The Basics of Psychological Stress

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Chronic Brain Injury
Discovery Themes at The Ohio State University
How Do We Define Stress?

Stress is the physiological and behavioral response to a real or perceived threat to homeostasis

Walter Cannon-1929
Constancy in an open system, such as our bodies represent, requires mechanisms that act to maintain this constancy...

Hans Seyle 1936
-built on Cannon’s ideas and defined stress as a “General Adaptation Syndrome”

Bruce McEwen-1993
“allostatic load” the cost of chronic exposure to fluctuating or heightened neural and neuroendocrine responses resulting from repeated or chronic environmental challenges that an individual reacts to as being particularly stressful
How Do We Define Stress?

It's not stress that kills us, it is our reaction to it.

— Hans Selye —
Why do we Care about Stress?

Stress, especially chronic stress has a negative influence on mental health.

Stress is linked to higher rates of anxiety and depression.

20-30% of the US population suffers from anxiety or depression.

Individuals with a brain injury 10 times more likely to suffer from depression.
Neuropsychiatric Impacts

Life & Social Impacts

Traumatic Brain Injury: The is danger is in what lies beneath the surface...

Over 70% of TBI patients continue to have secondary neurocognitive and behavioral complications after TBI
Psychological Stress is Interpreted by the Brain

Activation of circuits within “Fear and threat” appraisal centers

Prefrontal Cortex
Hippocampus
Amygdala
There are Two Major Stress Pathways from the brain to the body

1) NeuroEndocrine Activation
Hypothalamic-pituitary-adrenal (HPA) axis activation
→ Production of glucocorticoids (cortisol)

Cortisol: steroid hormone (Stress Hormone)
- increase glucose breakdown
- Anti-inflammatory
- Immune regulatory

2) Sympathetic nervous system (SNS) Activation.
→ production of catecholamines (norepinephrine & epinephrine (i.e., adrenaline))
- increase heart rate
- increase muscle tone
- Increase energy expenditure
- increase Immune readiness

"Fight of Flight” Response
Neuroendocrine Activation with Stress: Production of a Stress Hormone: Cortisol

- Hypothalamus
- Paraventricular Nucleus (PVN)
- CRH
- Pituitary Gland
- Adrenocorticotrophic Hormone (ACTH)
- Adrenal Gland
- Glucocorticoids (Cortisol)
- Kidney
- Stress hormone
- Immune system
  - Anti-inflammatory
- Metabolism

\[ \text{Hypothalamus} \rightarrow \text{CRH} \rightarrow \text{Pituitary Gland} \rightarrow \text{ACTH} \rightarrow \text{Adrenal Gland} \rightarrow \text{Cortisol} \rightarrow \text{Stress hormone} \rightarrow \text{Immune system} \rightarrow \text{Anti-inflammatory} \rightarrow \text{Metabolism} \]
Sympathetic Activation with stress and Production of “Stress” Neurotransmitters

- **Catecholamines**: Norepinephrine, Adrenaline
- **Heart rate**
- **Muscle tone**
- **Energy mobilization**
- **Immune system readiness**

The SNS is part of the Autonomic nervous system
These Stress Pathways Create a Circuit between the Brain and the Immune system

- **Brain**
- **Stress**

**Neuroendocrine Activation**
- Hypothalamus
  - CRH
- Pituitary gland
  - ACTH
- Adrenal gland
  - Glucocorticoids

**Sympathetic Nervous system (SNS) Activation**

**Immune System**
- Cytokines
- Inflammation

**Catecholamines**
Psychological Stress and Immune Function

Psychological Stress: The response to adverse changes in homeostasis provoked by perceived threat, fear, stress and other life events.

Duration and course of this stress, dramatically influences the physiological, behavioral, and immune Responses.

In general, acute stress has a positive influence on behavior and immune function (enhances immunity)

In general, chronic stress has a negative impact on behavior and immune function.

Reduces immunity, Disrupts endocrine system, and increases inflammation
Chronic Stress Pathways causes an imbalance in Circuit between the Brain and the Immune system.

- Brain
- Stress
- Neuroendocrine Activation
  - Hypothalamus
  - CRH
  - Pituitary gland
  - ACTH
  - Adrenal gland
- Glucocorticoids
- Glucocorticoid insensitivity
- Immune System

Sympathetic Nervous system (Overload)
- Inflammation
- Catecholamines

Inflammation

Brain

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How Do We Define Stress?
Symptoms of Stress... too many to list..

Stress is linked to anxiety and depression symptoms:

Nervousness, Fear, Anhedonia, Fatigue

Changes in mood

Disruption in sleep patterns

Increased sensitivity to pain

Stress is linked to muscle tightness, twitching, fatigue

Gastrointestinal disruption

Cognitive Disturbances
Chronic Stress Pathways causes an imbalance in the circuit between the Brain and Immune system

Inflammation (immune Mediated)
Cytokines, Chemokines, leukotrienes, Prostaglandins, Reactive oxygen species

Interleukin (II-1), IL-6, & Tumor Necrosis Factor-alpha
Psychological Stress and Immune Dysfunction

**Psychological Stress**
- Academic Stress
- Marital Discord
- Caregiving stress
- Low Social Economic Status
- Social Stress

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**Immune Dysfunction**

**Innate**
- NK Activity

**Cell Mediated**
- Wound Repair
- Circulating Inflammatory Cytokines
- Reactivation of Latent Virus

**Humoral**
- Antibody Production to Vaccination
- Infectious Episodes

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**Potential Complications**
- Increased clinical symptoms of an infection
- Decreased resiliency in recovery from infection
- Prolonged recovery from surgical procedures
- Behavioral/cognitive deficits
Role of Inflammation

*Communication between immune system and brain*

- **Beneficial Role (most of the time)**
  - Behavior (conserve energy)
  - Energy re-route
  - Enhanced Immunity

- **Maladaptive**
  - Neuropsychiatric Disorders
    - Anxiety
    - Depression
    - Post-traumatic stress disorder

*Inflammation does not cause anxiety and depression. But if it is present, it can make these conditions worse.*
Clinical Evidence of “Inflammatory” Leukocytes (white blood cells) in Individuals Suffering from Chronic Stress or Depression

Transcriptional fingerprint of chronic stress in human leukocytes

++ Inflammatory NFKb mediated genes

- Glucocorticoid mediated genes

This “fingerprint” is consistent with a more pro-inflammatory profile

Leukocytes (white blood cells)
Inflammation in the Brain Shifts the Energy Balance

Inflammatory Cytokines

- Sex Drive
- APPETITE
- MOOD
- GROWTH
- HPG AXIS
- HPT AXIS
- SLEEP
- FEVER
- ACUTE PHASE
- IMMUNE ACTIVATION
- SYMPATHETIC NERVOUS

HPA AXIS
Major Cell Types of the Brain: Microglia are the resident macrophage (immune cell) of the brain.
Inflammation can contribute to the neurobiology of affective disorders

- Inflammation
- Activation of HPA axis
- Altered energy metabolism
- Decreased social activity and lethargy
- Pain hypersensitivity
- Negative attentional bias
- Anhedonia
- Depression, Mood Changes

(Miller & Raison, Nature Reviews Immunology, 2016)
Evidence of Persistent “inflammation” after TBI in Humans

Coughlin et al. (2016) JAMA Neurology

TBI and Chronic Stress. Further Imbalance in The Circuit between the Brain and the Immune system.
Brain Injury and Chronic Stress Implications for Affective Disorders?

Increase in “Allostatic load”

Over 70% of TBI patients continue to have secondary neurocognitive and behavioral complications after TBI. High rate of mood disorders.
TBI and Chronic Stress. Can we fix the Imbalance in The Circuit between the Brain and Immune system?

Therapeutic Intervention
- This imbalance represents a target for novel interventions to reduce inflammation

- Classic Mood Stabilizers (SSRIs)

Healthy Living
Physical Exercise
Eating a Healthy Diet
Sleep Quality
Social network support
Keep Brain active (reading, puzzles, crafts, art)
Reducing the Allostatic load and rebalancing the system

REDUCTION in “Allostatic load”

Anti-inflammatory Intervention*
- Mood Stabilizers (SSRIs)
- Physical Exercise
- Eating a Healthy Diet
- Sleep Quality
- Social network support
- Keep Brain active

Injured Brain

Stressed Brain

Anti-Inflammatory

Pro-Inflammatory

*Note: The term “anti-inflammatory” refers to interventions that help reduce inflammation and stress on the body, thereby improving overall health and well-being.
Thank you!

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