Part I
Basics of the Stress Response

1

The Basics of the Stress Response
A Historical Context and Introduction

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An Introduction to Stress

Stress is a concept that everybody can identify with and yet, if asked to define stress, most people might indicate that it is synonymous with feeling overwhelmed, anxious, or under intense pressure. To this end, stress is typically thought about from the perspective of what causes it. However, an issue to consider when thinking about stress in terms of its source (i.e., the stressor) is the subjective dilemma that occurs when a stressful event or circumstance is not perceived the same way among different individuals. For example, riding a roller coaster may be a very pleasurable experience for one person while being an extremely unpleasant experience for another. It is unlikely the individual who enjoys the roller coaster would label it as a stressor. Nevertheless, that person's body undergoes similar internal physical reactions as the individual who perceives the roller-coaster ride negatively, highlighting the caveat that even fun and exciting experiences can be considered stressors based upon the objective methods of defining stress in terms of the neurobiological cascade of responses that underlie an arousing experience. However, a complex interplay between physiological, psychological, and behavioral processes that varies across situations precludes developing a singular definition of stress based solely on the physical response. Thus, both stressor and stress-response elements need to be taken into careful consideration when studying stress as a scientific construct. The goal of this chapter is to provide an introductory overview of these elements, including a brief historical perspective, and highlight the important relationship between stress, emotions, and neuropsychological health.

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Although stress is often perceived in a negative light, it is actually a very useful and highly adaptive response. The body understands the importance of stress, but also the potential damage that it can cause, and is therefore equipped with central and peripheral systems that both promote and suppress it (Sapolsky et al., 2000). Activation of these systems (i.e., the stress response) represents an evolutionarily conserved ability of an organism to deal with circumstances that require vigilance, arousal, and/or action (Neese and Young, 2000). In addition to facilitating the perception and processing of stress, the stress response is also designed to restore balance. To this end, the various neurotransmitters, peptides, and hormones that are released in response to stress serve a protective function for an organism (McEwen, 2000b). Importantly, these neurochemical mediators stimulate tissues to respond in an appropriate and adaptive manner to the stressful circumstance at hand (McEwen and Seeman, 1999). The physiological component of the stress response can be further modified by psychological processes, such as coping and appraisal, which can aide in (or potentially hinder) the restoration of balance.

The experience of too much stress over time can have adverse consequences on health and behavior, but never experiencing any stress would result in inactivity, boredom, and an inability to adequately respond to internal/external demands. For instance, stress can be useful to motivate and prepare organisms to deal with situations such as writing a research paper or escaping from a predator. To appreciate the function of stress in a given situation, it is important to consider the stressor. There are a number of internal and external causes of stress, and these are generally characterized into two categories. Systemic (also referred to as *physiological*) stressors represent a physically based threat to an organism without requiring cognitive processing. Systemic stressors can include internal factors, such as inflammation or hemorrhage, and external factors, such as a burn or bite. Psychogenic stressors represent a more psychologically based disturbance that requires cognitive processing. As such, psychogenic stressors typically involve an anticipatory component along with real-time appraisal. In general, stress has been popularly conceptualized as any physical or psychological event, whether it be actual or imagined, that disrupts homeostatic processes within an organism. Therefore, a more precise definition of a stressor is anything that jeopardizes a state of balance, or homeostasis, within an organism.

The Road to Conceptualizing Stress

In the sections that follow, we will elaborate further on the details of the stress response and the different types of stressors and regulation mechanisms. However, it is important to first acknowledge a few of the seminal findings that have shaped our modern understanding of these concepts, and touch upon one of the current influential perspectives on how the field views stress (i.e., allostasis). The original studies on the physiology of the stress response by Walter Cannon and Hans Selye

suggested initially that the body's reaction is nonspecific in nature, and thus that all stressors in general produce the same ends. For Cannon (1932) the focus was on exploring the sympathetic-adrenal (i.e., autonomic) response to an immediate stressor. His work established that an organism prepares itself to deal with a threat via release of epinephrine (also referred to as adrenaline) from the adrenal medulla, which subsequently activates the body's energy reserves by accelerating heart rate and blood pressure, mobilizing blood glucose levels, increasing respiration, and inhibiting unnecessary energy-utilizing processes such as digestion and reproduction. The ultimate result is to quickly prime an organism for a fight-or-flight (Cannon, 1929), or freeze, response (Bracha et al., 2004). Notably, Cannon helped develop the concept of homeostasis and stress by postulating that stress disturbs equilibrium, and that the autonomic response helps to restore one's internal processes (or milieu) to steady-state levels necessary for health and survival in the face of challenge (Cannon, 1932).

Selye (1956) expanded upon Cannon's work by investigating the other primary system involved in stress: the hypothalamic–pituitary–adrenal (HPA) axis (i.e., the endocrine system). Namely, Selye focused on the release of hormones (glucocorticoids, GCs) from the adrenal cortex and their role in the stress response. He coined the concept of a General Adaptation Syndrome (GAS), which represents a reliable pattern of physiological reactions that correspond to the body's attempt to mediate resistance to a threat. The GAS hypothesis consists of three stages: an alarm stage (i.e., physiological activation of the HPA axis and the sympathetic nervous system [SNS] in preparation to deal with the threat), a resistance stage (i.e., the period following the initial reaction to the threat whereby the body mediates ongoing stress and attempts to return to steady-state levels), and an exhaustion stage (i.e., when a prolonged stress response overexerts the body's defense systems, thus draining it of its reserve resources and leading to illness). GCs were thought to be the primary mediator of the GAS. Because a large variety of harmful, physically based stressors produced the GAS and consistently resulted in ulcers, enlarged adrenals, and a compromised immune system when administered chronically, Selye referred to the stress response as being nonspecific in nature. Thus, whereas Cannon viewed stress in terms of the stressor, Selye's approach was to view stress in terms of the components of the stress response. Although subsequent work would demonstrate that not all stressors result in the same physiological response (e.g., depending on factors such as type and source of stressor, duration, perception, and appraisal), Selye's invaluable contribution to the field was to pioneer the exploration of the relationship between GC physiology and stress.

Munck et al. (1984) proposed a novel way to think about the role of GCs in the stress response that countered Selye's general viewpoint that GCs direct the stress response. Selye's idea that chronic stress leads to the GAS going awry and causing pathology such as rheumatoid arthritis was not compatible with findings summarized by Munck that GCs produce anti-inflammatory effects and actually provide relief from symptoms of rheumatoid arthritis. Munck et al. (1984) therefore hypothesized that GCs work to suppress, rather than enhance, the normal defense

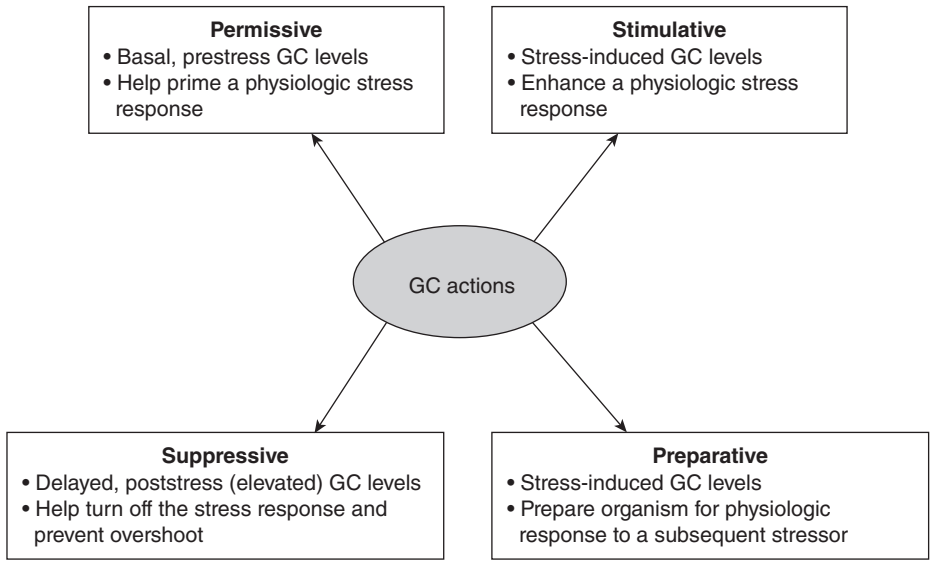

Figure 1.1 Overview of different types of GC actions with respect to the stress response. For a more detailed perspective refer to Table 1 in Sapolsky et al. (2000).

mechanisms that are activated by stress in order to prevent these systems from overshooting and seriously threatening homeostasis. In other words, GCs confer protection from the stress response. This hypothesis added to Selye's traditional view that the body is equipped to adapt to stressors, but had the added advantage of including a role of GCs that was in line with their actual physiological consequences. Sapolsky et al. (2000) updated Munck's view on GCs to include a more comprehensive set of preparative, simulative, permissive, and suppressive functions of GCs, depending on when examined with relation to the stressor, that further take into account the more rapid, as well as circadian, actions of GCs (see Figure 1.1 and Chapter 2 in this volume).

The predominately physiological-based concepts of homeostasis and the stress response were given a more psychologically based perspective through the works of John Mason and Richard Lazarus. For instance, Mason (1975) discovered that the GAS response could be modified based on situational and emotional factors, and that psychological interpretation of a stressor is necessary for the subsequent endocrine response to occur. Lazarus (1985) demonstrated that individual differences in various cognitive and motivational variables, such as appraisal and coping, can arbitrate the relationship between a stressor and the stress reaction. Thus, an evaluation of stressors determines their level of threat and their subsequent ability to elicit a stress response. Furthermore, Chrousos and Gold (1992) integrated the concept of individual differences based on genetic factors as an important consideration for measuring the stress response (see Chapters 26, 27, 28, and 29).

The body is designed to react in an efficient manner to the vast array of stressors it may experience. However, this reaction is clearly complicated, containing intricate physiological responses to restore homeostasis that are further modulated by environmental, behavioral, and psychological influences. There are instances (i.e., under intense or chronic conditions), though, when the demands that the stressors exert on the body outweigh the ability of the body to respond without a cost. Certainly over time there is an increasing price the body has to pay when continually trying to restabilize. To address this, a novel concept called *allostasis* was introduced to the stress field (McEwen, 1998). Allostasis refers to the ability of the body to achieve and maintain stability through change, and represents an adaptive coping mechanism in which various stress response processes are engaged during stress (McEwen, 2000a). Allostasis can be distinguished from homeostasis. In its purest sense, homeostasis refers to maintenance of processes that are essential for survival, and large divergences in these processes leads to death. Homeostasis by itself involves reaching a physiological equilibrium or set point in which adjustments carry no real price, whereas allostasis essentially refers to maintaining homeostasis throughout challenges and involves a network of mediators (e.g., behavioral, sympathetic, and neuroendocrine factors) that can exact a cost when the adjustments have to be maintained outside of their normal range for a period of time. The mediators of the stress response that fluctuate during a demand do not cause death, but rather, they maintain other homeostatic systems within the body, and can be stimulated even by the anticipation of a disturbance. To this end, the term allostasis is useful for illustrating the important distinction that adaptations are in place to promote and maintain survival mechanisms in the body, and that these adaptive responses are not confined to a critical range that implies death when breached. The cost (i.e., wear and tear) that these responses can exert over time, however, is referred to as *allostatic load* (McEwen, 2000a), and can result from either too much stress output (e.g., adrenal overactivity) or inefficient operation of the stress response system (e.g., inefficient shut-off or having an inadequate stress response to begin with). The key advantage of the allostatic concept is that it accounts for the ability of an organism to be adaptable and maintain its body in an altered state for a sustained period of time. The extent to which this occurs exacts a toll that could eventually manifest itself as a stress-related neuropsychological disorder (i.e., allostatic overload; see Chapters 16 and 17).

Overview of Stress-response Physiology

A detailed outline of the integration and execution of the various components of the stress response is beyond the scope of this chapter, but what follows is an introduction to the fundamentals of the SNS and HPA axis in relation to stress. At the most basic level, the stress response involves a series of SNS and endocrine responses that aim to restore stability within the body and promote the ability of an organism to deal with a threat. A critical feature of these systems is to mobilize energy

resources for instant use while simultaneously inhibiting body functions that are nonessential for immediate survival. Thus, heart rate, blood pressure, and blood glucose levels are elevated while digestive and reproductive processes are curtailed. Inflammation is reduced and pain perception is blunted. The immune response is immediately activated to promote defense, followed by processes put into place to prevent overshoot and the possibility of autoimmune damage. Components of the central nervous system (CNS) are activated, via neurotransmitter, neuropeptide, and hormonal messengers, to enhance learning and memory processes, and to further regulate maintenance of HPA output. Behavioral changes also occur, with organisms experiencing increased arousal and vigilance in order to identify and appraise threats within the environment.

At the core of an acute stress response is the initiation of the fight-or-flight response, which is characterized by its sympathetic-adrenal medullary components that serve as the *first response* to prepare the body for the energy resources it will require. Upon experiencing a threatening or stressful situation, the SNS is engaged and stimulates rapid release of catecholamine hormones (i.e., epinephrine and norepinephrine [or noradrenaline]) to direct autonomic processes. Norepinephrine is released from postganglionic fibers onto target organs, providing a local release of norepinephrine (see Figure 1.2). Sympathetic innervation of the adrenal medulla is cholinergic and arises from preganglionic fibers situated within the intermediolateral cell column of the spinal cord (Holgert et al., 1995). Upon activation, epinephrine and norepinephrine are released from the adrenal medulla into circulation. The collective result of SNS catecholamine release is a cascade of physiological effects including increased respiration rate, increased heart rate, dilation of skeletal muscle blood vessels, glycogen to glucose conversion, and vasoconstriction of digestive and reproductive organ blood vessels. These changes serve to selectively increase blood flow and oxygen/glucose availability to brain tissues and skeletal muscles that require energy to prepare for action (McCarty, 2000).

The hallmark neuroendocrine system response to stress involves activation of the HPA axis (see Figure 1.3). When a particular stressor is perceived, information is relayed to the parvocellular division of neurons located within the paraventricular nucleus (PVN) of the hypothalamus. It is from this brain control center that endocrine activity can be directed. Within the parvocellular neurons, the hypothalamic-releasing hormones known as corticotropin-releasing hormone (CRH; previously known as CRF) and arginine vasopressin (AVP) are synthesized. Upon PVN activation, the axons of these neurons projecting into the external zone of the median eminence release CRH and AVP into the portal blood system. This portal blood system feeds into the hypophysis (i.e., the pituitary gland), whereby CRH and AVP specifically target the synthesis and release of adrenocorticotrophic hormone (ACTH) from pituitary corticotrophs located specifically within the anterior pituitary. Although both CRH and AVP are ACTH secretagogues, CRH is considered to be more effective. Importantly, AVP synergistically potentiates CRH-elicited ACTH secretion, but by itself is actually a weak secretagogue (Rivier and Vale, 1983; Whitnall, 1993). As such, CRH is considered crucial for ACTH stimula-

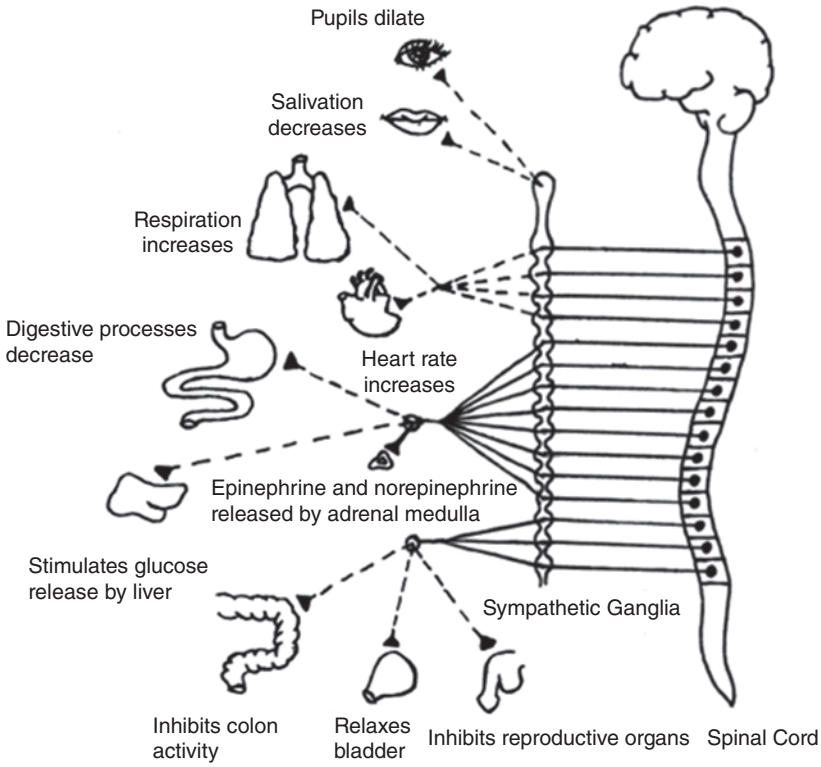

Figure 1.2 A basic representation of the SNS along with several of its targets. Activation of the SNS results in local release of catecholamines (i.e., norepinephrine) onto target organs, and stimulates additional catecholamine (i.e., both epinephrine and norepinephrine) release from the adrenal medulla. Solid lines represent preganglionic fibers and dashed lines represent postganglionic fibers.

tion during an acute stress response, whereas AVP is typically relegated to promoting maintenance of basal ACTH production (de Keyzer et al., 1997). However, during periods of chronic stress, AVP appears to play a more critical role in ACTH regulation. Indeed, under chronic stress conditions there is a marked shift in hypothalamic CRH/AVP signal in favor of AVP, as well as a downregulation of CRH receptors within the anterior pituitary, suggesting a dynamic role for AVP in mediating the stress axis (Scott and Dinan, 1998).

Stimulation of the anterior pituitary corticotroph cells via activation of a CRH/AVP receptor (i.e., CRH type 1 and V1b, respectively) results in a signal transduction cascade that leads to transcription and translation of the ACTH precursor protein, proopiomelanocortin (POMC), and subsequent cleavage of ACTH as one of its products. ACTH released into the circulating bloodstream travels to the adrenal gland, whereby it binds to cells located in the zona fasciculata of the adrenal cortex. The binding of ACTH to its receptor (i.e., melanocortin type 2) initiates a cascade

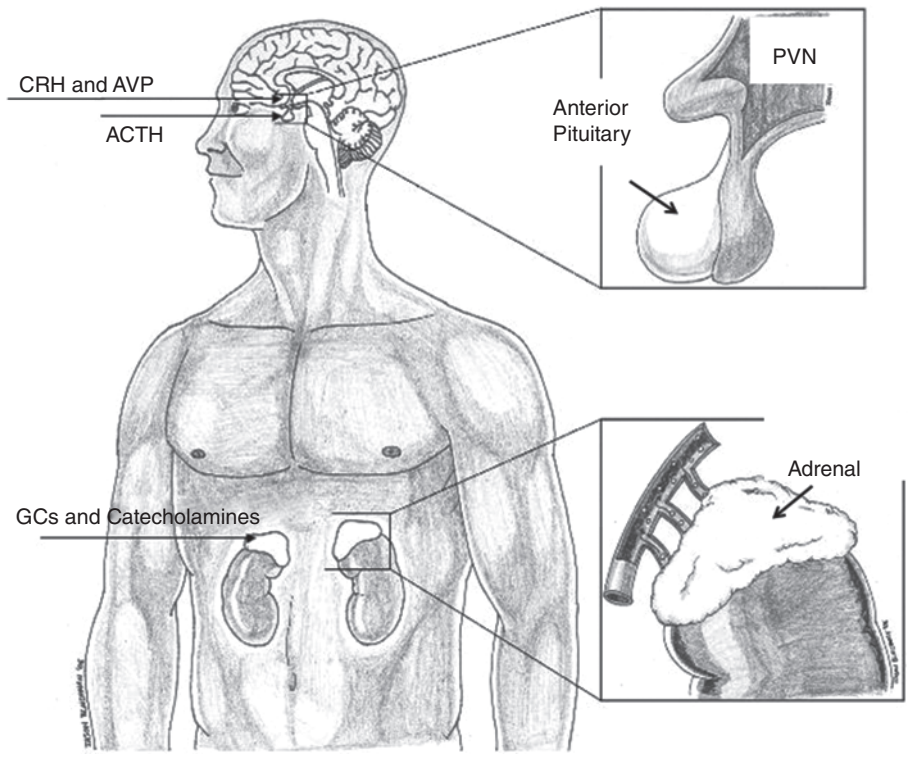

Figure 1.3 An illustration of the primary components of the HPA axis. In response to stress, CRH and AVP are released from parvocellular neurons within the PVN of the hypothalamus into the hypophysial portal blood system. CRH and AVP then stimulate synthesis and release of ACTH from the anterior pituitary gland. ACTH travels through the bloodstream to the triangular adrenal glands located above the kidneys where it stimulates the synthesis and release of GCs from the adrenal cortex. Activation of the SNS in response to stress concurrently stimulates the release of catecholamines from the adrenal medulla. *Source:* Figure drawn by Jason Blaichman. Used with permission of Sonia Lupien.

of intracellular enzymatic events that converts free cholesterol into GCs via a steroidogenic pathway (Hall, 2001). Subsequently, GCs (referred to as corticosterone in rats and cortisol in humans) diffuse away from the cell and are released into circulation. Within the blood, the highly lipophilic GCs bind reversibly to corticosteroid-binding globulin (transcortin) and serum albumin where they remain inactive while transported throughout the body. GCs remain inactive while in this bound state, and thus these binding proteins, through up- or downregulation, can be used to regulate GC actions. It is important to note that although ACTH is the predominate regulator of GC synthesis and production from the adrenal cortex, there are extra-ACTH forms of adrenal cortex regulation, including hormonal signals from the adrenal medulla, cytokine stimulation from peripheral circulation, and direct neu-

ronal control via SNS innervation of the adrenal cortex that also mediate GC release (Ehrhart-Bornstein et al., 2000; Ulrich-Lai and Engeland, 2005).

GCs act at two different receptor subtypes: mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs) (Reul and de Kloet, 1985; see also Chapter 3). Each receptor is characterized by a differential affinity profile for its endogenous ligands. MRs have a high and relatively equal affinity for both GCs and aldosterone. In contrast, GRs have a much lower affinity for GCs compared to MRs, but they are more selective for GCs over aldosterone (i.e., they are GC-preferring receptors). Given these differential receptor properties, it is generally believed that MRs are typically saturated under resting conditions, whereas GRs are predominately activated during periods of high GC levels (e.g., during a stress response). Moreover, GCs can be further regulated by enzymes 11β hydrosteroid dehydrogenase type 1 (11β-HSD1) or type 2 (11β-HSD2), which can activate or inactivate GCs, respectively (Funder et al., 1988; Seckl et al., 2005). The brain is nearly devoid of 11β-HSD2, which enables GCs to influence cells via both MRs and GRs. Traditional GRs are located within the cytoplasm of a cell and are translocated into the nucleus upon binding with a GC (which enters the cell via passive diffusion), where they subsequently function as transcription factors to regulate gene expression (Chrousos and Kino, 2009). GCs are able to produce faster actions, however, whereby they rapidly hyperpolarize and inhibit neuron firing within regions such as the hippocampus and hypothalamus, likely through an as-yet-unidentified cell membrane receptor subtype (Orchinik, 1998). Within the brain, MRs are more localized to sensory and limbic structure neurons (Reul et al., 2000) whereas GRs exhibit widespread distribution (Fuxe et al., 1985). Importantly, GR levels are high throughout limbic structures, the brainstem, the PVN, and the pituitary gland (de Kloet et al., 2005b).

GCs serve many important functions related to regulation of the stress response. In one respect, GCs play a permissive role in the stress response, such as stimulating gluconeogenesis, aiding the catabolic processes mediated by cathecholamines, priming neural regions involved in sensory processing, attention, and adaptive responding, and directing/regulating immune and inflammation response mediators (Dhabhar and McEwen, 1996; Buckingham, 2000; Sapolsky et al., 2000). On the other hand, GCs also play a suppressive/protective role via robust immunosuppressive and anti-inflammatory actions, as well as enhancing glucose transport to the CNS and cardiovascular tissues that require a high-energy demand (Buckingham, 2000; Sapolsky et al., 2000). Importantly, GCs also work within critical brain regions (e.g., hippocampus and amygdala) to facilitate learning and memory processes that promote adaptive behaviors in response to a particular stressor in the future (Korte, 2001; see also Chapters 8–12). Thus, GCs are essential in facilitating response to a pending or ongoing stressor and reducing the stress response once responding is no longer necessary, as well as preparing the organism for future threats. In general, the permissive actions of GCs are thought to be predominately mediated via MRs, given that these effects occur when GCs are at prestress basal levels in which the high-affinity MRs are saturated. The suppressive actions occur under conditions

of high, stress-induced levels of GCs in which the GRs are sufficiently occupied (de Kloet et al., 1998).

Although Selye originally proposed that the stress response is nonspecific, it has since been established that not all stressors elicit an identical combination of responses (Pacak et al., 1998). Although there is a general conformity among stressors' ability to provoke eventual release of GCs and catecholamines, the arrangement of responses of these hormonal signals fluctuates depending on factors such as the type of stressor, the current physical state on the organism, arousal/appraisal, and the use of psychological/behavioral coping mechanisms (Goldstein and Kopin, 2007; see also Chapter 29). In addition, each type of stressor is proposed to have its own *neurochemcial identity*, such as variations in the ratio of CRH/AVP release or variations in interactions between GCs and other transcription factors during negative feedback, which result in an altered picture of the overall stress response depending on the type of stressor (Jessop, 1999).

Overview of Key Stress Response Mediators

One of the key regulators of the HPA axis stress response is the GC products themselves. Following the initial reactions to a stressor, GCs function to return the organism back to a balanced state via negative-feedback mechanisms to suppress further HPA activity. GC-mediated negative feedback occurs at multiple levels, thus presenting a redundancy in regulation to ensure the stress response effectively serves its purpose without being detrimental. The key sites of action include regulation at the level of the hippocampus, PVN, and pituitary gland. Hippocampal activation via GCs (likely mediated through GRs) results in enhanced inhibitory γ-aminobutyric acid (GABA)-ergic tone surrounding the PVN, thus inhibiting HPA function (Joëls and de Kloet, 1993). At the PVN and anterior pituitary, GCs exert negative feedback primarily via GR activation and subsequent transrepression whereby the GC–GR complex interacts with transcription factors, such as activator protein 1 (AP-1), Nurr77, and cAMP-response-element binding protein (CREB), to prevent transcription of *CRH* and *POMC* genes (Pearce and Yamamoto, 1993; Martens et al., 2005).

In line with the different locations and mechanisms of GC feedback, there is also a temporal characterization involved. Rapid GC feedback occurs within seconds to minutes of the stress response, and is characterized by the ability of GCs to inhibit CRH/ACTH release prior to alterations in genomic processing, likely via interactions with cell membrane receptor molecules on PVN parvocellular neurons and pituitary corticotrophs (Dallman, 2005). An intermediate time course for GC feedback, typically beginning around 30 min following a stress response and lasting for hours, is characterized by protein synthesis blockade as discussed above and serves to blunt HPA activity without completely abolishing it (Dallman, 2000). A slower form of negative feedback also occurs following chronic, high-level exposure to GCs

over days or weeks, and is characterized by inhibited CRH/AVP and POMC mRNA expression throughout the PVN and anterior pituitary, resulting in lack of responsiveness to additional stressors (Keller-Wood and Dallman, 1984; Dallman, 2000). In addition to these mechanisms of GC feedback, local ACTH released from the anterior pituitary can also act at the level of the pituitary and the PVN to dampen release of itself and CRH/AVP via short-loop negative feedback (Sawchenko and Arias, 1995).

In addition to hormonal feedback, the HPA axis is regulated by a variety of CNS inputs, including the brainstem and corticolimbic structures. The nature of a stressor (i.e., a systemic stressor compared to a psychogenic) dictates the neural pathway that is utilized to activate/regulate the PVN (see Figure 1.4). For example, an internal

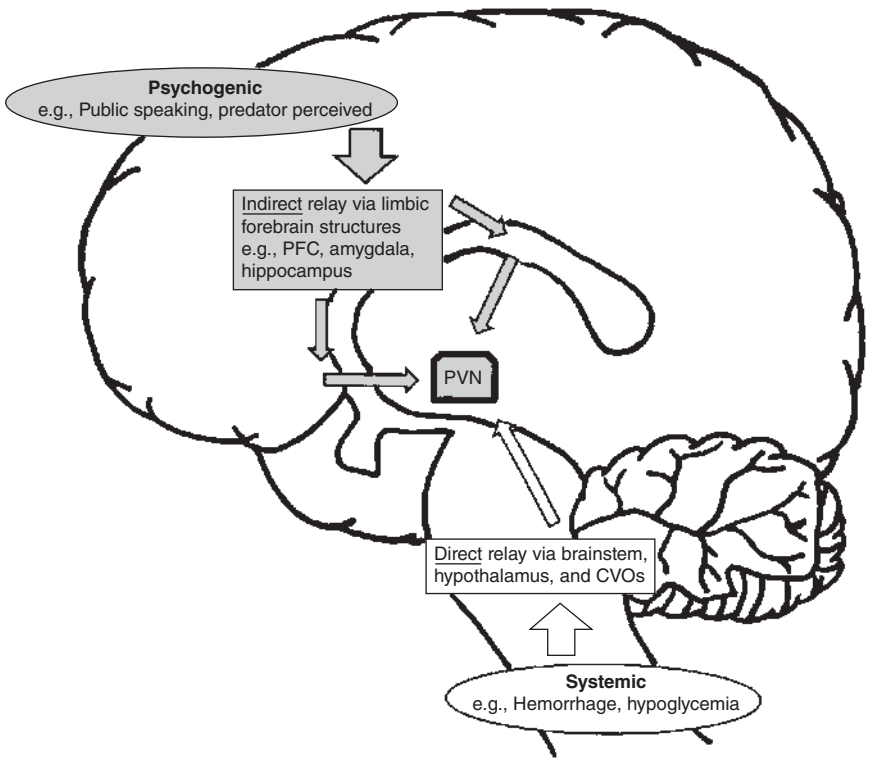

Figure 1.4 A basic overview of regional processing and input depending on type (psychogenic or systemic) of stressor. Psychogenic (psychological) stressors are relayed indirectly to the hypothalamic PVN via higher-level engagement of limbic forebrain structures that are involved in the anticipation and appraisal of potentially stressful circumstances. In contrast, systemic (physiological) stressors are relayed directly to the PVN via ascending input from brainstem structures, as well as other subnuclei of the hypothalamus and circumventricular organs (CVOs) containing osmoreceptors and additional homeostatic sensors. PFC, prefrontal cortex.

systemic stressor that possesses an immediate physiological threat, such as hemorrhaging, would likely be transmitted directly to the PVN via catecholaminergic projections arising from the nucleus tractus solitarus located in the brainstem (Herman and Cullinan, 1997). On the other hand, a psychogenic stressor that requires anticipation and evaluation, such as preparing to talk in front of a group, will primarily be processed by higher corticolimbic brain structures before being relayed indirectly to the PVN (Herman and Cullinan, 1997). Stressors that possess both a cognitive and physical component, such as restraint stress, will utilize both somatosensory processing in the brainstem nuclei and corticolimbic processing via regions such as the prefrontal cortex, hippocampus, and amygdala to stimulate the PVN (see Chapter 2 of this volume for further detail on psychogenic and systemic mechanisms).

The locus coerulus (LC)-noradrenergic system located within the pontine brainstem mediates the stress response by directing the processes of arousal and attention. In the face of a challenge, it is highly adaptive to experience-increased arousal and sensory processing in order to promote the detection and processing of a stressor while simultaneously ignoring nonessential features of the environment. Norepinephrine released from the brainstem serves as an alert signal that activates both the sympathetic and neuroendocrine legs of the stress response, as well as higher brain structures such as the prefrontal cortex (PFC), hippocampus, and amygdala involved in fear-related behaviors and memories (Chrousos, 2009). The PVN and LC share reciprocal connections, with CRH-containing neurons projecting to the LC and activating it via CRH type 1 receptors (Schulz et al., 1996). During a stress response, CRH increases tonic discharge of the LC and alters sensory responding by reducing overall signal-to-noise ratio (i.e., discharge in response to a novel stimulus is attenuated; Valentino and Foote, 1987). This pattern of LC firing is associated with a shift from focused attention to scanning attention (Valentino and Wehby, 1988), and allows an organism to stay alert and aroused within a dangerous or threatening environment. Furthermore, this attention pattern may facilitate acquisition of information related to a stressor, thereby giving an organism a better opportunity of forming a stress-related memory and retaining it for future retrieval. In general, norepinephrine release results in widespread increase in cortical and hippocampal electroencephalographic activation, further suggesting that CRH-elicited stimulation of the LC-noradrenergic system may increase arousal as well as additional behavioral/affective processes related to the stress response (Berridge, 2005).

Cytokines released during inflammation stress are also potent regulators of the HPA axis. Peripheral cytokines gain access to the hypothalamus (likely via openings in the blood–brain barrier, such as the median eminence, area postrema, and choroid plexus; Saper and Breder, 1994) and stimulate parvocellular CRH/AVP neurons (Habu et al., 1998). In addition, peripheral cytokines can be detected by sensory fibers that activate brainstem nuclei, which in turn send direct inputs to activate the PVN. Evidence also suggests that cytokine-mediated ACTH secretion can occur via a CRH-independent mechanism (Bethin et al., 2000). Indeed, cytokines

can act directly at the level of the anterior pituitary gland to stimulate POMC expression and subsequent ACTH release (Pereda et al., 2000). By activating the HPA axis, and subsequently eliciting GC secretion, cytokines effectively can regulate (i.e., repress) their own inflammatory effects.

Overview of the Stress Response Following Chronic Stress

The stress response can be remarkably different depending on factors such as history and duration of stress experience. Much of what has been discussed thus far has centered on the stress response elicited by an acute stressor. To reiterate, the cascade of endocrine, sympathetic, and CNS events that occur in response to an acute stressor serve an adaptive function of regulating appropriate physiological and behavioral reactions to a threat while simultaneously maintaining balance and preventing system overshoot/damage. However, circumstances in which an organism is exposed to chronic stress result in an altered stress-response profile. Chronic exposure to a repeated daily stressor, such as restraint stress, is associated with a profile of elevated HPA activity (i.e., high plasma ACTH and GC levels) that persists for the first few days but eventually returns to normal levels, possibly reflecting diminished regulatory input into the HPA axis (Kant et al., 1983). For instance, the phenotypic profile of HPA inputs following chronic restraint stress includes hypertrophy within the amygdala, dendritic remodeling and reduced cell proliferation within the hippocampus, and downregulation of MR and GR expression throughout the limbic system (see Conrad, 2006; de Kloet et al., 2005a; Joëls, 2011; see also Chapters 7 and 10). Sustained chronic stressors, such as chronic inflammation, are characterized by lasting high levels of plasma GCs and ACTH that do not return to baseline, likely due to dysregulated negative-feedback mechanisms (Harbuz et al., 2003). Interestingly, parvocellular PVN CRH expression and release is diminished under these conditions while AVP expression and release is elevated, suggesting that AVP may mediate high HPA axis activity during sustained chronic stress (Aguilera et al., 2008).

It has been well documented that an acute stressor can elicit an altered stress response depending on an organism's history with either that particular stressor or other stressors in general. For example, an animal repeatedly exposed to restraint stress, compared to a naïve animal, will demonstrate a blunted ACTH and GC response upon an acute exposure to restraint. In this case, acute exposure to restraint stress is referred to as a homotypic stressor for the animals with a prior history of chronic restraint (Dallman et al., 2000). In contrast, compared to a naïve animal, an animal with a history of chronic restraint stress will demonstrate an exaggerated ACTH and GC response upon exposure to a different type of stressor (e.g., foot shock). An acute stressor that is novel compared to the chronic stressor is referred to as a heterotypic stressor (Dallman et al., 2000). An elevated stress response to a heterotypic stressor is not limited to HPA axis output, as rats repeatedly exposed to immobilization stress also display an exaggerated sympathoadrenal stress response

to a heterotypic stressor compared to control (unstressed) animals (Dronjak et al., 2004). HPA axis modulation via amygdala input, which itself integrates information from the paraventricular thalamus and raphe nucleus while processing emotional and memory components of stressors, appears to be central in mediating an organism's habituation/adaptation to homotypic stressors and exacerbation to heterotypic stressors (Dallman et al., 2000).

Emotional Response to Stress

Humans typically interpret stress with an emotional response. In response to a stressor, SNS activation of visceral structures such as the heart, stomach, epidermis, and other organs generates physiological changes that may lead to a perception of an emotion (Heilman, 1994). This peripheral response is closely integrated with CNS components that are involved in the evaluation and regulation of emotion necessary for behavioral changes that allow an organism to adapt to the environment. For example, when confronted by a threatening individual in a dark alley, the arousal would elicit a physiological response (e.g., tachycardia and vasoconstriction) that not only prepares the individual to flee as a means of self-preservation, but also provides affective cues as a motivation strategy to immediately avoid a possibly harmful situation (Jelen and Zagrodzka, 2001). Learning (both implicit and explicit) as a result of prior exposure plays an important role in mediation of the stress response. In humans this includes imagination of rational or irrational events. For example, just imagining a negative stimulus or situation can elicit similar physiological responses and feelings as if in the actual presence of the elicitor (Behar et al., 2005).

Negative emotional responses can guide behaviors both subconsciously and consciously (Hermans et al., 2002), and influence the way an organism interacts with its environment. However, negative emotions elicited from a stressor are not always perceived as stressful. The experience of the emotion requires higher cognitive processes for evaluation of the organism's physiological state. Cognitive appraisal of stimuli (actual or imagined) can lead to positive or negative emotions. When the appraisal is of internally represented cognitive goals, interruption of attainment of these goals can also lead to negative emotions (e.g., anger) and subsequent stress (Damasio, 1999).

Stress and Cognition

GCs effect both memory consolidation and memory retrieval (Roozendaal, 2002; Chapters 8 and 9). The GC effect on memory consolidation depends primarily on noradrenergic activation of the basolateral complex of the amygdala and subsequent interactions with other brain regions (Roozendaal et al., 2004). For example, the human amygdala and hippocampus interact to encode emotional information

for learning and memory (Phelps, 2004). Furthermore, evidence indicates that negative emotional events enhance accuracy in recalling details of long-term memories (Kensinger, 2007). Although stress may elicit emotions that enhance learning and memory-related processes, GCs have an inverse effect when it comes to retrieval processes under stressful conditions (Kuhlmann et al., 2005).

In the following sections we delineate the neuroanatomical substrates of emotional regulation and related behaviors, as well as the effects of chronic stress on both the neurobiology and function of these regions and neural networks observed in individuals suffering from psychiatric disorders.

Neuroanatomy of Emotional Regulation

The ability to regulate emotional responses to stressors can theoretically impact long-term health outcomes as well as aspects of neuropsychological functioning. Both endogenous and exogenous stimuli can elicit a stress-related physiological response (Knight et al., 2005). As mentioned above, a number of neuroanatomical substrates and neurochemicals are responsible for eliciting and mediating a stress response. Recently, cognitive neuroscientists have focused on cognitive processes involved in top-down regulation of emotions as well as the neural underpinnings that support these processes (Pecchinenda et al., 2006; Dretsch and Tipples, 2008; Knight et al., 2010). Studies using functional magnetic resonance imaging have shown that emotional regulation depends on interactions between cortical and subcortical regions (Knight et al., 2010). This mediation has been referred to as implementation of cognitive control on limbic regions. In particular, the PFC plays a paramount role.

A multitude of processes of the PFC are implicated in regulation of emotional responses (see Figure 1.5). The PFC comprises approximately one third of the entire cortex, and lies anterior to the premotor cortex and supplementary motor area. The PFC may be subdivided into three regions: the dorsolateral prefrontal cortex (dlPFC), the orbitofrontal cortex (OFC), and the frontopolar prefrontal cortex (fPFC) (Happaney et al., 2004). The dlPFC receives input from the parietal and inferior temporal visual cortex and is primarily known for its involvement in spatial and object working memory (Roberts et al., 2004). Evidence reveals that the dlPFC is implicated in top-down regulation of emotion through learning processes and control of attention (Knight et al., 2010; McRae et al., 2009). The OFC constitutes part of the reward-processing network and is an important region for emotional regulation (Rolls, 2004). The OFC is part of the frontostriatal dopaminergic circuit which has strong connections to the amygdala and other parts of the limbic system, including connections with the basal ganglia, somatosensory cortices, and insula (Krawczyk, 2002). The anatomical positioning of OFC is optimal for the integration of affective and nonaffective information, and the regulation of motivational responses and emotional processing (Rolls, 2004). The fPFC, the most anterior part of the frontal lobes, is implicated in subgoal processing, multitasking,

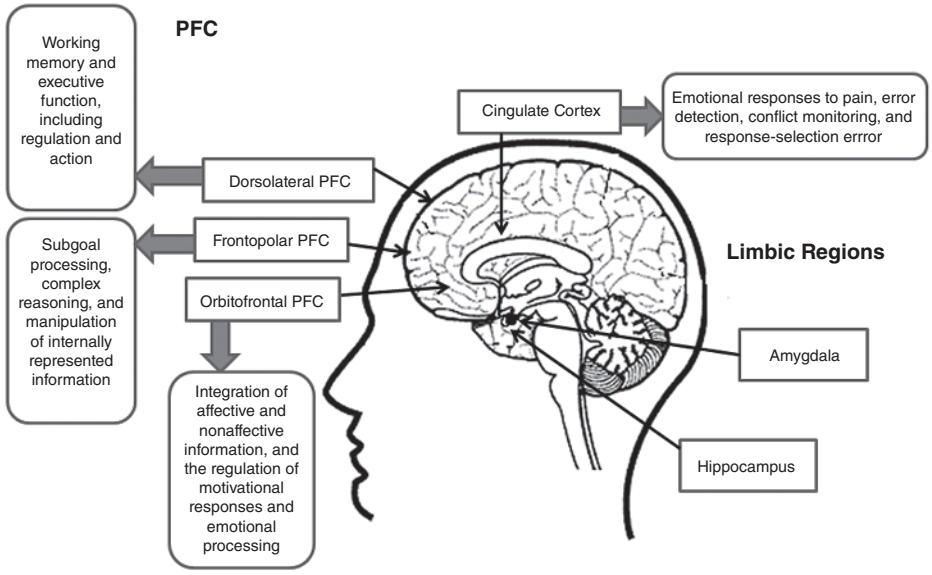

Figure 1.5 A depiction of specific regions of the PFC implicated in top-down regulation of emotional responses that rely on various limbic structures.

complex reasoning, and manipulation of mentally represented information (Krawczyk, 2002; Koechlin and Hyafil, 2007). The cingulate cortex, although not directly part of the PFC, has been shown to work closely with the dlPFC and OFC in regulatory processes that encompass the processing of pain, cognitive control, performance monitoring, error detection, conflict monitoring, and response selection (Carter et al., 1998; Shima and Tanji, 1998; Turken and Swick, 1999). More specifically, neuroimaging evidence suggests that the caudal anterior region of the cingulate is involved in pain processing (Bentley et al., 2003) and that the posterior cingulate is involved in self-reflecting on one's emotions (Ochsner et al., 2004). Although functionally there is some casual independence between regions and subareas of the PFC, there is considerable overlap in not only functionality, but also cortical layering, cellular density, and organization used for defining the cytoarchitecture of the frontal lobes. Most of these regions work in concert with midbrain structures as part of a neural network for regulating emotion, behavior, and motivation.

Stress Pathology: Brain Structure and Function

Much of the evidence supporting stress-related pathophysiological changes in various cortical and subcortical structures is derived from clinical studies. For

example, for posttraumatic stress disorder (PTSD) the neurobiological changes that impact both functions and structure have been well documented (Lanius et al., 2006). Individuals with depression and PTSD often display neurocognitive deficits in attention and memory (Rokke et al., 2002; Vasterling et al., 2002; Dretsch et al., 2010). However, some evidence suggests that these neurocognitive deficits are not a product of stress-related neurobiological changes, but rather represent premorbid vulnerability to the development of PTSD (Breslau et al., 2006).

Reductions in cortex volume, histopathologic changes, and abnormal activation of subregions of the OFC, such as the medial prefrontal cortex (mPFC), are also implicated in the mediation of the stress response and emotional behaviors associated with mood disorders (Drevets, 2000). Reduced hippocampal volume has been linked with depression (Rao et al., 2010) and anxiety disorders such as PTSD (Karl et al., 2006). Brain-imaging techniques have shown that PTSD is associated with reduced overall white matter and smaller hippocampal volume (Villarreal et al., 2002) and abnormal functioning of the amygdala, cingulated cortex, and mPFC (Williams et al., 2006).

Stress Resilience: Genes, Endophenotype, and Neuropsychological Functioning

Individual resilience to stress can be studied at many levels (see Figure 1.6). The degree to which individuals respond physiologically and emotionally to stressors, the time that it takes to recover from the response, and the temporal frequency and duration of stressful events must all be taken into consideration when discussing resilience. The complex interplay of genetics with environmental factors, such as the serotonin transporter gene and traumatic experiences in early life, can modify capacity to cope with stressors and contribute to psychopathology (Feder et al., 2009). By comparing group differences characterized by the serotonin transporter allele, neuroimaging research suggests that the stress response is mediated by genetic variations in neurotransmitter modulation (Hariri et al., 2002; Heinz et al., 2007). Other evidence reveals that amygdala activation in response to stress is mediated by variations in neuropeptide Y haplotype (Zhou et al., 2008). Neuropeptide Y is abundantly expressed in regions of the limbic system that are induced by stress and arousal, and is implicated in the assignment of emotional valences to stimuli and memories (Heilig, 2004). Many other genetic haplotypes and polymorphisms, such as catechol-O-methyltransferase (also known as COMT) and brain-derived neurotrophic factor, have been implicated in resilience to stress (Feder et al., 2009). Although many gene–gene and gene–environment interactions that underpin individual systems (e.g., HPA axis) and neural circuitry (e.g., regulation of emotion and behavior) of resilience to stressors have been identified, there is a need for continued advancements in neuroscience techniques to further explore these interactions.

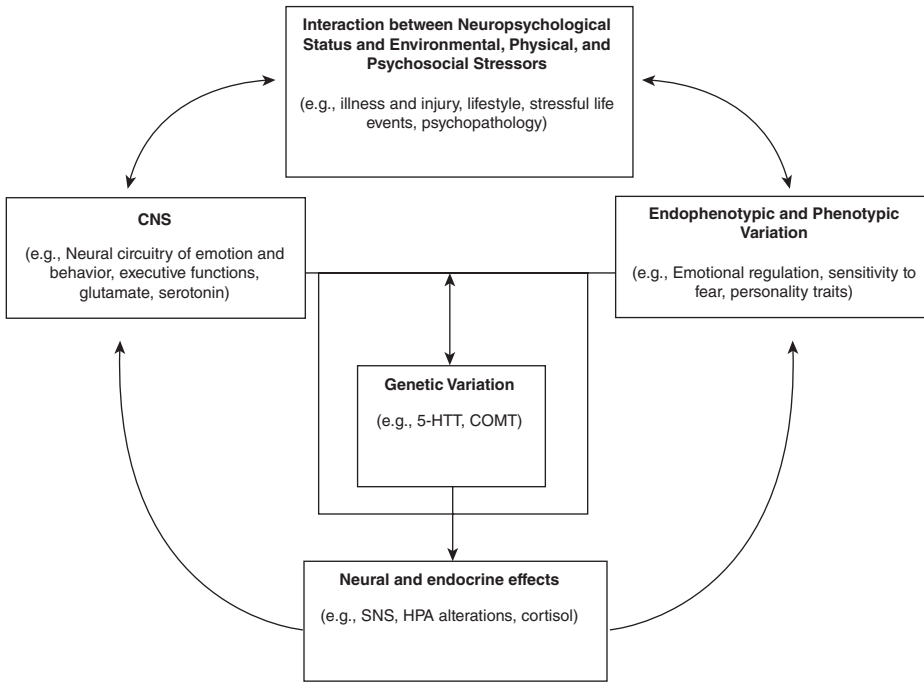

Figure 1.6 A representation of direct and causal linkages between neurobiological systems and environmental and psychosocial stressors. COMT, catechol-O-methyltransferase; 5-HTT, 5-hydroxytryptamine transporter.

Evidence also reveals that the genetic influence on stress response can be expressed outwardly, as observed with intermediary phenotypes (Krueger, 2000). For example, cognitive vulnerabilities, which are trait-like characteristics such as negative attributional style and rumination, are posited to contribute to both the development and maintenance of PTSD symptoms (Elwood et al., 2009). Twin studies have provided evidence which suggests that self-perceptions of coping with stress contribute to stress response, as indexed by endocrine markers (Wüst et al., 2000). Hence, personality trait differences influence the perception of acute and chronic stress and have been shown to mediate mental health outcomes (Lawrence and Fauerbach, 2003).

Given that resilience to stress is such a dynamic concept, the integrity of neuropsychological functioning may be one of the paramount predictors of stress resiliency. For example, executive functions moderate all of the stages of the stress response—exposure, reactivity, recovery, and restoration (Williams et al., 2009)—and have been associated with temperament, personality, and psychopathology (Hariri, 2009). Furthermore, persistent findings of impaired executive functioning in stress-related disorders, such as PTSD, provide some evidence of a vulnerability factor (Leskin and White, 2007). In fact, general intelligence (IQ) has been associ-

ated with decreased risk for the development of PTSD (Breslau et al., 2006). Resilience to stress requires many levels of investigation on genetic, endophenotypic, phenotypic, and psychosocial mediators of neural circuits that regulate fear, reward, emotion, and behavior. The concerted interactions of such systems underpin successful coping and resilience to stress.

Concluding Remarks

The stress response is an evolutionary mechanism that is essential for bioregulation to allow internal adaptation as well as to prepare an organism for manipulation of behavior and environment to maintain homeostasis. Across organisms there is a well-defined set of SNS and endocrine systems in place to stimulate and regulate the stress response. The CNS also plays an important role in further initiating, processing, and modifying components of the stress response.

The human stress response, although an adaptive process, is mediated by genes and moderated by higher neuropsychological processes, which can result in chronic and eventually deleterious effects on individual biological systems, including those that impact cardiovascular, metabolic, immunological, and neurological health. In the most complex organ in the body, the brain, neurobiological alterations in response to chronic stress are becoming better understood with advancements in the neurosciences. In particular, brain-imaging techniques have provided evidence of both structural and functional abnormalities associated with various stress-related psychopathologies such as PTSD and depression. Although some of the differences between healthy individuals and those suffering from a psychiatric condition, such as PTSD, may have etiologies that differ depending on interactions with the environment, evidence suggest that such differences reflect premorbid vulnerability factors. Even though strides have been taken to understand the gene–environment interplay that contributes to the development of stress-related psychopathology, much work still needs to be completed to understand how to increase resiliency, optimize interventions, and improve the efficacy of treatments for such conditions.

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