EFFECTS OF STRESS THROUGHOUT THE LIFESPAN ON BRAIN, BEHAVIOR AND COGNITION

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EFFECTS OF STRESS THROUGHOUT THE LIFESPAN ON THE BRAIN, BEHAVIOR AND COGNITION

- Prenatal Stress
- Postnatal Stress
- Stress in Adolescence
- Stress in Adulthood
- Stress in Aging
- A Model of Stress Effects Throughout Life
- Future Directions for Research and Social Policy
“The General Adaptation Syndrome”

Hans Selye (1936)/ Cannon (1932) : the general adaptation syndrome, a classic, stereotyped theory of stress

1) **Alarm reaction**: adrenal medulla releases epinephrine, and the adrenal cortex produces glucocorticoids, promoting adaptation and restoring homeostasis (*allostasis*)

2) **Resistance**: defense and adaptation are optimal (*allostatic load*)

3) **Exhaustion**: persistence of stress response – which may lead to illness or death (*allostatic overload*)
STRESS INCREASES THE RISK OF ILLNESS

- Increased heat rate and blood pressure
- Impact of stress hormones on immune processes – corticosteroid suppresses immune system
- Disturbance of the digestive system

Increased Risk of Disease
EFFECTS OF STRESS THROUGHOUT THE LIFESPAN ON THE BRAIN, BEHAVIOUR AND COGNITION

Lupien, S. et al., Nature Reviews/Neuroscience, Volume 10, 434-445 (June 2009)

• Chronic exposure to stress hormones, whether it occurs during the prenatal period, infancy, childhood, adolescence, adulthood or aging, has an impact on brain structures involved in cognition and mental health.

• The specific effects on the brain, behavior and cognition emerge as a function of the timing and the duration of the exposure.

• Some effects also depend on the interaction between gene effects and previous exposure to environmental adversity.

• Advances in animal and human studies have made it possible to synthesize these findings.

• A model is developed to explain why different disorders emerge in individuals exposed to stress at different times in their lives.
THE SCOPE OF THIS REVIEW COVERS THE EFFECTS OF STRESS ON THE BRAIN BEHAVIOR AND COGNITION DURING CRITICAL LIFE PASSAGES

- PRENATAL LIFE
- INFANCY
- ADOLESCENCE
- ADULTHOOD
- OLD AGE
PERIODS OF INCREASED SENSITIVITY TO STRESS

• During both early childhood and old age the brain is particularly sensitive to stress, probably because it undergoes important changes during these periods.

• Research relates exposure to early-life stress with increased reactivity to stress and cognitive deficits in adulthood.

• The effects of stress at different life periods interact.
Stress response. In response to stress, the hypothalamus releases corticotropin releasing hormone (CRH) which stimulates the pituitary gland to release of ACTH into the general circulation.

Adrenocorticotropic hormone (ACTH) stimulates the adrenal cortex to release cortisol into the general circulation. Cortisol is the main glucocorticoid secreted by the adrenal cortex (regulates sugar).

The hypothalamus also stimulates the adrenal medulla to release the catecholamines, epinephrine (adrenalin) and norepinephrine (noradrenaline), into the general circulation (fight or flight; neuronal control).

Catecholamines mobilize stored fat and make the heart beat faster and stronger.
When the brain detects a threat, a coordinated physiological response involving autonomic (regulates key involuntary functions of the body: the heart; the smooth muscles, including the intestinal tract), neuroendocrine (e.g., HPA axis), metabolic and immune system components is activated.

A key system in the stress response that has been extensively studied is the hypothalamus-pituitary-adrenal (HPA) axis.

Neurons in the hypothalamus release corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP).

This triggers the subsequent secretion of adrenocorticotrophic hormone (ACTH) from the pituitary gland, leading to the production of glucocorticoids by the adrenal cortex.

In addition, the adrenal medulla releases catecholamines (adrenaline and noradrenaline).

The responsiveness of the HPA axis to stress is in part determined by the ability of glucocorticoids to regulate ACTH and CRH release, by binding to two corticosteroid receptors, 1) the glucocorticoid receptor (GR); and 2) the mineralocorticoid receptor (MR).

Following activation of the system, and once the perceived stressor has subsided, feedback loops are triggered at various levels of the system (that is, from the adrenal gland to the hypothalamus and other brain regions such as the hippocampus and the frontal cortex) in order to shut the HPA axis down and return to a set homeostatic point.

By contrast, the amygdala (regulates emotionality), which is involved in fear processing, activates the HPA axis in order to set in motion the stress response that is necessary to deal with the challenge.

Major systems and factors that respond to stress, include the autonomic nervous system, the inflammatory cytokines and the metabolic hormones. All of these are affected by HPA activity and, in turn, affect HPA function, and they are also implicated in the pathophysiological changes that occur in response to chronic stress, from early experiences into adult life.
Stress, Illness and the Immune System

• The immune system is a collection of billions of cells that travel through the bloodstream. They move in and out of tissues and organs, defending the body against foreign bodies (antigens), such as bacteria, viruses and cancerous cells.

• The main types of immune cells are two types of white blood cells (leukocytes) – lymphocytes and phagocytes.

• There are two types of lymphocytes:
  • B cells - produce antibodies which are released into the fluid surrounding the body’s cells to destroy the invading viruses and bacteria.
  • T cells - if the invader gets inside a cell, these (T cells) lock on to the infected cell, multiply and destroy it.
STRESS AND SUPPRESSION OF THE IMMUNE SYSTEM

• The stress hormone cortisol can suppress the effectiveness of the immune system (e.g., lowers the number of lymphocytes).

• Stress can also indirectly suppress the immune system when a person uses unhealthy coping strategies such as drinking and smoking.

• Stress is linked to headaches, infectious diseases (e.g. flu), cardiovascular disease, diabetes, asthma and ulcers.
STRESS AND THE IMMUNE SYSTEM

- Experiencing a stressful situation, as perceived by the brain, results in the stimulation of the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic–adrenal–medullary (SAM) axis.

- The production of adrenocorticotropic hormone by the pituitary gland results in the production of glucocorticoid hormones. The sympathetic-adrenal-medullary axis (SAM) can be activated by stimulation of the adrenal medulla to produce the catecholamines adrenaline and noradrenaline, as well as by 'hard-wiring', through sympathetic-nervous-system innervation of lymphoid organs.

- Leukocytes have receptors for stress hormones that are produced by the pituitary and adrenal glands and can be modulated by the binding of these hormones to their respective receptors. In addition, noradrenaline produced at nerve endings can also modulate immune-cell function by binding its receptor at the surface of cells within lymphoid organs.

- These interactions are bidirectional in that cytokines produced by immune cells can modulate the activity of the hypothalamus. APC, antigen-presenting cell; IL-1, interleukin-1; NK, natural killer.
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• These interactions are bidirectional in that cytokines produced by immune cells can modulate the activity of the hypothalamus. APC, antigen-presenting cell; IL-1, interleukin-1; NK, natural killer.
Schematic representation of the regulation of the HPA axis under chronic stress.

1) Corticotropin Releasing Hormone (CRH) and arginine vasopressin (AVP) stimulate 2) adrenocorticotropin hormone (ACTH) secretion by the anterior pituitary.

3) ACTH triggers glucocorticoids release from the adrenal cortex. In an acute stress response, glucocorticoids regulate CRH and ACTH release in a negative feedback loop.

However, in chronic stress, sustained glucocorticoids synthesis becomes detrimental to metabolic, endocrine, and immunologic processes leading to pathological states.

Mind Body Medicine (MBM) plays a role in maintaining stress hormone levels within their normal range. MBM may also affect the release of CRH and ACTH by helping to quiet the mind. Solid arrows: positive regulation; dotted lines: negative feedback, and dotted arrows: normalizing effects.
Now, there are about 20,000 moments of 3 seconds in a 16-hour day, so this is what life consists of; it consists of a sequence of moments. Each of these moments is actually very rich in experience, so if you could stop somebody and ask, "What is happening to you right now?" A great deal is happening to us at any one of these moments. There is a goal, there is a mental content, there is a physical state, there is a mood, there might be some emotional arousal. Many things are happening. And then you might ask, "What happens to these moments?"

Mindfulness and stress management. Through learning skills to develop a nonjudgmental attention to stimuli in the internal and external environments, the human stress response is diminished, resulting in improved mental and physical health and a more positive state of mind.
**PRENATAL STRESS**

**ANIMAL STUDIES**

• Early exposure has programming effects on the HPA axis and the brain.

• A single or repeated exposure of a pregnant female to stress increases maternal corticoid secretion which passes thru the placenta to reach the fetus.

• This in turn, increases fetal HPA axis activity and modifies brain development.

• Corticoids are important for normal brain development.

• Exposure to prenatal stress has 3 major effects on adult behavior: learning impairments (hippocampus); enhanced sensitivity to drugs of abuse (dopamine system); increases in anxiety and depression related behaviors (amygdala)
HUMAN STUDIES:
Retrospective studies on mothers who had prenatal stress suggest long-term neurodevelopmental effects:

1. Maternal depression, anxiety and corticoid therapy during pregnancy have been linked to lower birthweight.

2. Maternal stress during pregnancy has been linked to increased HPA activity at different ages, e.g., 6 months, 5 years, 10 years.

3. Disturbances in child development (neurological, cognitive and behavioral) have been linked to stress and maternal depression during pregnancy, and with fetal exposure to exogenous corticoids.

4. Behavioral disturbances during childhood include: conduct problems, ADHD, depression sleep disorders, drug abuse, mood and anxiety disorders.

5. Low birthweight combined with lower levels of maternal care is associated with reduced hippocampal volume during adulthood.
POSTNATAL STRESS

HUMAN STUDIES:
1. Corticoid levels rise in children who attend full-day, out of home day care centers.
2. Corticoid levels rise more for toddlers than for older preschool aged children.
3. Less supportive care produces larger increases but to date there is no evidence that these increases associated with daycare affect development.
4. Children exposed to long hours of poor care early in development have increased risk for behavior problems later in development.
5. Parent-child interactions and mother’s psychological state also influence the child’s HPA axis activity.

6. Beginning early in the first year, sensitive parenting is associated with either smaller increases or less prolonged activations of the HPA system to everyday frustrations.

7. Offspring of depressed mothers are at risk of heightened activity of the HPA axis or of developing depression during adolescence.

8. Pre-school aged children of depressed mothers show electroencephalographic (EEG) patterns in frontal lobe activity associated with low empathy and behavioral problems.
STRESS IN ADOLESCENCE

• The adolescent period is associated with heightened stress-induced activity of the HPA axis, which may be related to dramatic changes in sex steroid levels.

• The adolescent brain might be especially sensitive to elevated levels of glucocorticoids, and thus to stress.

• Depression, anxiety and other forms of psychopathology increase in prevalence in adolescence.

• Periods of heightened stress often precede the first episodes of these disorders.

• Possibly heightened HPA reactivity during adolescence increases sensitivity to the onset of stress related mental disorders.
Adolescence is a period in which the long-lasting effects of earlier exposures to stress become evident.

Youth who grew up in poor economic conditions have higher baseline glucocorticoid levels; also teens whose mothers were depressed in the early post-natal period.

High early morning glucocorticoid levels that vary markedly from day to day during the transition to adolescence predict increases risk for depression by age 16.

Stress during adolescence results in alterations in grey matter volume, the neuronal integrity of the frontal cortex, and reduced size of the anterior cingulate cortex (motivation).

The hippocampus, which develops mainly in the first years of life is less affected by adversity in adolescence.
MISSING LINK TO SCHIZOPHRENIA

In a landmark study researchers from the Broad Institute, Harvard Medical School and Boston Children’s Hospital have pinned down a molecular process in the brain that helps trigger schizophrenia.

• A person’s risk of schizophrenia is dramatically increased if they inherit variants of a gene important to “synaptic pruning” – the healthy reduction during adolescence of brain cell connections that are no longer needed.

• Steven Hyman, a former director of the National Institute of Mental Health, calls it "the most significant mechanistic study about schizophrenia ever."

• C4 and numerous other genes reside in a region of chromosome 6 involved in the immune system, which clears out pathogens and similar cellular debris from the brain. The study's researchers found that one of C4’s variants, C4A, was most associated with a risk for schizophrenia.

• The discovery explains the apparent involvement of immune molecules, the disorder's typical onset in late adolescence and early adulthood, and the thinning of gray matter seen in autopsies of patients.
• There is an inverted U-shaped relationship glucocorticoid levels and cognitive performance.

• Most studies show that acute glucocorticoid elevations increase memory for emotional material; they impair retrieval of neutral information.

• A large number of studies report elevated glucocorticoid levels in people with depression; low levels have been found in people with PTSD.

• Low cortisol levels seems to develop in childhood in response to trauma or neglect; low cortisol may predict vulnerability to developing PTSD in response to trauma in adulthood.
STRESS IN ADULTHOOD (Cont.)

• Studies of adults who suffered childhood abuse also reveal hyper-reactivity of the HPA axis in abused depressed individuals and hypoactivity in those with PTSD.

• Decreased hippocampal volume and functions are landmark features of depression and PTSD.

• One study found that a smaller hippocampus in women with major depression was associated with experiences of childhood trauma; whereas depressed women with without such trauma had hippocampal volumes similar to healthy controls.

• Decreased hippocampal volume could be a pre-existing risk factor for PTSD that could be genetic and rooted early in life.
STRESS IN AGING

• Animal studies give rise to the glucocorticoid cascade hypothesis – there is a relationship between cumulative exposure to high glucocorticoid levels and hippocampal atrophy.

• Aged individuals with Alzheimer’s Disease present both memory impairments and hippocampal atrophy; research studies have demonstrated that corticoid levels in this population are higher than in controls.

• Additionally, chronic glucocorticoid treatment has been shown to worsen cognition in people with Alzheimer’s Disease.

• The frontal lobe also seems to be sensitive to glucocorticoid effects during aging.

• Excess amounts potentially have negative effects on prefrontal cortex neuron’s survival and function.
ALZHEIMER’S & THE BRAIN

In a Healthy Brain
An intricate network of billions of nerve cells communicate using electrical signals that regulate thoughts, memories, sensory perception and movement.

In Alzheimer’s Patients
Neurons gradually die when genes like ApoE4 and other factors promote the formation of abnormal amyloid protein plaques.

Amyloid initially forms as amyloid precursor protein (APP).
Enzymes break APP into short fragments.
The fragments clump together, forming plaques.

Once plaques form, tau, a protein that stabilizes a neuron’s lengthy arms, may start to break down.

When tau no longer stabilizes the axons, the neuron shrivels and dies, leaving behind its tangled carcass.

TREATMENT
To prevent the death of neurons, researchers hope to aim for as many of the genetic, amyloid and tau targets as possible.
INVISIBLE PATIENTS

DEMENTIA TAKES A TOLL ON CAREGIVERS, TOO.

BY LAUREN R. WEINSTEIN
DECEMBER 10, 2015

Stress, Nautilus Magazine; Michael Segal, Editor In Chief

Illustration by Molly Mendoza, December 3, 2015; http://nautil.us/issue/31/stress/stress
When Meryl Comer was 48 and in the prime of her career as a broadcast journalist, her husband Harvey was diagnosed with early onset Alzheimer’s disease.

“I was told he was too dangerous. No facility would take him. So I left my career to take care of him.”

Hide the keys so he doesn’t hurt anyone...

The car is in the shop...

But I want to drive!

She hides the keys.
"I lived forward from crisis to crisis."

He never checks the garage.

Emergencies in the middle of the night.

Walking six miles a day to prevent outbursts at sundown.
“I was always trying to read and anticipate what he needed—looking into vacant eyes and trying to read from the expression.”

“His grasp was a lock.”
“Clocks were irrelevant. It might take me an hour and a half to feed him. I could never keep him on a schedule.”
"The only way I got him to sit was by reading him his research papers."

Before he got sick, Harvey was a physician and scientist.
Only once did Harvey acknowledge his illness or her.

If you are my wife, this must be hard on you.

“This disease sucks you under, with the victim.”
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The Life Cycle Model of Stress

- How the effects of chronic or repeated exposure to stress (or a single exposure to severe stress) at different stages in life depend on the brain areas that are developing or declining at the time of the exposure.

- Stress in the prenatal period affects the development of many of the brain regions that are involved in regulating the hypothalamus-pituitary-adrenal (HPA) axis — that is, the hippocampus, the frontal cortex and the amygdala (programming effects).

- Postnatal stress has varying effects: exposure to maternal separation during childhood leads to increased secretion of glucocorticoids, whereas exposure to severe abuse is associated with decreased levels of glucocorticoids. Thus, glucocorticoid production during childhood differentiates as a function of the environment (differentiation effects).

- From the prenatal period onwards, all developing brain areas are sensitive to the effects of stress hormones (broken blue bars); however, some areas undergo rapid growth during a particular period (solid blue bars).

- From birth to 2 years of age the hippocampus is developing; it might therefore be the brain area that is most vulnerable to the effects of stress at this time.

- By contrast, exposure to stress from birth to late childhood might lead to changes in amygdala volume, as this brain region continues to develop until the late 20s.

- During adolescence the hippocampus is fully organized, the amygdala is still developing and there is an important increase in frontal volume. Consequently, stress exposure during this period should have major effects on the frontal cortex.

- Studies show that adolescents are highly vulnerable to stress, possibly because of a protracted glucocorticoid response to stress that persists into adulthood (potentiation/incubation effects).

- In adulthood and during aging the brain regions that undergo the most rapid decline as a result of aging (red bars) are highly vulnerable to the effects of stress hormones. Stress during these periods can lead to the manifestation of incubated effects of early adversity on the brain (manifestation effects) or to maintenance of chronic effects of stress (maintenance effects). PTSD, post-traumatic stress disorder.
The Life Cycle Model of Stress

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**Effect on HPA axis**
- Programming effects
- Differentiation effects
- Potentiation/incubation effects
- Maintenance/manifestation effects
- Maintenance/manifestation effects

**Outcome**
- ↑ Glucocorticoids
- ↑ Glucocorticoids (maternal separation)
- ↓ Glucocorticoids (severe trauma)
- ↑↑ Glucocorticoids
- ↓↓ Glucocorticoids
- ↑ Glucocorticoids (depression)
- ↓ Glucocorticoids (PTSD)
- ↑ Glucocorticoids (cognitive decline)
- ↓ Glucocorticoids (PTSD)
STRUCTURE AND FUNCTION OF THE HUMAN BRAIN

- **Anterior Cingulate** (motivation)
- **Motor**
- **Sensory**
- **Corpus Callosum**
- **Frontal Lobe** (planning)
- **Occipital Lobe** (vision)
- **Temporal Lobe** (language)
- **Cor tex**
- **Parietal Lobe** (movement)
- **Dorsolateral Prefrontal** (executive & logical)
- **Olfactory Bulb**
- **Hypothalamus**
- **Amygdala** (basic emotions)
- **Hippocampus** (memory)
- **Lateral Orbitofrontal** (appropriate social/emotional response)
- **Entorhinal Cortex** (memory)
- **Cerebellum** (coordinate movement)
- **Brain Stem** (body basics)
- **Limbic System**
Sex and Gender:

- Sex refers to biology; gender refers to roles and identity.
- Most studies on the effects of stress on the brain, behavior and cognition have been done on male animals or humans.
- A gender gap (two girls to one boy) emerges in early adolescence for risk of depression.
- Risk of depression increases in adolescent girls with decreasing age of menarche (first menstrual period).
- An increased sensitivity of girls to family/environmental adversity combined with interactions between cortisol and gonadal steroids might explain increased risk of depressive disorders in girls.
Exposure to Environmental Toxins:

- Children in many places around the world are chronically exposed to a range of common toxins.
- These agents are lipophilic and bioaccumulate, e.g. lead and bisphenol A (BPA), an industrial chemical used to make certain plastics since the 1960’s.
- Some research has shown that BPA can seep into food or beverages from containers made with BPA.
- These chemicals may be transferred to humans through food and food additives and the fetus through the placenta and to infants through mother’s milk.
- They may have health effects on the brain, behavior and prostate gland of fetuses, infants and children.
- Pre and post-natal exposure to lead is associated with increased cortisol responses to acute stress in children.
- Endocrine disrupting chemicals is associated with earlier age of menarche in girls.
- Both the timing of sexual maturation and stress reactivity may be sensitive to low levels of endocrine-disrupting chemicals in the environment.
Attention to circadian rhythm and the molecular clock:

• Sleep deprivation, shift work, and jet lag all disrupt normal biological rhythms and have major impacts on health.

• Rhythm abnormalities might lead to greater vulnerability to stress at different ages.

• Most studies on humans and animals do not measure the circadian fluctuations of cortisol levels.

• Studies assessing multiple time points for glucocorticoid secretion across a whole day or several days are needed to document the complex relationships between reactivity to stress and circadian (dis)organization.
After more than 35 years of research on the negative effects of stress on the brain, it is now time to turn our attention to the potential positive impact of early intervention on brain development. These results could help us to develop social policies that treat the problem of early life-stress at its roots – that is in the family home.

Lupien, McEwen, Gunnar, and Heim

*Effects of stress throughout the lifespan on the brain, behaviour and cognition*

**HOW TO MAKE STRESS YOUR FRIEND**

[https://www.ted.com/talks/kelly_mcgonigal_how_to_make_stress_your_friend#t-646775](https://www.ted.com/talks/kelly_mcgonigal_how_to_make_stress_your_friend#t-646775)

Kelly McGonigal:
TED Global 2013 · 14:28 · Filmed Jun 2013 10,134,853