A Trauma-, Adversity-, and Social-Justice-Informed Perspective on Biological, Psychological, and Behavioral Health

Real or Perceived Invalidation, Marginalization, Stigmatiation, and/or Lack of Resources, Safety, Protection, and/or Support Result in Hypersensitization of the Glucocoticoid Stress System and Dysregulate its Regulation of Biological, Psychological, and Behavioral Health

Hypersensitization of the Glugocorticoid Stress System (C) Mediates the Differential Impacts of Real or Perceived Invalidation, Marginalization, Stigmatization, Descrimination, and/or Lack of Resources, Safety, Protection, and/or Support (A) on Physical, Mental/Psychological, and Behavioral Health Outcomes (B)

# The Glucocoticoid Stress System Mediates Acute and Chronic (Lifetime) Stress Ressponses

## The HPA Axis Uses Negative Feedback to Coordinate Glucocorticoid Responses to Stress

Stress often gets a bad rap. Although stress can feel uncomfortable, it plays an important role in regulating nearly all processes and functions in our bodies and lives (Bienertova-Vasku et al., 2020; Bray, 2018; Lu et al., 2021; McEwen, 1998; McEwen & Akil, 2020; McEwen & Gianaros, 2011; McEwen, Gray, et al., 2015; McEwen & Mirsky, 2002; McEwen & Morrison, 2013; McEwen & Sapolsky, 1995; Rudland et al., 2020).

At the systemic level, the hypothalamic-pituitary-adrenal axis (HPA) coordinates neuroendocrine stress responses through peripheral release of glucocorticoid hormones (cortisol in humans) into the bloodstream (Fig. 1)(Bray, 2018; Herman et al., 2003; Herman et al., 2016; Herman & Mueller, 2006; Herman et al., 2005). Cortisol (primary stress hormone in humans) is secreted primarily from the adrenal cortex in the periphery (Pura & Kreze, 2005; Robel & Baulieu, 1994). It is lipophilic and readily crosses the blood brain barrier to act on central tissues in the brain (Pura & Kreze, 2005; Robel & Baulieu, 1994; Ulrich-Lai & Herman, 2009). Among the central tissues that respond to glucocorticoid (cortisol) exposure, the hippocampus is the primary target for glucocorticoid activation in the brain (McEwen et al., 1968). Furthermore, the ventral subiculum of the ventral hippocampus is the primary limbic region that utilizes glucocorticoid feedback to dampen and terminate stress responses (Barr et al., 2017; Herman et al., 2003; van Haarst et al., 1997).

Diagram of a diagram of stress

Description automatically generated

Figure : The Hypothalamic-Pituitary-Adrenal Axis (HPA) coordinates neuroendocrine stress responses. In response to stress, the paraventricular nucleus of the hypothalamus induces a signaling cascade that ultimately stimulates peripheral secretion of glucocorticoid hormones (cortisol in humans, corticosterone in rodents) into the bloodstream. Glucocorticoids are lipophilic and can readily cross the blood brain barrier to act on central tissues. The hippocampus is the primary target for glucocorticoid activation and the ventral hippocampus is thought to be the primary limbic region that utilizes glucocorticoid feedback to inhibit HPA axis activity through activation of its glucocorticoid and mineralocorticoid receptors. This can dampen and terminate stress responses. Note: the ventral hippocampus is thought to induce inhibition onto the HPA axis by exciting inhibitory projections from the Bed Nucleus of the Stria Terminalis (BNST) via the fimbria/fornix (not shown)(Cullinan et al., 1993). Corticosterone is also thought to inhibit HPA activity at the level the PVN, anterior pituitary, and through other limbic regions (ex: medial prefrontal cortex, not shown), and may excite HPA activity through its actions in the basolateral amygdala (BLA) (Herman et al., 2003; Herman et al., 2016; Herman & Mueller, 2006; Herman et al., 2005)

## The Glucocorticoid Stress System Regulates Homeostatic and Non-Homeostatic (Allostatic) Conditions, Ranges, Changes, Processes, Reponses, Functions & Systems

### **Cortisol: The molecular unit by which the body maintains homeostasis and allostasis**

The glucocorticoid stress system mediates and regulates nearly all homeostatic and non-homeostatic (allostatic) conditions, ranges, changes, processes, responses, functions, and systems in the body (Herman et al., 2003; Lu et al., 2021; McEwen, 2017c, 2020; McEwen & Akil, 2020). In humans, the glucocorticoid stress hormone cortisol is the molecular unit by which the human body maintains homeostasis or pushes itself outside of homeostatic range (into allostasis) in order to adapt to “non-normative” or extreme conditions (experiences and environments) (McEwen, 1998; McEwen & Akil, 2020). As such, it may not be surprising that the glucocorticoid stress system regulates every single bodily organ, organ system, function, and process in the human body (both in homeostasis and allostasis) (McEwen, 1998; McEwen & Akil, 2020).

### **Cortisol Regulation of the Life Cycle**

Throughout the lifespan, cortisol regulation of serotonin coordinates our birth, development, migration, growth, aging/senescence, and end of life processes(McEwen, 2017a).

### **Sleep & Wakefulness**

### Neurobiological (Cognition, Mentation, Sensation, Perception, Emotion, Action)

Cortisol contributes to the transition from sleep to wakefulness (E. Knezevic et al., 2023; Mohd Azmi et al., 2021; Walker et al., 2020). At the **neurobiological level, morning glucocorticoid (cortisol) surges** result in dopamine output surges that assist in the transition from mental/cognitive sleep to wakefulness and provide us with motivation to “seize day” and direct our energy toward specific tasks that are assigned dopaminergic salience (e.g., “value”), ranging from seeking, preparing, and consuming coffee and breakfast, maintaining our social hygiene through washing/bathing and clothing routines, prioritizing, planning, scheduling and implementing our daily and long-term schedules and activities (Bray et al., 2020; E. Knezevic et al., 2023; Mohd Azmi et al., 2021; Walker et al., 2020). Cortisol regulation of the **nigrostriatal dopamine system** enables us to translate our cognitive processes into physical actions {Bray, 2020 #3575;Bray, 2018 #2912}.

### Biophysical (Orthostatic Changes, Motion, Movement, Action)

At a more physical/biological level, morning glucocorticoid surges impact our **respiratory and heart rates, blood pressure, and blood glucose levels,** enabling us to transition orthostatically from the supine sleeping position to prone standing and moving positions (E. Knezevic et al., 2023; Mohd Azmi et al., 2021; Walker et al., 2020).

At the end of the day, diminished cortisol levels contribute to the neurobiological and physical transition from wakefulness to sleep and rest.

### **Daily Processes, Functions, & Activities**

### Biophysical (Orthostatic Changes, Motion, Movement, Action)

Cortisol also sustains our physical and mental/neurobiological processes throughout the day. Continued glucocorticoid regulation of **heart and respiratory rate, blood pressure, and metabolism** throughout the day enable us to access and sustain a variety of ranges of motion and movements, including sleeping/resting/napping, sitting, standing, walking, running, coordinating our limbs and appendages for fine-tuned motor skills and functional movement processes (E. Knezevic et al., 2023; Mohd Azmi et al., 2021; Walker et al., 2020).

### Neurobiological (Cognition, Regulation, Executive Function)

At the neurobiological level, continued glucocorticoid (cortisol) regulation of the **mesolimbic and nigrostriatal dopamine system (as well as nearly all other neurotransmitter systems)** enables us to focus, direct, and redirect our attention to a variety of internal and external stimuli and process, rank/value, coordinate, and enact/implement a variety of internal and external short- and long-term responses to those stimuli {Bray, 2020 #3575;Bray, 2018 #2912}.

### **Environmental Awareness & Response**

### Interoceptive Awareness: Internal Sensation & Perception

Glucocorticoid modulation of dopamine output associated with interoceptive cues (e.g., cues about changes in our internal environments such as heart rate and blood pressure (as addressed above) as well as thirst, hunger, body temperature, etc.) can dictate the salience (value) of these cues and our conscious awareness of them and sensitivity to them in turn {Bray, 2022 #7840}{Schaan, 2019 #10482}{Schulz, 2015 #9201}{Koehnle, 2010 #10483}{Ouzir, 2016 #10484}.

In relation to life sustaining activities (e.g., thirst, hunger, body temperature), stress then enables homeostatic regulation of these activities and active responses when levels become allostatic (non-hoeostatic) (McEwen, 1998; McEwen, 2010, 2016).

### Thirst, Hunger, & Hydration/Nutrition- Seeking, Engaging, Appetitive, & Consumption Behaviors

Cortisol regulation of the gastrointestinal and immune systems enable us to take in samples of the external environment in the form of food and metabolize the food into energy, develop immune screening and signaling processes and responses to generate internal signals about our external environment (e.g., its nutritional diversity and safety), fuel life-sustaining microbes that live in our gut and support our many functions, and excrete what is not needed (James et al., 2023; Emilija Knezevic et al., 2023).

### External Sensation & Perception

Cortisol contributes to the tight regulation of our sensory systems (Emilija Knezevic et al., 2023). For example, cortisol enables stress to induce vasoconstriction that reduces the size of our field of vision to prioritize greater far-sided acuity while prolonged cortisol exposure can contribute to the sensitization of a variety of sensory receptors, resulting in heightened sensation that can help us gain awareness and understanding of our external environment (James et al., 2023). This is important in environments where there is perceived risk for danger (heightened senses of sight, smell, sound, and touch can help us avoid danger and navigate to safety more quickly).

### Regulation of the kidneys and liver further regulate vital filtration, detoxification, and excretion systems (Bray, 2018; Bray et al., 2016; Chapman et al., 2013; Cornide-Petronio et al., 2017; Edwards & Stewart, 1991; Güler et al., 1992; Hughes et al., 2012; Jiang et al., 2022; Kleeman et al., 1975; Lapp et al., 2019; Murphy & West, 1964; Sharma & Singh, 2020; Stewart & Edwards, 1991; Tchernof & Després, 2013; Trevisi et al., 2013).

### **Everything**

Glucocorticoid regulation of cardiovascular system, respiratory system, musculoskeletal systems, developmental systems and processes, blood and lymph tissues and systems, skin and immune systems and functions, kidney and filtration systems and processes, liver and detoxification systems, adipose tissues (which respond to inflammation), hormone, endocrine, reproductive, and metabolic systems and processes, brain and neurobiological systems and processes, and the psychological (sensation and perception) and behavioral responses in turn.

## Distress, Trauma, & Adversity Dysregulate the Stress System

Like all other systems in the body, the stress system has homeostatic ranges it operates well within, specifically in relation to context, dose and duration (amount of cortisol exposure tissues can handle with resiliency), and timing (differential impacts of cortisol during developmental vs post-developmental life stages.

## Pharmacotherapy of Eustress (“Good Stress”) & Distress (“Bad Stress”): Context, Dose, Duration, & Timing Matter

* 1. Impacts of Dose
     1. Inverted U // “Goldilocks” Stress Curve
     2. Eustress vs. Distress
     3. Trauma vs. Adversity (“Big T” vs. “Little-T” Trauma)
  2. Impacts of Context (Control)
     1. Controllable vs. Uncontrollable Stressors
     2. Uncontrollable Stressors have higher dose response
  3. Impacts of Timing
     1. Childhood Trauma and Adverse Childhood Experiences
        1. Trauma/Adversity during Development
        2. The HPA Axis coordinates GC stress responses. Limbic Brain Regions (e.g., hippocampus, amygdala, and prefrontal cortex) involved in negative feedback loop; response to glucocorticoid receptor activation by imposing negative feedback (inhibition) onto the hypothalamus, thus terminating glucocorticoid release in response to stress (and GC stress responses in turn).
        3. Stressors that occur during the ongoing development of this system tend to be less regulated (because the regulatory anatomy has not yet fully developed). This can result in prolonged tissue exposure to potentially cytotoxic or sub-cytotoxic levels of cortisol (and other stress hormones) that can cause irreparable tissue dysregulation or damage at the cellular, molecular, organ system, and behavioral levels.
        4. The result is that the natural development of the glucocorticoid stress system and the HPA Axis (that together mediate and coordinate stress responses) can become dysregulated, resulting in dysfunction of these systems for the remainder of the lifespan. Together, the glucocorticoid stress system and the HPA axis regulate nearly every organ system and function in the body, including (a) the stress system itself, (b) metabolism, (c) immune function (and inflammatory responses, e.g., inflammatory responses to stress), (d) the cardiovascular system and function (e.g., vasoconstriction, blood pressure, heart rate), (d) and a variety of neurobiological functions, including (d.1) cellular and molecular neurotransmitter signaling/release and receptor expression and function that mediate reward and emotive responses (e.g., response to reward, emotion, perceived threat, stress, etc.), (d.2) capacity for inhibition and regulation of a variety of neurobiological processes (e.g., reward responses, emotions, stress itself, etc.), (d.3) the ability of the brain to form and support new brain cells and synaptic connections that foster new cognitive, emotive, and (e) psychological processes of sensation and perception and (f) behavioral patterns in turns.
        5. This is not an exhaustive list. The glucocorticoid stress system mediates respiratory processes, kidney processes, liver processes, skin processes, lymph processes, development, nearly every organ system and life processes in the human body that we know.
        6. These changes occur at the cellular, molecular, tissue, organ, and organ systems levels, including cellular/molecular, genetic, and epigenetic factors.

## Different forms of stress

### (e.g., adverse childhood experiences (ACEs), adverse lifetime experiences (ALEs), prolonged, chronic, acute on chronic, etc.).

* 1. This can result in prolonged tissue exposure to potentially cytotoxic or sub-cytotoxic levels of cortisol (and other stress hormones) that can cause irreparable tissue dysregulation or damage at the cellular, molecular, organ system, and behavioral levels.
  2. The result is that the natural development of the glucocorticoid stress system and the HPA Axis (that together mediate and coordinate stress responses) can become dysregulated, resulting in dysfunction of these systems for the remainder of the lifespan. Together, the glucocorticoid stress system and the HPA axis regulate nearly every organ system and function in the body, including (a) the stress system itself, (b) metabolism, (c) immune function (and inflammatory responses, e.g., inflammatory responses to stress), (d) the cardiovascular system and function (e.g., vasoconstriction, blood pressure, heart rate), (d) and a variety of neurobiological functions, including (d.1) cellular and molecular neurotransmitter signaling/release and receptor expression and function that mediate reward and emotive responses (e.g., response to reward, emotion, perceived threat, stress, etc.), (d.2) capacity for inhibition and regulation of a variety of neurobiological processes (e.g., reward responses, emotions, stress itself, etc.), (d.3) the ability of the brain to form and support new brain cells and synaptic connections that foster new cognitive, emotive, and (e) psychological processes of sensation and perception and (f) behavioral patterns in turns.
  3. This is not an exhaustive list. The glucocorticoid stress system mediates respiratory processes, kidney processes, liver processes, skin processes, lymph processes, development, nearly every organ system and life processes in the human body that we know.
  4. These changes occur at the cellular, molecular, tissue, organ, and organ systems levels, including cellular/molecular, genetic, and epigenetic factors.

## Glucocoirtoicd Stress System & Neurobiological Stress Responses

## Healthy/Normative & Dysregulating Stressors and Stress Responses

## Epigenetic Underpinnings for Stress Dysregulation

* Mourtzi et al., 2021, “Glucocorticoid Signaling and Epigenetic Alterations in Stress-Related Disorders.” (<https://pubmed.ncbi.nlm.nih.gov/34073101/>).
* Sousa, 2016. " Stress Neuromatrix" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4759204/>).
* Reul et al., 2015 “Glucocorticoids, epigenetic control and stress resilience” (<https://pubmed.ncbi.nlm.nih.gov/27589660/>).
* Hunter, 2012 “Epigenetic effects of stress and corticosteroids in the brain” (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3329877/>).
* Hyman, 2009 (<https://pubmed.ncbi.nlm.nih.gov/19238182/>).
* (Caradonna et al., 2022; Gray et al., 2017; Hoffmann & Spengler, 2012; Hyman, 2009; Marrocco et al., 2020; McEwen, 2010, 2016, 2017a, 2017b, 2017c, 2018, 2019, 2020; McEwen, Bowles, et al., 2015; McEwen & Bulloch, 2019; McEwen, Gray, et al., 2015; McEwen et al., 2016)

## Stress Impacts on the Body

* E.g., cortisol dysregulation, inflammation & immune dysfunction, metabolic dysregulation, weight gain/hyperglycemia, etc.
* [Roberts & Karatsoreos, 2021, "Brain–body responses to chronic stress: a brief review,"](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8725649/pdf/facrev-10-83.pdf)
* [McEwen 2017 "Neurobiological and Systemic Effects of Chronic Stress."](https://pubmed.ncbi.nlm.nih.gov/28856337/)
* [Sousa, 2016. " Stress Neuromatrix."](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4759204/)

## Stress on the Brain

* E.g., reduced inhibition, reduced regulatory ability (of emotions, reward responses, etc.) reduced neuroplasticity and neurogenesis; increased cognitive rigidity, impulsivity, compulsivity, rumination & repetitive behaviors, etc.
* [Roberts & Karatsoreos, 2021, "Brain–body responses to chronic stress: a brief review,"](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8725649/pdf/facrev-10-83.pdf)
* [McEwen 2017 "Neurobiological and Systemic Effects of Chronic Stress."](https://pubmed.ncbi.nlm.nih.gov/28856337/)
* [Sousa, 2016. " Stress Neuromatrix."](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4759204/)
* [McEwen & Gianaros, 2011. "Stress- and allostasis-induced brain plasticity."](https://pubmed.ncbi.nlm.nih.gov/20707675/)
* [Zhang et al., 2019. "Chronic Stress Remodels Synapses in an Amygdala Circuit-Specific Manner."](https://pubmed.ncbi.nlm.nih.gov/30060908/)

## Stress Impacts on Neurogenesis, Neuroplasticity, & Neural Remodeling

* McEwen 2017 "Neurobiological and Systemic Effects of Chronic Stress." (<https://pubmed.ncbi.nlm.nih.gov/28856337/> )
* McEwen & Gianaros, 2011, "Stress- and allostasis-induced brain plasticity." [(https://pubmed.ncbi.nlm.nih.gov/20707675/).](https://pubmed.ncbi.nlm.nih.gov/20707675/)
* Price & Duman, 2020, "Neuroplasticity in cognitive and psychological mechanisms of depression: an integrative model." [(https://pubmed.ncbi.nlm.nih.gov/31801966/).](https://pubmed.ncbi.nlm.nih.gov/31801966/)
* Zhang et al., 2019, "Chronic Stress Remodels Synapses in an Amygdala Circuit-Specific Manner." [(https://pubmed.ncbi.nlm.nih.gov/30060908/).](https://pubmed.ncbi.nlm.nih.gov/30060908/)
* [PubMed search here](https://pubmed.ncbi.nlm.nih.gov/?term=chronic%20stress%20and%20neuroplasticity).
* For some of the more technical findings, see [Barr & Dokas, 2001Links to an external site.](https://onlinelibrary.wiley.com/doi/abs/10.1002/jnr.1159?sid=nlm%3Apubmed), [Daskalakis et al., 2015Links to an external site.](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4644789/),  and [Fleischer et al., 2023.](https://pubmed.ncbi.nlm.nih.gov/38169784/)
* These describe how stress hormones interact with brain-derived neurotrophic factor (BDNF, which is like fish food for brain cells) to influence neurogenesis and neural plasticity and remodeling in turn. The latter is from my graduate advisor's lab. :)

## Psychological and Behavioral Impacts of Stress (and their Neurobiological Underpinnings):

* E.g. Rumination, Isolation, Impulsivity and Compulsivity, Anxiety, Depression, PTSD Substance Use/Abuse, Food/Eating Disorders…

### **General:**

* McEwen & Gianaros, 2011, "Stress- and allostasis-induced brain plasticity." [(https://pubmed.ncbi.nlm.nih.gov/20707675/).](https://pubmed.ncbi.nlm.nih.gov/20707675/)
* Zhang et al., 2019, "Chronic Stress Remodels Synapses in an Amygdala Circuit-Specific Manner." <(https://pubmed.ncbi.nlm.nih.gov/30060908/).>

### **Depression & Anxiety:**

* Price & Duman, 2020, "Neuroplasticity in cognitive and psychological mechanisms of depression: an integrative model." [(https://pubmed.ncbi.nlm.nih.gov/31801966/).](https://pubmed.ncbi.nlm.nih.gov/31801966/)
* Zhang et al., 2019, "Chronic Stress Remodels Synapses in an Amygdala Circuit-Specific Manner." [(https://pubmed.ncbi.nlm.nih.gov/30060908/).](https://pubmed.ncbi.nlm.nih.gov/30060908/)

### **PTSD:**

* Castro-Vale et al., 2016. " Genetics of glucocorticoid regulation and posttraumatic stress disorder--What do we know?" (<https://pubmed.ncbi.nlm.nih.gov/26872620/>).
* Zhang et al., 2019, "Chronic Stress Remodels Synapses in an Amygdala Circuit-Specific Manner."<(https://pubmed.ncbi.nlm.nih.gov/30060908/).>

### **Addiction:**

* Koob & Schulkin, 2019 "Addiction and stress: An allostatic view." (<https://pubmed.ncbi.nlm.nih.gov/30227143/>).
* My graduate work fits in here if you want the neuro-cellular, molecular, anatomical and physiological underpinnings:
  + - * + Barr, Bray, Forster, 2017. “The Hippocampus as a Neural Link between Negative Affect and Vulnerability for Psychostimulant Relapse,” (<https://www.intechopen.com/chapters/57312>).
        + Bray et al., 2020, "Corticosterone in the ventral hippocampus differentially alters accumbal dopamine output in drug-naïve and amphetamine-withdrawn rats" (<https://pubmed.ncbi.nlm.nih.gov/31881169/>).
        + Bray et al., 2016. "Amphetamine withdrawal differentially affects hippocampal and peripheral corticosterone levels in response to stress" (<https://pubmed.ncbi.nlm.nih.gov/27208490/>).
* Wiss, Avena, Gold, 2020. "Food Addiction and Psychosocial Adversity: Biological Embedding, Contextual Factors, and Public Health Implications." (<https://pubmed.ncbi.nlm.nih.gov/33207612/>)

### **Disordered Eating, Eating Disorders, & Food Addiction**

* Wiss, Avena, Gold, 2020. "Food Addiction and Psychosocial Adversity: Biological Embedding, Contextual Factors, and Public Health Implications." (<https://pubmed.ncbi.nlm.nih.gov/33207612/>).
* Kuckuck et al., 2023. "Glucocorticoids, stress and eating: The mediating role of appetite‐regulating hormones." (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10077914/>).

## Neuropsychoimmunology

* Exploring links between psychology, neurobiology, & immunology
* How the brain and psychology are inter-related to immune function and inflammation that drive thoughts and behaivors in turn (“not just woo-woo”).
* Miller et al., 2009. "Parental support and cytokine activity in childhood asthma: the role of glucocorticoid sensitivity" (<https://pubmed.ncbi.nlm.nih.gov/19181373/>).
  + Wright 2009 "Stress and acquired glucocorticoid resistance: A relationship hanging in the balance." (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4807974/>).
  + Wright 2009 summarizes Miller et al., 2009.
  + High vs. low rating of perceived parental support linked to low (anti-) vs. high (pro-) inflammatory response to stress and asthma in children. Links between psychology (perceived parental support), neurobiology (glucocorticoid/cortisol response to stress), immunology (inflammatory response to glucocorticoids (e.g., cortisol and stress) and asthma (Miller et al., 2009; Wright, 2009).
* Dr. Zwickey gave an excellent review of this topic in a [2022 Podcast episode](https://cc.bingj.com/cache.aspx?q=%22022+Neuropsychoimmunology%22+with+%22Heather+Zwickey%22+Integrative+Psychiatry+Review+March+15%2c+2022&d=4738289980028343&mkt=en-US&setlang=en-US&w=XIr5kf0kpBZqufbq4kxQRMKKFj1vNMtJ) on the "‎Integrative Psychiatry Review" Podcast.
  + The episode is titled "[022 Neuropsychoimmunology with Heather Zwickey.](https://cc.bingj.com/cache.aspx?q=%22022+Neuropsychoimmunology%22+with+%22Heather+Zwickey%22+Integrative+Psychiatry+Review+March+15%2c+2022&d=4738289980028343&mkt=en-US&setlang=en-US&w=XIr5kf0kpBZqufbq4kxQRMKKFj1vNMtJ)" (March 15, 2022).
  + Typically, it is accessible on iTunes [here](https://cc.bingj.com/cache.aspx?q=%22022+Neuropsychoimmunology%22+with+%22Heather+Zwickey%22+Integrative+Psychiatry+Review+March+15%2c+2022&d=4738289980028343&mkt=en-US&setlang=en-US&w=XIr5kf0kpBZqufbq4kxQRMKKFj1vNMtJ). However, it may not be accessible currently.

## Stress Vulnerability

### Lack of Unconditional Acceptance/Validating/Support (e.g., lack in perceived parental support, invalidation, marginalization, under-resourced, etc.).

### **Stress response to maternal separation**

* + - * ([Hyman, 2009](https://naropa.instructure.com/courses/6335/files/1000800?wrap=1); Schmidt et al., 2004; [Biggio et al., 2014](https://pubmed.ncbi.nlm.nih.gov/24745548/)).
      * [Maternal separation & alcohol consumption.](https://pubmed.ncbi.nlm.nih.gov/?term=Maternal+separation+AND+alcohol+consumption)
      * [Maternal separation and self-administration.](https://pubmed.ncbi.nlm.nih.gov/?term=Maternal+separation+AND+%28self-administration+OR+self+administration%29)

### **Stress, Inflammatory, Immune Response to Perceived Lack of Parental Support**

* + - * [Miller et al., 2009. "Parental support and cytokine activity in childhood asthma: the role of glucocorticoid sensitivity."](https://pubmed.ncbi.nlm.nih.gov/19181373/)
      * [Wright 2009 "Stress and acquired glucocorticoid resistance: A relationship hanging in the balance."](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4807974/)
      * High vs. low rating of perceived parental support linked to low (anti-) vs. high (pro-) inflammatory response to stress and asthma in children. Links between psychology (perceived parental support), neurobiology (glucocorticoid/cortisol response to stress), immunology (inflammatory response to glucocorticoids (e.g., cortisol and stress) and asthma (Miller et al., 2009; Wright, 2009).

### **Contributions of Invalidation, Marginalization, & Under-Resourced Experiences & Environments in Mental Health**

* + - * Bray et al., 2022, “Binge Eating Disorder Is a Social Justice Issue: A Cross-Sectional Mixed-Methods Study of Binge Eating Disorder Experts’ Opinions,” (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9141064/>).

## Stress Resilience

### Resilience Actions & Interventions

* + - * E.g., voluntary exercise, environmental enrichment, mindfulness and meditation).

### **Exercise**

* + - * Reul et al., 2015, "Glucocorticoids, epigenetic control and stress resilience." [(https://pubmed.ncbi.nlm.nih.gov/27589660/).](https://pubmed.ncbi.nlm.nih.gov/27589660/) (Highlights role of voluntary exercise).

### **Environmental Enrichment**

* + - * Orock et al., 2021, "Environmental enrichment prevents stress-induced epigenetic changes in the expression of glucocorticoid receptor and corticotrophin releasing hormone in the central nucleus of the amygdala to inhibit visceral hypersensitivity." (<https://pubmed.ncbi.nlm.nih.gov/34390704/>). (Role of environmental enrichment).

Barr, J. L., Bray, B., & Forster, G. L. (2017). The Hippocampus as a Neural Link between Negative Affect and Vulnerability for Psychostimulant Relapse. In A. Stuchlik (Ed.), *The Hippocampus*. <https://doi.org/10.5772/intechopen.70854>

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