# Stress

## OVERVIEW

This document provides an overview of the scientific community's current understanding of the biological mechanisms behind the stress response, what happens when the stress response system is overloaded, and possible ways to increase resilience in high-stress environments.

## What is stress?

The word 'stress' is used in conversation to mean worry or concern. But in the medical sciences, **stress** is physical. It is a neurobiological response to experiences or environmental conditions, referred to as **stressors**, that cause feelings of anxiety or discomfort. It is often accompanied by changes in heart rate and digestion. While stress is often thought of as something to be avoided, not all stress is bad. In fact, some stress can be good and can help a person adaptively cope with daily routine challenges[1].

A useful way to think about stress is that it is a physical state that the human body has a need to alleviate or reduce. The human body is driven by a desire to maintain **homeostasis**, or a state of stability or constancy. For example, humans maintain a relatively constant body temperature; if the internal temperature gets too high, sweating can promote cooling the body down. In the same way, the body needs to maintain homeostasis in the face of stressors. The process by which the body responds to stressors in an effort to restore homeostasis is called **allostasis**.

Stress can be classified as "good" (leading to positive outcomes), "tolerable" (causing distress but managed with coping mechanisms), or "**toxic**" (unable to be managed with coping mechanisms)[2]. Stress can also be **acute** (caused by distinct life events such as the death of a loved one or a school exam) or **chronic** (caused by long-term exposure to adverse conditions such as poverty or parental neglect)[3].

Here we use Figure 1 to describe different ways we can experience stress. In one case, a person might be crossing the street when a car comes at them quickly and unexpectedly (Stage 1), which is recognized as an immediate threat (Stage 2). The sympathetic nervous system is responsible for the immediate "fight or flight" response that allows the person to quickly mobilize an adaptive stress response (Stage 3). This system releases chemicals like epinephrine, which trigger a number of reactions (increased heart rate, slowing of digestion, etc.) that allow the body to focus all of its resources on fleeing from the danger. Once a threat is over, the sympathetic nervous system stops activating the fight of flight response and the parasympathetic nervous system, the other branch of the autonomic (automatic) nervous system, works to get the body back to a baseline state and restore homeostasis ("rest and digest"; Stage 4).

**Stress**
neurobiological response to a disruption in the adaptive functioning of an individual or system

**Stressors**
experiences or environmental conditions that cause a stress response

**Homeostasis**
a state of stability that the body tries to maintain; includes the regulation of body temperature, blood pressure, blood sugar, etc.; is disrupted under stressful conditions

**Allostasis**
the process by which the body responds to stressors to restore homeostasis

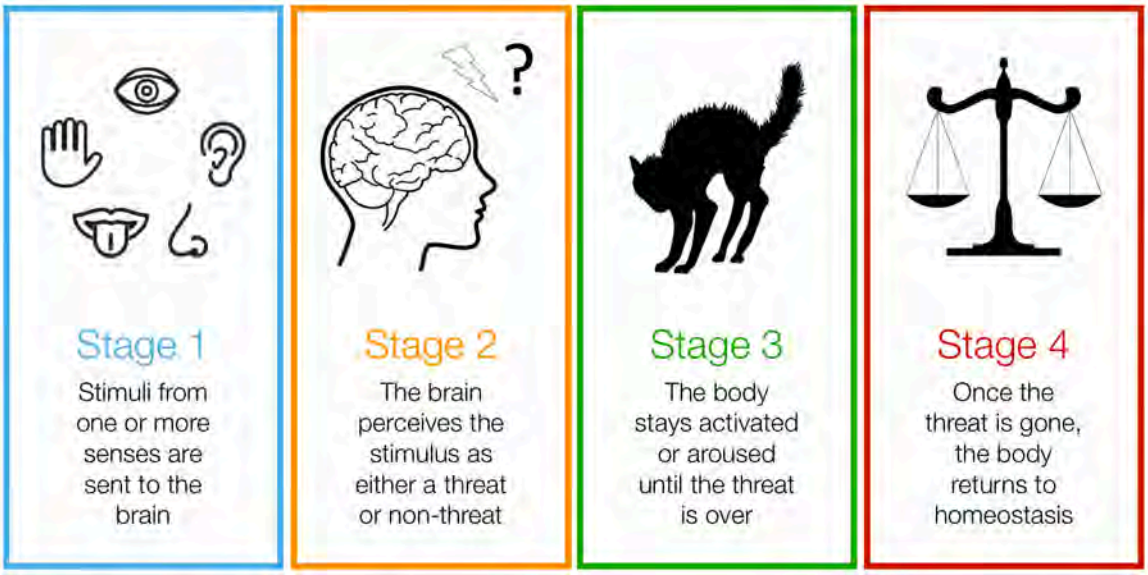


Figure 1. Stages of a typical stress response.

But a real threat doesn't have to be present for the body to have this response. The perception of a stressor also triggers a biological stress response. Consider two students preparing for an upcoming exam. Student 1 might feel some pressure to do well ("I'd like to impress the professor with my knowledge") and perceive the exam as a mild stressor that initiates a stress response (Stage 2). This stress response might include feelings of anxiety, an elevated heart rate, and/or an increase in general arousal and alertness (Stage 3). In response to these feelings, Student 1 engages in some healthy coping mechanisms that she has learned help manage her stress response such as taking deep breaths, talking to her mother, and devising a study schedule. These behaviors make her feel sufficiently confident in her knowledge and the remaining arousal she feels in response to the acute stressor of an impending exam has been found to improve learning and memory. After the exam, the stress response is reduced (Stage 4). This student has gone through all 4 stages in Figure 1.

Student 2, on the other hand, feels much more pressure in the period leading up to the exam ("If I don't do well on this exam and all of my other exams, I will have to leave school and my life will be ruined"), perceives the exam as a very large threat, and experiences a much stronger and prolonged stress response in Stage 3. In addition to the acute stressor of the exam, he is also living in a state of chronic stress (he has no familial support system to turn to and he has to worry about his basic life needs day-to-day). He has the same need as Student 1 to reduce the stress response, but no amount of studying reduces the physiological symptoms (elevated heart rate, sweating, fast breathing, etc.) that are paired with psychological symptoms such as frustration and aggravation. With no effective coping mechanisms or chances for his stress response to return to baseline levels, Student 2 is living in a state of chronic, toxic stress in Stage 3 that will likely impact his memory and performance in a negative way. In this case, the stress response is no longer adaptive or appropriate to the

**Toxic stress**
A large neurobiological stress response caused by an extreme experience that shapes the brain in a negative way

**Acute stress**
stress caused by distinct life events (e.g., the death of a loved one)

**Chronic stress**
stress caused by long-term exposure to adverse conditions (e.g., poverty)

**Hypothalamic-pituitary-adrenal (HPA) axis**
Feedback loop among three endocrine glands (hypothalamus, pituitary gland, and adrenal glands) that helps the body respond to stress and maintain homeostasis

**Corticotropin-releasing hormone (CRH)**
hormone released by the hypothalamus in response to stress; stimulates the pituitary gland to release ACTH which in turn stimulates the adrenal glands to release stress hormones including cortisol

**Cortisol**
hormone with many functions; functions related to the stress response are an increase in blood sugar and suppression of the immune system

**Allostatic load**
harm that results from long-term dysregulation (over- or underactivity) of the processes involved in the stress response

immediate stressor and can result in pathology in the long-term. If the stressor is either very extreme or lasts for a long time, all the positive effects of stress on learning and memory become negative.

## The biology of the stress response in brief detail

The stress response is triggered by something called the **hypothalamic-pituitary-adrenal (HPA) axis**. The cascade of events starts with the release of **corticotropin-releasing hormone (CRH)** from the hypothalamus (a small region near the center of the brain) and culminates in the release of **cortisol**, a hormone with wide-reaching effects, from the adrenal cortex which is located above the kidneys. In the short term, cortisol suppresses processes not necessary for immediate survival (e.g., metabolic processes involved in digestion) and makes glucose more available to fuel the fight-or-flight response. Elevated levels of cortisol can increase energy usage, enhance cognitive abilities, strengthen immune reactions, and encourage the body to restore homeostasis (this is why a mild stress response helped Student 1 do well on the exam in the earlier example). When a stressor is no longer perceived as a threat, cortisol levels are allowed to return to baseline and the system can prepare to respond to future stressors.

The same processes that work to restore homeostasis in response to acute stress can become maladaptive in the face of chronic stress. Long-term exposure to stressors can cause harm through the chronic over- or underactivity of stress response mechanisms, a phenomenon known as **allostatic load**[2]. For example, sustained elevated levels of stress hormones like cortisol may reverse the

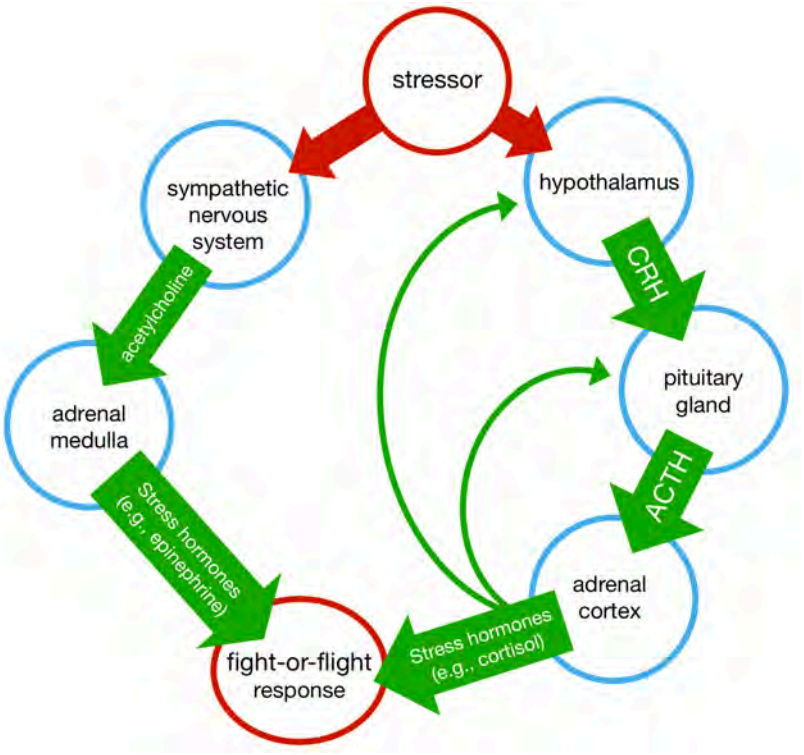


Figure 2. Simplified model of the processes involved in the dual-pathway stress response.

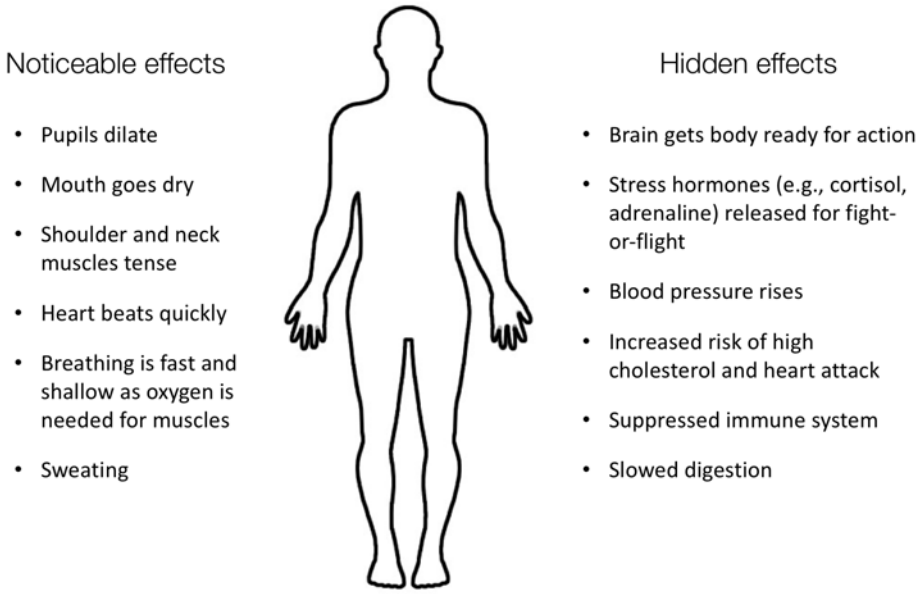


Figure 3. Noticeable and hidden effects of the stress response.

positive effects of the short-term stress response, leading to worsened cognitive functions, weaker immune responses, and metabolic disorders (as in the example of Student 2). An experience of chronic or prolonged stress may lead to the development of anxiety disorders or mood disorders, such as depression[2]. Individuals suffering from stress may also experience an inability to sleep, a decreased or increased appetite, a propensity towards alcohol or drug consumption, and a decreased interest in social or physical activities. This lack of activity may also lead to other health problems, such as gaining weight and the development of heart or metabolic disorders like diabetes.

**Amygdala**
subcortical brain region heavily involved in emotion processing and regulation, particularly for fear and anxiety

**Hippocampus**
brain region associated with memory, emotion, and learning; can be damaged by prolonged exposure to elevated cortisol levels

**Prefrontal cortex (PFC)**
brain region associated with higher-level cognitive functions like decision-making and emotion regulation

## Brain regions affected by stress response are developing in childhood and adolescence

In brain development, experience is important but the timing of experience may be even more important. There are specific regions of the brain that are still maturing throughout adolescence that are affected more extremely by stress in early life. It is intuitive that stressful experiences shape changing systems more than systems that are already developed. These regions include the **amygdala, hippocampus**, and **prefrontal cortex (PFC)**. In addition, adolescents exhibit more intense hormone responses (see Figure 2) compared to adults[1]. This puts them at particular risk for the negative biological consequences of stressful experiences.

Experiencing chronic stress results in over-excitability of the amygdala, a region involved in the regulation of emotions, particularly fear[3]. This chronic over-excitability is linked to structural changes in this brain area that may not

**Social buffering**
Prevention or reduction of stress response activity due to the presence of a social partner (e.g., parent)

**Anxiety**
a feeling of worry or nervousness

**Ventral striatum**
subcortical brain structure involved in reward-seeking behavior; includes the nucleus accumbens

be reversible. In this way, if a child experiences an extreme or chronic stressor and his or her stress response is not managed so that the system returns to homeostasis (Stage 4), the lasting effects are on brain regions that then become overly excitable by nature. In other words, stress early in life shapes the developing amygdala to be overly active. Over time the initial stressor may go away, but now the individual can have inappropriately emotional responses (due to amygdala over-activity) to even non-stressful situations.

Chronic stress is also linked to physiological changes in the hippocampus and prefrontal cortex. These regions, along with the amygdala, are also all connected to each other. Together, they support learning and memory as well as control over thought and action (Figure 4)[4]. Social deprivation, or the lack of a loving and dependable caregiver in one's life, has also been linked to the disrupted development of fear learning[5]. Children tend to depend on adult care, and a strong caregiver relationship can prevent or lessen the activation of the stress response even when the child is exposed to severe stressors through what is known as parental **social buffering**. Social buffering is especially important early in life when stress response mechanisms are still developing. Without effective parental social buffering, the normal development of the prefrontal cortex and the child's regulation of fear can be altered[6]. Adults reporting more early-life stressors are more likely to experience problems controlling **anxiety**[3]. In a similar manner, animals that are separated from their mothers exhibit a greater HPA axis response and accelerated amygdala development, and they are more aggressive and anxious as adults[3]. This suggests that the effectiveness of caregiving is connected to the maturation of fear learning and responses.

Another brain region influenced by stress is the **ventral striatum**, an area

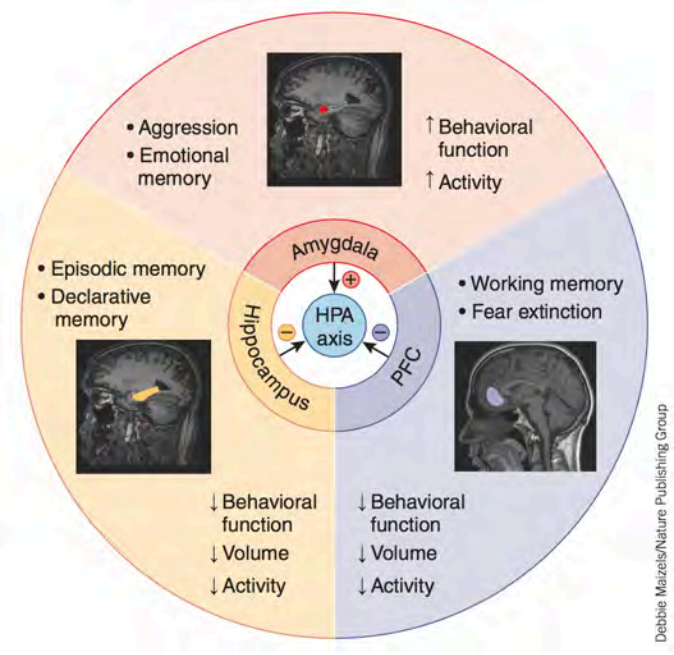


Figure 4. Interconnected brain areas affected by (and involved in) the stress response (Chattarji et al., 2015).

**Resilience**
the ability of an individual or system to successfully change or adapt in response to disturbances or threats

**Susceptibility**
sensitivity of an individual, group, or demographic to different environments; also referred to as vulnerability

associated with reward behavior[7]. Reward-seeking behavior is common and normal in adolescence. This is a time when teens seek the support of peers and explore what life is like outside of their nuclear family. While some reward-seeking is good, extreme reward-seeking (drug use, joining gangs) can be deadly. This type of behavior has been studied using a game in which participants are asked to pump up virtual balloons for rewards. In this game, the size of the possible reward increases with the size of the balloon, but continuing to pump up the balloon comes with the risk of popping it and losing all possible reward. Adolescents who were raised in institutional or orphanage care did not take as much risk as adolescents who did not experience significant early life stress on this game (i.e., they stopped inflating the balloons sooner)[8,9]. They also showed a reduced brain response in the ventral striatum to emotionally-rewarding stimuli (i.e., happy faces) compared to other adolescents[10]. In a different study, adolescents who were raised in institutional care did not seem to differentiate between predictions of low, medium, or high reward, whereas those who did not have a history of stress responded more strongly to the predictions of medium or high reward[11]. The impact of early life stress on ventral striatum development makes it harder for those individuals to identify potential reward values and thus less equipped to make decisions about when to seek reward versus avoid risk.

In impacting the developing amygdala, PFC, and hippocampus, stress experienced early in life impacts empathy, cognitive flexibility, learning and memory, control over actions and emotions, language and communication, and reasoning ability.

## Resilience & susceptibility

**Resilience** is the ability to overcome negative or challenging events (to return the body to homeostasis as in Stage 4 of Figure 1). Individual people vary in their **susceptibility** or neurobiological sensitivity to environmental influences, and these differences in susceptibility can lead to increased or decreased resilience to adversity[12]. For example, a study of differences in susceptibility found that children with highly reactive immune systems had higher illness rates when they lived in high-stress conditions but lower illness rates when they lived in low-stress conditions, while children with less reactive immune systems had similar illness rates regardless of the environment[13]. In other words, children with high immune reactivity were more vulnerable to the negative impacts associated with high-stress environments.

Can resilience be manufactured? There is evidence that several methods and activities can help to increase resilience to stress. One idea is to stop the cascade of events in the HPA axis early (Figure 2), for example by blocking the release of CRF at the top of the axis. One method for doing this is by reappraising potential stressors so that they are no longer perceived as threats. Another approach is to down-regulate (or reduce) the amount of cortisol release

depicted in Figure 2. There are myriad experiences that science has shown are effective in regulating cortisol levels. These include cardiovascular activity, high-fat diets, parental or maternal buffering of stressors, enriching physical spaces, regular sleep patterns, perceived control over one's environment, and some measure of being able reduce uncertainty and predict what comes next (Spotlight box). Each of these findings can be translated in many different ways for curriculum or intervention development. For example, perceived control over stressors can mean simply *knowing* why your body reacts the way that it does to an emotionally charged or stressful circumstance. This allows the individual to make predictions about when the stress response will end, and what strategies they can use to end it. In this way, the individual can reduce the intensity of the biological cascade by turning down the volume, so to speak, on the arousal and over-activity in his or her own system (ending Stage 3 in Figure 1). For the same reason, meditation and mindfulness-based stress reduction therapy have been found to help increase volume and density of the amygdala, hippocampus, and prefrontal cortex, as well as strengthen their connections to each other[2]. These areas, associated with emotion regulation and perspective-taking, are thus enhanced by these perceived-control practices, which in turn helps to counter or help one deal with the effects of stress in future instances.

SPOTLIGHT ON

## Strategies for manufacturing resilience

- Maternal buffering
- Cardiovascular activity
- Perceived control over stressors
- Sleep patterns
- Environmental predictability
- Social/environmental enrichment
- Meditation

## References


1. Romeo, R. D. The Teenage Brain: The Stress Response and the Adolescent Brain. *Curr. Dir. Psychol. Sci.* **22,** 140–145 (2013).
2. McEwen, B. S. In pursuit of resilience: stress, epigenetics, and brain plasticity. *Ann. N. Y. Acad. Sci.* **1373,** 56–64 (2016).
3. Ganzel, B. L., Kim, P., Gilmore, H., Tottenham, N. & Temple, E. Stress and the healthy adolescent brain: Evidence for the neural embedding of life events. *Dev. Psychopathol.* **25,** 879–889 (2013).
4. Chattarji, S., Tomar, A., Suvrathan, A., Ghosh, S. & Rahman, M. M. Neighborhood matters: Divergent patterns of stress-induced plasticity across the brain. *Nat. Neurosci.* **18,** 1364–1375 (2015).
5. Gunnar, M. R., Hostinar, C. E., Sanchez, M. M., Tottenham, N. & Sullivan, R. M. Parental buffering of fear and stress neurobiology: Reviewing parallels across rodent, monkey, and human models. *Soc. Neurosci.* **10,** 474–478 (2015).
6. Gee, D. G. *et al.* Early developmental emergence of human amygdala – prefrontal connectivity after maternal deprivation. *Proc. Natl. Acad. Sci. U. S. A.* **110,** 15638–15643 (2013).
7. Tottenham, N. & Galvan, A. Stress and the adolescent brain: Amygdala-prefrontal cortex circuitry and ventral striatum as developmental targets. *Neurosci. Biobehav. Rev.* **70,** 217–227 (2016).
8. Humphreys, K. L. *et al.* Exploration-exploitation strategy is dependent on early experience. *Dev. Psychobiol.* **57,** 313–321 (2015).
9. Loman, M. M., Johnson, A. E., Quevedo, K., Lafavor, T. L. & Gunnar, M. R. Risk-taking and sensation-seeking propensity in postinstitutionalized early adolescents. *J. Child Psychol. Psychiatry Allied Discip.* **55,** 1145–1152 (2014).
10. Goff, B. *et al.* Reduced nucleus accumbens reactivity and adolescent depression following early-life stress. *Neuroscience* **249,** 129–138 (2013).
11. Mehta, M. A. *et al.* Hyporesponsive reward anticipation in the basal ganglia following severe institutional deprivation early in life. *J. Cogn. Neurosci.* **22,** 2316–2325 (2010).
12. Boyce, W. T. Differential susceptibility of the developing brain to contextual adversity and stress. *Neuropsychopharmacology* **41,** 142–162 (2016).
13. Boyce, W. T. *et al.* Psychobiologic reactivity to stress and childhood respiratory illnesses: results of two prospective studies. *Psychosom. Med.* **57,** 411–422 (1995).



Document prepared by Heidi Baumgartner & Dima Amso