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Edited by Steven M. Southwick, Brett T. Litz, Dennis Charney and Matthew J. Friedman

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Section 1

Pathways to resilience

Chapter

Neurobiology of resilience

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Introduction

Resilience is commonly conceptualized as the ability to adapt and thrive despite experiencing adversity (Masten *et al.*, 1995; Elder, 1998; Masten & Coatsworth, 1998). A resilient individual has been tested (Rutter, 2006) and continues to demonstrate healthy psychological and physiological stress responses (McEwen, 2003; Charney, 2004). For most, it is possible to conjure an image of such a person: a woman who chooses to work with sexual assault survivors after she herself is raped; a child growing up in poverty who earns a scholarship to college; a hurricane survivor who rebuilds her own home and helps to revitalize her community.

For over three decades, scientists have worked to identify the states and traits characteristic of resilience, with the aim of developing more effective and more diverse evidence-based prophylactic and treatment interventions to combat the deleterious impact of stress on human body and brain. While the value of understanding the neurobiological substrates of resilience has always been appreciated, the lack of tools available to assess the integrity of neural structure and function has impeded progress. Hence, early research on resilience focused on illuminating the psychological and social determinants of stress resistance (Rutter, 1985; Masten & Coatsworth, 1998; Masten, 2001; Bonanno, 2004).

While recent advances in scientific technology have made the exploration of biological processes associated with resilient phenotypes more feasible, it remains constrained by reliance on behavioral observations and self-report to identify resilient individuals. Because we have very few direct measures of neural health, a person's descriptions of his or her internal experience and the degree of functional impairment observed must serve as its proxy. Hence, it is not surprising that

researchers have had difficulty operationalizing resilience on a neurobiological level. Some neuroscientists have focused on the capacity to experience stress without developing mental illness (Conrad & Hammen, 1989; Tiet *et al.*, 1998; New *et al.*, 2009); others have placed less emphasis on the development of psychiatric symptoms and, instead, focus on the ability to recover from a mental illness with (or without) treatment (Nitschke *et al.*, 2009).

We believe that a different archetype will be necessary as neuroscience progresses and scientists come to define neural health with increasingly accurate biological assays, and become less dependent on behavioral measures. In order to articulate the formulation of resilience employed in this chapter, we return to its original meaning as defined by physicists: the capability of an object to resume its original size and shape after deformation. While maintaining a clear parallel with the definition of resilience utilized in psychosocial investigation, this signification is more easily translated into a neurobiological model: acute adaptations in neural systems in response to stress constitute deformation, and the ability of those systems to resume optimal or pre-stress operations is resilience.

Allostasis and resilience

Homeostasis is the maintenance of the small set of physiological states that must be rigidly preserved to ensure survival. Even minute changes in variables such as temperature, osmolarity, pH, or oxygen tension will result in death. In contrast, a multitude of other parameters can be, and often are, altered. Such modifications constitute the body's efforts to respond to and counteract stressors that could disturb homeostasis. Sterling and Eyer (1988) introduced the term allostasis to describe this dynamic regulation of secondary

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[More information](#)**Section 1: Pathways to resilience****Table 1.1** Key terminology.

Term	Definition
Homeostasis	Maintenance of those states essential to survival (pH, osmolarity, temperature, oxygen tension, etc.)
Stress	Stimulus or stimuli that threaten homeostasis
Allostasis	Dynamic regulation of non-essential set-points in response to stress in order to preserve critical variables
Allostatic load	The damage the body incurs as a result of allostasis
Resilience	The degree to which the body is able to minimize allostatic load

set-points in defense of homeostasis. Subsequently, McEwen and Stellar (1993) observed that, while essential to survival, any allostatic deviation from the optimal internal milieu takes a toll on the body. They coined the phrase “allostatic load” to refer to the physiological cost of adaptation to stressors. In this context, the severity of the allostatic load, as a measure of the brain’s inability to resume its pre-allostatic state, is inversely proportional to the degree of resilience. That is, resilience is the capacity to minimize allostatic load. Table 1.1 summarizes these definitions.

In this chapter, we begin by reviewing the systems most directly involved in the acute stress response, highlighting both their contribution to allostasis and their allostatic load. The genetic, physiological, psychological, and environmental factors that appear to contain allostatic load and, therefore, promote resilience are also delineated. Subsequently, we describe other variables whose allostatic role is less clear but are known to modulate the intensity and efficacy of the acute processes and, therefore, to influence resilience. We conclude with a discussion of emerging integrated models of resilience and the potential applications of this work.

Acute stress-response systems

The hypothalamic–pituitary–adrenal axis

The hypothalamic–pituitary–adrenal (HPA) axis, composed of the hypothalamus, pituitary, and adrenal glands, is the primary mechanism responsible for coordinating the body’s response to stress. When a stimulus is perceived as threatening, the paraventricular nucleus of the hypothalamus releases corticotropin-releasing hormone (CRH) and arginine-vasopressin into the portal vessels. These subsequently trigger the production and secretion of adrenocorticotrophic hormone (ACTH) from the anterior lobe of the pituitary.

This, in turn, stimulates increases in the production and release of the glucocorticoids cortisol and dehydroepiandrosterone (DHEA) from the adrenal gland (Rosenfeld *et al.*, 1971). The glucocorticoids travel throughout the body inciting the physiological changes required to cope with the stressor.

Allostatic contribution

Cortisol promotes arousal, attention, and memory formation and increases blood glucose and blood pressure, while suppressing growth, reproductive, and immune processes. By comparison, DHEA, its sulfated derivative (DHEA-S), and its metabolites have antiglucocorticoid and antiglutamatergic properties in several tissues, including the brain (Browne *et al.*, 1992), and appear to support memory and cognition (Rose *et al.*, 1997). They deter corticosteroid-induced hippocampal neurotoxicity by interfering with the glucocorticoid receptor (GR) uptake in the hippocampus (Kimonides *et al.*, 1998; Bastianetto *et al.*, 1999; Morfin & Starka, 2001), and they amplify long-term potentiation of hippocampal neurons, likely by modulating transmission at the N-methyl-D-aspartate (NMDA) receptor (Chen *et al.*, 2006).

Allostatic load

Chronic excessive cortisol exposure is thought to increase vulnerability to hypertension, immunosuppression, osteoporosis, insulin resistance, truncal obesity, dyslipidemia, dyscoagulation, atherosclerosis, cardiovascular disease (Whitworth *et al.*, 2005), anxiety, and depressive disorders (Carroll *et al.*, 2007). A substantial body of literature exploring cortisol dysregulation in major depressive disorder (MDD) and post-traumatic stress disorder (PTSD) has emerged in the past few decades (reviewed by Handwerger, 2009). Handwerger concluded that the available literature links the development of PTSD after single-trauma exposure to chronic

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(if not acute) reductions in basal cortisol levels, relative suppression of the cortisol response in the low-dose dexamethasone suppression test, and heightened cortisol responses in anticipation of, and in response to, stress. These findings support a hypothesis that the GRs of the HPA axis are hypersensitive in single-trauma PTSD. However, as Handwerger (2009), notes, patients with PTSD and histories of chronic or multiple traumas such as child abuse often display different patterns of cortisol dysregulation than either healthy volunteers or individuals with PTSD precipitated by a single adulthood trauma. She posits that this mediator may account for conflicting findings in the literature (e.g., Baker *et al.*, 2005; Inslicht *et al.*, 2006; Wheler *et al.*, 2006).

In addition to the exact impact of trauma history, what remains unclear is the timeline of the onset of cortisol dysregulation observed in patients with PTSD. Is it a pre-existing risk factor or does it emerge only in the aftermath of the trauma? Studies showing that glucocorticoid administration inhibits traumatic memory formation (Bierer *et al.*, 2006) support a vulnerability model. For example, patients undergoing surgery and/or hospitalization in the intensive care unit who are pre-treated with stress doses of glucocorticoids are less likely to have traumatic memories of their hospital stay after discharge than patients treated with placebo (Brunner *et al.*, 2006; Schelling *et al.*, 2006; Weis *et al.*, 2006). In contrast, studies showing that individuals with elevated cortisol at the time of trauma are more likely to be subsequently diagnosed with PTSD could be cited as evidence of a post-hoc model (Baker *et al.*, 2005; Inslicht *et al.*, 2006).

Handwerger's (2009) review also concluded that 40–60% of adults with MDD display hypercortisolism and non-suppression in the dexamethasone suppression test. This pattern may be even more common in psychotic than non-psychotic depression. In contrast, when changes in cortisol levels following exposure to acute stressors are assessed, no clear pattern distinguishes patients with MDD from controls. A recent study with a very large sample (1588) also documented statistically significant morning basal cortisol elevation in patients with present or a history of MDD but failed to differentiate between those with MDD and healthy volunteers in cortisol response to the dexamethasone suppression test (Vreeburg *et al.*, 2009).

Factors promoting resilience

Several animal models and some investigations in humans suggest that the relative efficiency of the HPA

axis is predictive of the degree of resilience (de Kloet *et al.*, 2005). That is, its successful acute activation when triggered by a threat, and subsequent and timely deactivation when danger has passed, are adaptive and promote physical and mental health. Conversely, both hypo- and hyperactive HPA axis activity are associated with psychological and physical illness. Hence, factors that enhance the functioning of the feedback mechanisms that regulate the axis are likely to promote resilient phenotypes.

Single nucleotide polymorphisms

Single nucleotide polymorphisms (SNPs) that influence HPA reactivity have been identified in the genes coding for the mineralocorticoid receptor (MR), GR, gamma-aminobutyric acid (GABA) A receptor, α -adrenoceptor (Masten *et al.*, 1995), μ -opioid receptor, as well as the serotonin transporter, catechol-O-methyltransferase (COMT), monoamine oxidase A, brain-derived neurotrophic factor (BDNF), and angiotensin-converting enzyme. Comprehensive reviews are available elsewhere (Derijk & de Kloet, 2008; Derijk, 2009) but many SNPs will be briefly discussed in this chapter.

Ratio of dehydroepiandrosterone to cortisol

The ratio of DHEA and its derivatives to cortisol has proved to be predictive of adaptive responses to stress in multiple populations (Morgan *et al.*, 2004). The ratio of DHEA-S to cortisol was positively correlated with performance during rigorous survival training (Morgan *et al.*, 2004) and negatively correlated with dissociative symptoms (Korte *et al.*, 2005). This ratio is also negatively correlated with the severity of negative mood symptoms in women with PTSD (Rasmussen *et al.*, 2004). Secretion of DHEA in response to ACTH injections in these same women was highest in those reporting the mildest symptoms (Rasmussen *et al.*, 2004). Higher DHEA plasma levels have been positively correlated with improvement and effective coping in an investigation of veterans being treated for PTSD (Morgan *et al.*, 2004; Yehuda *et al.*, 2006a) and negatively correlated with depressive symptoms (Goodyer *et al.*, 1998; Gallagher & Young, 2002; Young *et al.*, 2002).

The inverse relationships observed between DHEA levels and psychopathology prompted researchers to test its viability as a treatment. Use of DHEA outperformed placebo in 145 patients with human immunodeficiency/acquired immunodeficiency syndrome

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(HIV/AIDS) being treated for MDD (Rabkin *et al.*, 2006): 51% of patients randomized to DHEA reported symptom relief in comparison to only 31% of those assigned to the placebo group when assessed with the Hamilton Depression Rating Scale and the Clinical Global Impression Scale.

Integrity of feedback mediated by glucocorticoid and mineralocorticoid receptors

Functional variants have been identified in humans of the genes for brain MRs and GRs, which are involved, respectively, in setting the threshold and in regulating the termination of the HPA axis response to stress (de Kloet *et al.*, 2007). For example, carriers of the N363S variant of GR were shown to exhibit higher cortisol responses to the Trier Social Stress Test, a stress-inducing public speaking and mental arithmetic task (Krishnan *et al.*, 2007). Interestingly, four SNPs of *FKBP5* (rs9296158, rs3800373, rs1360780, and rs9470080), a gene coding for a "chaperone" protein that regulates GR sensitivity, were found to interact with severity of childhood abuse in the prediction of PTSD symptoms in adults (Bradley *et al.*, 2008). Another study demonstrated an association between genetic variation in *FKBP5* and inefficient recovery of HPA axis activity after the Trier Social Stress Test in healthy participants, identifying a potential risk factor for chronically elevated cortisol levels and, ultimately, stress-related psychopathology (Derijk & de Kloet, 2008).

Extrahypothalamic corticotropin-releasing hormone

Allostatic contribution

In addition to its role in the HPA pathway, CRH also contributes to the inhibition of a variety of neurovegetative functions, such as food intake, sexual activity, growth, and reproduction. Increased activity of extrahypothalamic CRH-containing neurons in the amygdala appears to activate fear-related behaviors, while those in the cortex may reduce reward expectation.

Two G-protein-coupled CRH receptors have been characterized, CRH-1 and CRH-2. Both are expressed in the pituitary, the hippocampus, the amygdala, and throughout the neocortex (with greater density in the prefrontal, cingulate, striate, and insular cortices). Only CRH-1 has been detected in the locus coeruleus, the nucleus of the solitary tract, the thalamus, and the

striatum, and only CRH-2 in the choroid plexus, certain hypothalamic nuclei, the nucleus prepositus, and the bed nucleus of the stria terminalis (Sanchez *et al.*, 1999). Mice bred to be deficient in either CRH-1 or CRH-2 display contradictory behavioral profiles when exposed to stress. The CRH-1-deficient mice demonstrate less anxiety-like behavior and fail to mount an adequate stress response in comparison with controls, while CRH-2-deficient mice evince more anxiety-like behavior and are hypersensitive to stress (Bale *et al.*, 2000; Coste *et al.*, 2000). Trials of CRH-1 antagonists indicate that this receptor activates the behavioral, endocrine, and visceral responses to stress; in contrast, CRH-2 generally serves to dampen these effects (Tache & Bonaz, 2007). However, CRH-2 does have some anxiogenic effects; it appears to enhance the CRH-1-mediated suppression of feeding behavior, for example, and to augment stress-induced behaviors via action in the lateral septum of the amygdala (Bakshi *et al.*, 2002). What is more, stress appears to modify CRH receptor expression in the rodent dorsal raphe nucleus, increasing the CRH-2 and decreasing the CRH-1 availability (Waselus *et al.*, 2009). Therefore, additional research will be required to illuminate the complex interactions between these receptors.

Allostatic load

As described above, CRH-1 signaling appears to be primarily anxiogenic. Exposure to excessive CRH during development appears to have a lasting and deleterious impact on mental and social health. In adults, increased levels of CRH in cerebrospinal fluid have been linked to PTSD and major depression (Bremner *et al.*, 1997; Baker *et al.*, 1999; Nemeroff, 2002). The data from studies measuring plasma CRH levels in patients with PTSD are mixed (Voisey *et al.*, 2009).

Factors promoting resilience

Early life stress has been linked to chronically high levels of CRH in human and animal studies (Heim & Nemeroff, 2001), providing yet more evidence that environmental stability during childhood equips a body to resist damage when stressed. Yet genetic factors appear to mediate the impact of childhood trauma on CRH system integrity. A recent study in two independent populations found that polymorphisms and haplotypes of the gene for CRH (e.g., a haplotype formed by three SNPs in intron 1) affected the influence of child abuse on depressive symptoms in adulthood, with certain alleles (rs7209436, rs242940) and haplotypes exerting a protective effect (Bertoni *et al.*,

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2006). In addition, scientists were able to reverse social impairments associated with developmental exposure to high levels of CRH by administering a CRH antagonist to the dorsal raphe of rodents (Lukkes *et al.*, 2009), suggesting that these compounds may be effective treatments for people suffering from social anxiety stemming from early adverse experiences.

Monoamines

Monoamines (norepinephrine [NE], serotonin [5-HT], and dopamine) were the original neuromodulators implicated in emotion regulation. Hence, it is hardly surprising that they have been identified as players in allostasis.

Norepinephrine

The locus coeruleus is co-activated with the HPA axis in response to stress. This is a nucleus located within the dorsal wall of the rostral pons in the lateral floor of the fourth ventricle, and the primary site of NE genesis in the brain. Having the hypothalamus, amygdala, and prefrontal cortex as both afferents and efferents, the locus coeruleus plays a key role in regulating emotional and physiological reactions to stimuli.

Allostatic contribution

When provoked by stress, the locus coeruleus contributes to the excitation of the HPA axis and the sympathetic nervous system, while inhibiting the parasympathetic nervous system, resulting in a state of arousal. Further inhibition of the prefrontal cortex allows instinctual “fight or flight” behaviors to dominate, unchecked by the more nuanced cognitions of the forebrain (Charney & Bremner, 1999). Researchers recently demonstrated that NE levels in the prefrontal cortex also, in part, determine the dopaminergic response to stress. Higher levels of NE appear to favor dominance of mesolimbic dopamine signaling and active coping, lower levels of NE leading to mesocortical dopamine signaling and passive coping.

The activation of the HPA and locus coeruleus–NE systems under acute stress also facilitates the encoding and relay of aversively charged emotional memories, beginning at the amygdala. Animal studies have shown that injections of NE into the amygdala enhance memory consolidation; in contrast, blocking NE activity during stress impedes the encoding of fearful memories. In rats, blocking the lateral nucleus of the amygdala to the effects of NE during reactivation of a fearful

memory prevents the process of memory reconsolidation and appears to permanently impair that memory (Debiec & LeDoux, 2006).

Allostatic load

Although locus coeruleus activity is important for mounting an effective stress response, hyperactivity or sustained activity of the locus coeruleus is likely deleterious and is associated with depression, anxiety disorders, fear, intrusive memories, and an increased risk of hypertension and cardiovascular disease (Charney *et al.*, 1987, 1992; Southwick *et al.*, 1997; Wong *et al.*, 2000; Geraciotti *et al.*, 2001). For example, both plasma and cerebrospinal fluid levels of NE were found to be elevated in patients with PTSD (Yehuda *et al.*, 1995; Baker *et al.*, 1997).

The neuron response in the locus coeruleus to stress-related stimuli is mediated in part by α_2 -adrenoceptors, which are inhibitory autoreceptors localized to the cell bodies of locus coeruleus neurons. These α_2 -adrenoceptors serve an important role in providing negative feedback and containment of the NE response to stress. Antagonism of α_2 -adrenoceptors with idazoxan or yohimbine increases the response of locus coeruleus neurons to excitatory stimuli without altering their baseline firing rate (Simson & Weiss, 1988). Neumeister and colleagues (2005) found that humans homozygous for a polymorphism that compromises the integrity of α_2 -adrenoceptor function had higher levels of NE at rest and more sustained increases in NE, heart rate, and anxiety in response to a yohimbine challenge compared with non-carriers.

Exposure to stressors from which the animal cannot escape results in behavioral deficits termed *learned helplessness*. The learned helplessness state is regarded as an animal model of MDD and is associated with depletion of NE (Bremner *et al.*, 1996). The depletion of NE during exposure to an inescapable stressor may function as a blockade of α_1 -adrenoceptors and precipitate hypersensitization of locus coeruleus neurons to stimuli (Simson & Weiss, 1988).

Factors promoting resilience

Variables that promote efficiency and/or prevent hypersensitivity or chronic activation of the NE system would likely result in resilience. For example, the levels of COMT, which degrades NE and dopamine, would influence the quality and duration of NE activation. Polymorphisms in the gene that codes for COMT have been identified and found to affect cognition and

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anxiety levels. Individuals with low functioning COMT variants (hence, higher levels of circulating NE) tend to have better attention and working memory, but higher anxiety (Heinz & Smolka, 2006). Individuals with low functioning COMT also exhibit higher neural responsiveness in the limbic system and visuospatial attention system when presented with unpleasant stimuli, suggesting that they have heightened reactivity to potential threats (Smolka *et al.*, 2005).

There is also evidence linking severe stress in early life to hyperfunctioning of the locus coeruleus–NE system in adulthood. In one study of police recruits, participants watched aversive videos and subsequently gave saliva samples. Those recruits with a history of childhood trauma had significantly higher levels of a salivary metabolite of NE than did control peers (Otte *et al.*, 2005).

Beta-blockers (e.g., propranolol), agents that prevent stimulation of β -adrenoceptors by both NE and epinephrine, inhibit some aspects of memory consolidation when administered to animals immediately before or after a learning task. These findings suggested that treatment with beta-blockers in the acute aftermath of trauma exposure might prevent PTSD. Propranolol, in comparison with placebo treatment, was associated with greater reductions in physiological reactivity when recalling memories of trauma three months later (Pitman *et al.*, 2002). Unfortunately, subsequent similar investigations have failed to replicate the promising results (Orr *et al.*, 2006).

Serotonin

Serotonin has been implicated in the regulation of a number of complex processes including anxiety, fear, mood, aggression, and impulse control. However, because 5-HT has at least 17 unique receptors and additional enzymes and proteins that influence its metabolism and release, it remains exceedingly difficult to understand exactly how it exerts its influence (Cools *et al.*, 2008; Dayan & Huys, 2009). Researchers have approached the study of 5-HT by exposing humans or animals believed to have compromised 5-HT signaling (5-HT-impaired subjects) to stressors and observing the results. In humans, genetic testing can identify individuals with specific polymorphisms known to impair the function of their 5-HT system for participation in experiments. Alternatively, the quantity of 5-HT available can be reduced via nutritional manipulation (tryptophan depletion). Animals can be genetically or physically modified.

Allostatic contribution

Such investigations of 5-HT-impaired subjects have demonstrated that 5-HT tempers physiological responsiveness to threats in part via modulation of amygdala and prefrontal activation (Inoue *et al.*, 1993; Cools *et al.*, 2005; Heinz *et al.*, 2005; Pezawas *et al.*, 2005). Stress exposure triggers more activity in those regions in 5-HT-impaired individuals than in controls (Cools *et al.*, 2008). Furthermore, multiple studies in humans and animals have revealed a negative association between tonic 5-HT levels and negative bias (reviewed by Cools *et al.*, 2008). That is, 5-HT-impaired individuals have more difficulty perceiving and processing positive and rewarding stimuli than aversive stimuli. This 5-HT impairment has also been linked to impulsivity. In animals, 5-HT impairment results in an inability to refuse or ignore rewarding stimuli. In humans, it renders individuals less likely to refuse or ignore a stimulus that was once rewarding, even if it is no longer rewarding. These 5-HT-impaired subjects also make more commission errors on go–no-go cognitive tests. These tests ask participants to act (“go”) in some situations and to refrain from acting (“no-go”) in others. The 5-HT-impaired subjects are as likely as controls to act when acting is appropriate. However, they are more likely to act even when acting is not appropriate, demonstrating a failure of inhibitory mechanisms (reviewed by Cools *et al.*, 2008). This 5-HT impairment is also thought to contribute to the pathophysiology of MDD, PTSD, and other anxiety disorders. Although this was originally inferred from the serendipitous discovery that agents that increased 5-HT transmission were often effective antidepressants, decades of additional research have documented more direct evidence to support this hypothesis. For example, the density of 5-HT_{1A} receptors is reduced in depressed patients when they are depressed as well as in remission (Belda & Armario, 2009), and density is also decreased in patients with panic disorder (Bogdan & Pizzagalli, 2006).

Given that 5-HT impairment is associated with increased physiological responsiveness to stress, increased attention to negative stimuli, and impulsivity, as well as with MDD and PTSD, it is possible to deduce that effective 5-HT neurotransmission would contribute to allostasis in situations where tranquility, optimism, and/or behavioral control are adaptive.

Allostatic load

There is no evidence that physiologically appropriate levels of 5-HT are harmful. However, agents that

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facilitate its neurotransmission have a clear allostatic load. Common side-effects of selective serotonin reuptake inhibitors such as fluoxetine and citalopram include sexual dysfunction, such as reduced desire, deficits in the ability to achieve orgasm, or quality of orgasm; nausea; dry mouth; headache; diarrhea; rash; nervousness, agitation, and restlessness; increased sweating; and weight gain. Serotonin syndrome, one of the most severe of the possible adverse effects, is characterized by the presence of symptoms in three domains: cognitive (mental confusion, hypomania, hallucinations, agitation, headache, coma); autonomic (shivering, sweating, hyperthermia, hypertension, tachycardia, nausea, diarrhea); and somatic (myoclonus [muscle twitching], hyperreflexia [manifested by clonus], tremor). As indicated by the range of risk imposed by the symptoms listed in each domain, cases can range from mild to severe (Boyer & Shannon, 2005).

Factors contributing to resilience

Given the wealth of data implicating suboptimal 5-HT signaling in the pathophysiology of mood and anxiety disorders, any factors that promote the health of this system would likely support resilience. Numerous studies have explored the role of genetics, and specifically a well-known polymorphism in the gene for the serotonin transporter (*5HTTLPR*) in conferring vulnerability to depression. Three genotypes are possible: two copies of the long allele (LL), two copies the short allele (SS), or one of each (SL). A handful of studies found that the short allele renders individuals more likely to develop MDD after stressful life experiences (Caspi *et al.*, 2003; Gillespie *et al.*, 2005). However, two recent meta-analyses concluded that the relationship between these variables is not significant (Munafo *et al.*, 2009; Risch *et al.*, 2009). Verhagen and colleagues (2009) suggest that the effect of the *5HTTLPR* polymorphism on MDD is co-dependent on the presence of co-morbid disorders and sex. In their work, the S-allele of the *5HTTLPR* polymorphism has been associated with significantly lower rates of particular lifetime co-morbid disorders. Therefore, they argue that the presence of co-morbid psychiatric disorders should be taken into account to clarify the association of the *5HTTLPR* polymorphism with MDD phenotypes.

In animal models, embryonic and early postnatal shutdown of expression of a type of 5-HT receptor (5-HT₁), via either genetic (e.g., knockout mice) or environmental (e.g., high levels of juvenile CRH) means, produces an anxiety phenotype that endures,

even following the restoration of the receptors (Heisler *et al.*, 1998; Parks *et al.*, 1998; Gross *et al.*, 2002). Reductions in these same 5-HT₁ receptors in adulthood create only a state-dependent anxious phenotype, reinstating the receptors restores original behavior. These results suggest that altered function of 5-HT receptors early in life can produce long-term abnormalities in the regulation of anxiety behaviors (Gross *et al.*, 2002) and underscores the importance of early childhood environment in inclining an individual to resilience or vulnerability to mood and anxiety disorders.

Interactions between the 5-HT and other neuromodulating systems also appear to be relevant to the efficacy of its signaling. For example, increases in adrenal steroid release, characteristic of an active HPA axis, result in a corresponding decrease in 5-HT₁ receptor density and mRNA levels by activating MRs (Lopez *et al.*, 1998). There may also be important functional interactions between 5-HT_{1A} and benzodiazepine receptors. One study of 5-HT_{1A} knockout mice reported a downregulation of benzodiazepine GABA α₁- and α₂-receptor subunits as well as benzodiazepine-resistant anxiety in the elevated-plus maze (Sibille *et al.*, 2000). However, a subsequent study did not replicate these results using mice with a different genetic background (Pattij *et al.*, 2002), raising the possibility that genetic background can affect functional interplay between 5-HT_{1A} and benzodiazepine systems.

Dopamine

With five known receptors, dopamine is another multitasking neuromodulator, involved in numerous psychological and physiological processes (psychosis and movement among the most well known). Its function in the experience of reward and pleasure has been most thoroughly investigated in mood and anxiety disorders. The “mesocorticolimbic” dopamine pathway, composed of neurons in the ventral tegmental area, ventral striatum (nucleus accumbens), amygdala, medial pre-frontal cortex, ventral pallidum and mediodorsal thalamus, is thought to be most relevant to reward. This circuit is linked to brain regions involved in attention, goal-directed behavior, motivation, reinforcement, emotion regulation, cognitive function, and social interactions. Dopamine neuron activity in the ventral tegmental area is dependent upon expectation of and receipt of reward: the neurons are activated in response to a reward (e.g., food, sex, social interaction), or even the expectation of a reward, and are inhibited by an

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aversive stimulus or the absence of an expected reward (Carter *et al.*, 2009). (However, certain dopaminergic neurons are also activated by aversive stimuli, suggesting their involvement in mood regulation more generally [Carter *et al.*, 2009].) Hence animal models suggest that the response of the dopaminergic system changes as a function of the nature and duration of the stress experienced by an animal.

Allostatic contribution

Exposure to brief, novel stressors appears to result in an immediate increase in mesolimbic dopamine release (Puglisi-Allegra *et al.*, 1991; Pascucci *et al.*, 2007). These changes in signaling serve to arouse the animal and catalyze coping behaviors. If the animal determines that it is possible to behaviorally modulate the dose or intensity of the stressor, increased mesolimbic dopamine release can be maintained regardless of the severity or duration of exposure (Puglisi-Allegra *et al.*, 1991). The animal continues to struggle as long as the behavior is rewarded.

However, if coping tactics are ineffective (and the stress is uncontrollable), the animal does not receive the reward it originally expected. Mesolimbic dopamine transmission will drop off to lower than normal levels, contributing to the inhibition of behavioral responses to stress (Puglisi-Allegra *et al.*, 1991; Pascucci *et al.*, 2007). This may serve as a survival mechanism in situations where conservation of energy better serves the animal than continuing a futile struggle.

In addition, Belda and Armario (2009) explored the impact of dopamine antagonists on HPA axis activity with immobilization stress in rats. Both D₁ and D₂ receptor antagonists reduced HPA axis activity and the duration of activation, indicating that dopamine stimulates HPA axis activity during and after stress via these receptors.

Allostatic load

Stress reduces sensitivity to reward in humans (Bogdan & Pizzagalli, 2006), and altered reward circuitry appears to characterize both MDD (Nestler & Carlezon, 2006) and PTSD. Indeed, an increasing number of studies implicate the mesocorticolimbic circuit in both resilience and vulnerability to developing mood and anxiety symptoms. Special forces soldiers, considered highly resilient because of their ability to perform well even under extreme stress, showed increased reactivity of reward-processing regions compared with healthy civilian controls (Vythilingam *et al.*, 2009). Conversely,

dissatisfaction with social rewards in healthy males was associated with increased activation in prefrontal (top-down control) areas during performance of a monetary task (Siegrist *et al.*, 2005).

Patients with PTSD are both less likely to expect a reward and experience less satisfaction upon receipt of a reward than controls (Hopper *et al.*, 2008). Further, functional magnetic resonance imaging (fMRI) investigations suggest that they demonstrate less activation in the nucleus accumbens and medial prefrontal cortex in response to reward (Sailer *et al.*, 2008). However, their activation does not differ from controls in response to a loss or disappointment. In rodents, exposure to a social defeat paradigm (time in a cage with a larger aggressive animal) increased activity of dopamine neurons in the ventral tegmental area via increased activity-dependent release of BDNF onto nucleus accumbens neurons. Animals that recovered normal functioning after the exposure upregulated potassium channels in the ventral tegmental area, minimizing the increase in neuronal excitability and in BDNF release (Eisch *et al.*, 2003; Meaney & Szyf, 2005). Those that continued to demonstrate anxious behaviors did not (Eisch *et al.*, 2003, Krishnan *et al.*, 2008).

In a study conducted by Pizzagalli and colleagues (2009), subjects with MDD, in contrast to controls, showed attenuated responses to reward in the left nucleus accumbens and the caudate bilaterally. However, there were no group differences in these regions in response to neutral or negative outcomes. In this same sample, self-reported severity of anhedonia and depressed mood group were associated with reduced caudate volume bilaterally. In imaging investigations, individuals with a history of MDD, but no present clinically significant depressive symptoms, were less responsive to pleasant visual stimuli in the ventral striatum than were controls. In contrast, they were more responsive to aversive visual stimuli in the caudate nucleus. When the visual stimuli were paired with corresponding olfactory stimuli, subjects with MDD evinced relatively less activity in the prefrontal cortex (McCabe *et al.*, 2009). Adolescents with MDD have also been shown to mount a weaker striatal response but a more robust dorsolateral and medial prefrontal cortex response than controls during reward anticipation and reward outcome (Forbes *et al.*, 2009). Altered activation of reward circuits in depressed compared with healthy adolescents was associated with self-reports of reduced positive affect in naturalistic settings (Forbes *et al.*, 2009). Differential reward system function has

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also been demonstrated in children of depressed versus never-depressed parents (Monk *et al.*, 2008).

Factors contributing to resilience

States and traits that facilitate effective functioning of mesolimbic dopamine signaling and buttress the circuitry of reward might promote active coping and decrease vulnerability to MDD and anxiety. For example, the persistence of the state of reduced mesolimbic dopaminergic transmission that results from uncontrollable stress appears to be, in part, genetically determined; some strains of mice become sensitized to the reduction in mesolimbic dopamine and re-initiate coping behaviors, while others will evince progressively fewer and fewer coping behaviors (Puglisi-Allegra *et al.*, 1990). In humans, genes affecting the integrity of dopamine signaling influence severity of PTSD. An SNP (C957T) in the gene for the D₂ receptor (*DRD2*) has been linked to PTSD risk. Individuals with PTSD are more likely to carry the C allele compared with the controls (Voisey *et al.*, 2009). In a study of combat veterans with PTSD, the A1+ allele of *DRD2* was associated with increased PTSD symptoms and higher co-morbid anxiety and depression (Lawford *et al.*, 2006). The A1+ allele has previously been linked to social dysfunction in children, compromised visuospatial functioning in adolescents, and increased family stress (Lawford *et al.*, 2006).

The A2 allele of *DRD2* appears to confer MDD risk. Occurrence of stressful life events was associated with increased risk of subsequent depressive symptoms in individuals with the A2/A2 genotype. No such association was detected in participants with A1/A1 or A1/A2 genotypes (Elovainio *et al.*, 2007).

Exposure to stress during development also appears to alter functioning of dopaminergic circuitry. Adult rats exposed to social defeat as adolescents had lower levels of medial prefrontal cortex dopamine, increased NE in the dentate gyrus, and decreased NE in the dorsal raphe (Watt *et al.*, 2009).

The Val158Met COMT polymorphism also appears to contribute to variability between individuals in neural responses to reward anticipation, even in healthy individuals.

Neuropeptides**Neuropeptide Y**

Neuropeptide Y (NPY), composed of 36 amino acid residues and one of the most abundant neuropeptides, is involved in regulation of feeding and sexual

behavior, circadian rhythms, cardiovascular symptoms, and the immune and stress responses (Hökfelt *et al.*, 1998). There are at least four metabotropic, G-protein-coupled NPY receptors expressed in the human brain (Y₁, Y₂, Y₃, Y₅) (Blomqvist & Herzog, 1997) whose activation precipitates inhibitory responses such as the inhibition of cyclic AMP accumulation (Lin *et al.*, 2004).

Allostatic contribution

There are important interactions between NPY and CRH (Heilig *et al.*, 1994; Britton *et al.*, 2000): NPY counteracts the anxiogenic effects of CRH at various locations within the stress-anxiety circuit, including the amygdala, hippocampus, hypothalamus, and locus caeruleus. Activation of the Y₁ receptor inhibits several metabolic and behavioral stress responses, including gastrointestinal effects, anxious behavior, and decreased sleep (Eva *et al.*, 2006).

Allostatic load

No known health risks are associated with excess exposure to NPY. However, knockout models have revealed that each of the NPY receptors have unique purposes. For example, while mice without any NPY display increased levels of anxious behavior (spending less time in the open field on the open field test) and increased startle amplitude (Bannon *et al.*, 2000), Y₂ receptor knockout mice display less anxious behavior than controls, suggesting that Y₂ receptors may be anxiogenic.

Mice bred to overexpress NPY are more vulnerable to developing obesity when maintained on a high-sucrose diet, and as their age advances (Kaga *et al.*, 2001). They are also relatively hypersensitive to ethanol (Thiele *et al.*, 1998).

Factors promoting resilience

In general, increased levels of NPY seem to promote resilience and reduce anxiety in both animal models and humans. In a study of special forces soldiers, who are considered to be highly stress resilient, higher NPY levels during rigorous military training were associated with better performance (McGaugh, 2004). Other studies found higher plasma and cerebrospinal fluid NPY in combat-exposed veterans without PTSD than in those with PTSD (Sah *et al.*, 2009). These findings in humans are consistent with recent studies in rats: central administration of NPY in rats inhibits the development, and promotes the extinction, of fear conditioning, with NPY antagonists exerting the opposite actions. These effects

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are mediated at least in part via the amygdala (Morgan *et al.*, 2000). Moreover, intra-amygdala NPY administration promotes resilient responses to stress, in the form of reduced anxiety-like behaviors in response to acute restraint (Yehuda *et al.*, 2006b).

Elevated NPY is negatively correlated with depression and anxiety in human and animal models (Heilig *et al.*, 1993, 2004; Karlsson *et al.*, 2005). A variety of antidepressant drugs increase NPY levels in humans and animals (Nikisch *et al.*, 2005; Goyal *et al.*, 2009; Bjornebekk *et al.*, 2010). Electroconvulsive therapy has produced similar elevations in animal studies (Mikkelsen & Woldbye, 2006; Nikisch & Mathe, 2008).

Galanin

Galanin is a neuropeptide composed of 30 amino acid residues and with three known receptors (GAL-1, GAL-2, GAL-3). All are thought to be involved in allostasis (Walton *et al.*, 2006). A dense galanin fiber system originates in the locus coeruleus and innervates the hippocampus, hypothalamus, amygdala, and prefrontal cortex among other areas (Perez *et al.*, 2001). Galanin-releasing neurons are thought to be located immediately adjacent to the central amygdala and appear to be activated by non-noradrenergic afferents that themselves are activated by NE (Barrera *et al.*, 2006).

Allostatic contribution

Both GAL-1, an autoreceptor (Sevcik *et al.*, 1993; Xu *et al.*, 2001), and GAL-2 appear to be anxiolytic. Knockout mice for GAL-1 and GAL-2 evince increased anxiety-like behavior (Holmes *et al.*, 2003; Rajarao *et al.*, 2007; Lu *et al.*, 2008a). Galanon, a non-specific galanin agonist, has been shown to elevate GABA levels in the rat amygdala and results in anxiolytic effects in some (open-maze and hyperthermia), but not all (mouse tail suspension, rat forced swim) animal models (Unschuld *et al.*, 2008). Galanin reduces NE, 5-HT, and dopamine levels in the prefrontal cortex via inhibition (Holmes & Picciotto, 2006). Hence, scientists have proposed that galanin recruitment during stress may serve as a buffer, minimizing the intensity of the anxiety experienced as a result of NE over-activation (Karlsson & Holmes, 2006). Galanin-overexpressing transgenic mice are unresponsive to the anxiogenic effects of the α_2 -adrenoceptor antagonist yohimbine. Consistent with this observation, galanin injected directly into the central nucleus of the amygdala blocked the anxiogenic effects of stress, which is associated

with increased NE release in the central nucleus of the amygdala (Khoshbouei *et al.*, 2002).

Allostatic load

The GAL-3 receptor has anxiogenic effects. Galanin acting at the GAL-3 receptor may precipitate decreases in 5-HT signaling by hyperpolarizing 5-HT neurons in the dorsal raphe nucleus and reducing levels of 5-HT in the hippocampus and prefrontal cortex, leading to increased vulnerability to anxiety and isolation. In animal models, GAL-3 antagonists have increased prosocial behaviors and decreased anxiety and depression-like behaviors (Swanson *et al.*, 2006; Kozlovsy *et al.*, 2009).

Factors promoting resilience

In humans, certain polymorphisms of the gene for the GAL-3 receptor have been linked with anxiety and alcoholism (Belfer *et al.*, 2006). In a recent study exploring an animal model of galanin functioning in PTSD, rats were exposed to a predator. Those rats who exhibited minimal anxiety-like symptoms after the exposure were observed to have a lasting upregulation of galanin mRNA in the C area of the hippocampus in the prefrontal cortex, while those who became symptomatic evinced galanin mRNA downregulation in the same areas (Kozlovsy *et al.*, 2009). In addition, those symptomatic animals treated with galanon displayed fewer anxiety-like behaviors and upregulated their galanin mRNA. Immediate post-exposure treatment with galanon significantly reduced prevalence rates of extreme responders, reduced trauma-cue freezing responses, corrected the corticosterone response, and increased CA1 expression of 5-HT_{1A} and BDNF mRNA compared with controls treated with saline.

Agents modulating the efficacy and intensity of the acute stress response**Sex hormones (gonadal steroids)**

Epidemiological studies have repeatedly demonstrated that women are twice as likely to suffer from depressive and anxiety disorder. It appears that this gender disparity in risk and resilience is mediated in part by the impact of sex hormones on HPA axis activity.

Testosterone

Testosterone, a steroid hormone from the androgen group derived from cholesterol, induces protein