increased inflammatory pathways.

Summary

Animal studies of early life stress replicate these biological and behavioral changes in adults, indicating that they are a good model to understand the mechanism of these sustained processes.

Animal studies have revealed that early life stress causes an experience-dependent and stable change in the biological regulation of the glucocorticoid receptor gene that decreases levels of glucocorticoid receptors resulting in glucocorticoid resistance.

This model holds true in human populations which have found that child abuse and early life adversity are related to increased repression of the glucocorticoid receptor gene and reduced levels of the glucocorticoid receptor into adulthood.

Summary

This phenotype of early life stress is believed to represent a “defensive” phenotype which primes an organism to survive in persistent conditions of adversity.

Alternately, warm parental care early in life produces the opposite phenotype, primarily one of resilience to adversity which is matched by increased glucocorticoid receptor sensitivity, reduced biological responses to stress and lower activity in inflammatory pathways.

Thus, environmental and familial conditions of early life are key to the programming of the stress axis throughout life, and consequently mental and physical health as adults.