# Chapter 1
# The Brain on Stress: The Good and the Bad

**Bruce S. McEwen**

**Abstract** Stress is a universal human experience and the word "stress" has many connotations and meanings. This review is intended to give a balanced overview of the good and bad sides of the response to stressful experiences. The brain is the central organ of stress and adaptations and has the capacity for considerable structural and functional plasticity which, though diminishing over the lifecourse, is nevertheless present in the adult brain. The brain not only perceives what is stressful but it determines the behavioral and physiological responses of neuroendocrine and autonomic systems that directly and indirectly regulate the metabolic and immune systems. The brain is also the target of circulating hormones and mediators of immune and metabolic systems. Glucocorticoids play a key role in most, if not all, of these actions and their positive, as well as negative effects will be discussed. As a way of avoiding ambiguity of the word "stress," the concepts of allostasis and allostatic load and overload will be introduced to provide biological basis for understanding the interactions of brain and body and influences of stressful experiences and resulting "lifestyle" on both brain and body. Early life experiences have lasting effects on brain and body and emerging evidence suggest that the reactivation of plasticity mechanisms in the brain may be useful in modifying and even reversing effects of experiences in early life, as well as in adult life.

## 1.1 Introduction

"Stress" is a commonly used word in daily life that refers to experiences that cause feelings of anxiety and frustration because they push us to the limits of our ability to successfully cope. Besides time pressures and daily hassles at work and home, there are stressors related to economic insecurity, poor health, and interpersonal conflict. There are also situations that are life-threatening—accidents, natural disasters, violence—and these evoke the classical "fight or flight" response. In contrast to daily

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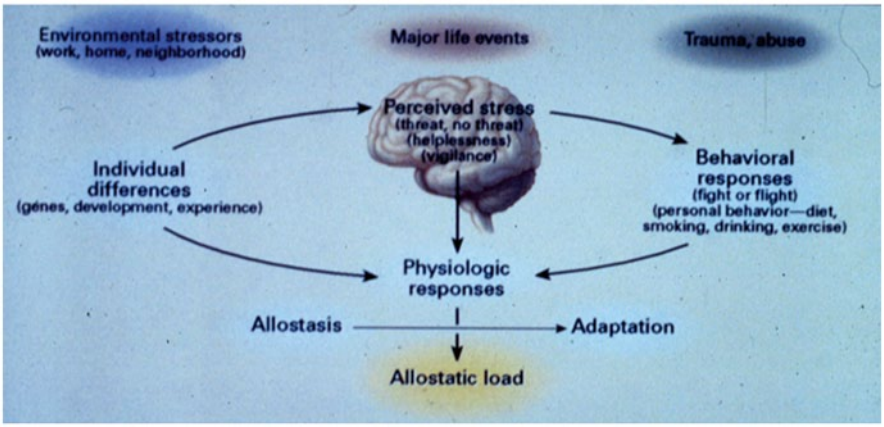


**Fig. 1.1** Central role of the brain in allostasis and the behavioral and physiological response to stressors. (From McEwen 1998 by permission)

hassles, these stressors are acute, and yet they also usually lead to chronic stress in the aftermath of the tragic event.

The most common stressors are ones that operate chronically, often at a low level, and that cause us to alter the way we live. For example, being "stressed out" may cause us to be anxious and/or depressed, to lose sleep at night, to eat comfort foods and take in more calories than our bodies need, and to smoke or drink alcohol excessively. Being "stressed out" may also cause us to neglect seeing friends, or to take time off or engage in regular physical activity as we, for example, sit at a computer and try to get out from under the burden of "too much to do in so little time." Often we are tempted to take medications—anxiolytics, sleep promoting agents—to help us cope, and, with time, our bodies may increase in weight….

The brain is the organ that decides what is stressful and determines the behavioral and physiological responses, whether health promoting or health damaging (Fig. 1.1). And the brain is a biological organ that changes under acute and chronic stress and directs many systems of the body—metabolic, cardiovascular, immune—that are involved in the short- and long-term consequences of being stressed out. What does chronic stress do to the body and the brain? This chapter summarizes some of the current information placing emphasis on how the stress hormones can play both protective and damaging roles in brain and body, depending on how tightly their release is regulated, and it discusses some of the approaches for dealing with stress in our complex world.

## 1.2 Types of Stress

"Stress" can be classified into three types: good stress, tolerable stress, and toxic stress (http://developingchild.harvard.edu/library/reports_and_working_papers/policy_framework/). Good stress is a term used in popular language to refer to the

experience of rising to a challenge, taking a risk and feeling rewarded by an often positive outcome. A related term is "eustress." Good self-esteem and good impulse control and decision-making capability, all functions of a healthy architecture of the brain, are important here! Even adverse outcomes can be "growth experiences" for individuals with such positive, adaptive characteristics.

"Tolerable stress" refers to those situations where bad things happen, but the individual with healthy brain architecture is able to cope, often with the aid of family, friends, and other individuals who provide support. Here, "distress" refers to the uncomfortable feeling related to the nature of the stressor and the degree to which the individual feels a lack of ability to influence or control the stressor (Lazarus and Folkman 1984).

Finally, "toxic stress" refers to the situation in which bad things happen to an individual who has limited material and social support; this person may also have brain architecture that reflects effects of adverse early life events, such as growing up in a chaotic home, as well as abuse and neglect, that have impaired the development of good impulse control and judgment and adequate self-esteem. Here, the degree and/or duration of "distress" may be greater and the ability to cope and show resilience is impaired. With toxic stress, the inability to cope is likely to have adverse effects on behavior and physiology, and this will result in a higher degree of allostatic overload, as will be explained below.

### *1.2.1 Allostasis and Allostatic Load: Protection versus Damage in the Response to Stressors*

In spite of the refinement, the word "stress" is still an ambiguous term and has connotations in common usage that make it less useful in understanding how the body handles the events that are stressful, and insight into these processes can lead to a better understanding of how best to intervene, a topic that will be discussed at the end of this chapter. There are two sides to this story: on the one hand, the body responds to almost any event or challenge by releasing chemical mediators—e.g., catecholamines that increase heart rate and blood pressure—and help us cope with the situation; on the other hand, chronic elevation of these same mediators—e.g., chronically increased heart rate and blood pressure—produce a chronic wear and tear on the cardiovascular system that can result, over time, in disorders such as strokes and heart attacks. For this reason, the term "allostasis" was introduced by Sterling and Eyer (Sterling and Eyer 1988) to refer to the active process by which the body responds to daily events and maintains homeostasis (allostasis literally means "achieving stability through change"). Because chronically increased allostasis can lead to disease, we introduced the term "allostatic load or overload" to refer to the wear and tear that results from either too much stress or from inefficient management of allostasis, e.g., not turning off the response when it is no longer needed. Other forms of allostatic load are summarized in Fig. 1.2 and involve not turning on an adequate response in the first place or not habituating to the recur-

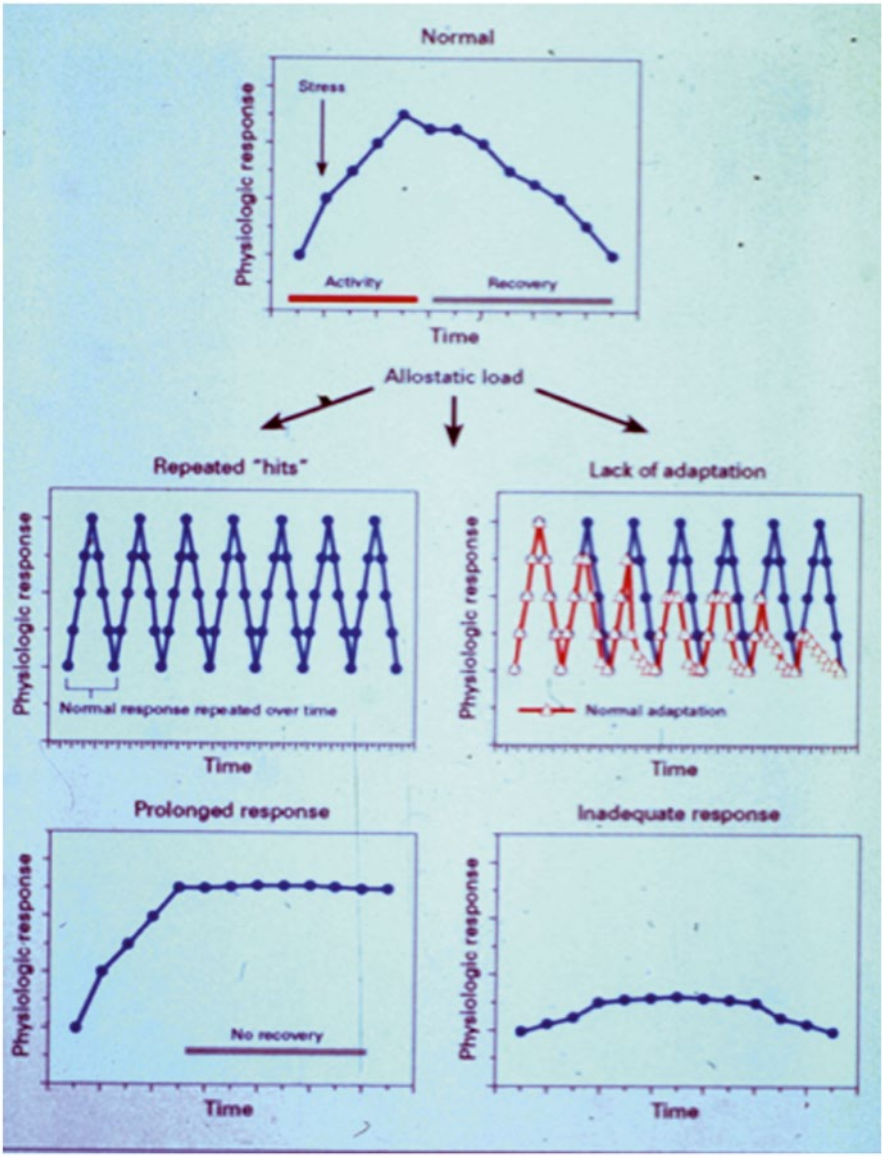


**Fig. 1.2** Four types of allostatic load. The *top panel* illustrates the normal allostatic response, in which a response is initiated by a stressor, sustained for an appropriate interval, and then turned off. The remaining panels illustrate four conditions that lead to allostatic load: *top, left* repeated "hits" from multiple stressors; *top, right* lack of adaptation; *bottom, left* prolonged response due to delayed shut down; and *bottom, right* inadequate response that leads to compensatory hyperactivity of other mediators (e.g., inadequate secretion of glucocorticoid, resulting in increased levels of cytokines that are normally counter-regulated by glucocorticoids). (From McEwen 1998 by permission)

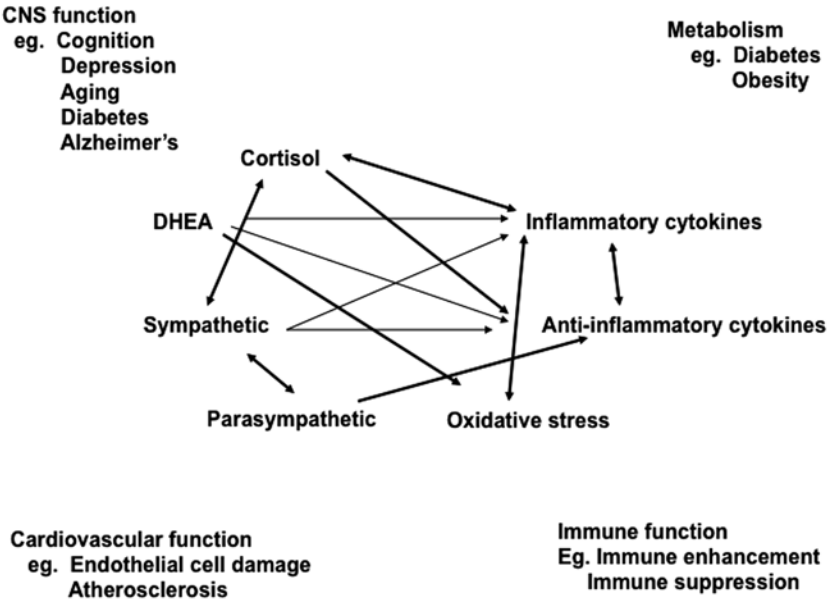


**Fig. 1.3** Nonlinear network of mediators of allostasis involved in the stress response. *Arrows* indicate that each system regulates the others in a reciprocal manner, creating a nonlinear network. Moreover, there are multiple pathways for regulation—e.g., inflammatory cytokine production is negatively regulated via anti-inflammatory cytokines as well as via parasympathetic and glucocorticoid pathways, whereas sympathetic activity increases inflammatory cytokine production. Parasympathetic activity, in turn, contains sympathetic activity. *CNS* central nervous system, *DHEA* dehydroepiandrosterone. (Modified from McEwen 2006)

rence of the same stressor and thus leading to a persistent response rather than dampening the allostatic response. This is well illustrated by the lack of habituation of the salivary cortisol response to a repeated public speaking challenge in individuals with low self-esteem (Kirschbaum et al. 1995). Such individuals are reported to have a smaller hippocampus and have low self-esteem and locus of control (Pruessner et al. 2005).

Thus, protection and damage are the two contrasting sides of the physiology involved in defending the body against the challenges of daily life, whether or not we call them "stressors." Besides adrenalin and noradrenalin, there are many mediators that participate in allostasis, and they are linked together in a network of regulation that is nonlinear (Fig. 1.3), meaning that each mediator has the ability to regulate the activity of the other mediators, sometimes in a biphasic manner.

Glucocorticoids produced by the adrenal cortex in response to adrenocorticotropic hormone (ACTH) from the pituitary gland are the other major "stress hormones." Pro- and anti-inflammatory cytokines are produced by many cells in the body, and they regulate each other and are, in turn, regulated by glucocorticoids and catecholamines (Bierhaus et al. 2003). Whereas catecholamines can increase proinflammatory cytokine production, glucocorticoids are known to inhibit this

production (Sapolsky et al. 2000). And yet, there are exceptions—proinflammatory effects of glucocorticoids that depend on dose and cell or tissue type (Dinkel et al. 2003). The parasympathetic nervous system also plays an important regulatory role in this nonlinear network of allostasis, since it generally opposes the sympathetic nervous system and, for example, slows the heart and also has anti-inflammatory effects (Borovikova et al. 2000; Thayer and Lane 2000).

What this nonlinearity means is that when any one mediator is increased or decreased, there are compensatory changes in the other mediators that depend on time course and level of change of each of the mediators. Unfortunately, we cannot measure all components of this system simultaneously and must rely on measurements of only a few of them in any one study. Yet the nonlinearity must be kept in mind in interpreting the results.

A good example of the biphasic actions of stress, i.e., "protection versus damage" is in the immune system, in which an acute stressor activates an acquired immune response via mediation by catecholamines and glucocorticoids and locally produced immune mediators and, yet, a chronic exposure to the same stressor over several weeks has the opposite effect and results in immune suppression (Dhabhar and McEwen 1999; Dhabhar et al. 2012a). The acute immune enhancement is good for enhancing immunization, fighting an infection, or repairing a wound, but is deleterious to health for an autoimmune condition such as psoriasis or Krohn's disease; on the other hand, the immune suppression is good in the case of an autoimmune disorder and deleterious for fighting an infection or repairing a wound. In an immune sensitive skin cancer, acute stress is effective in inhibiting tumor progression while chronic stress exacerbates progression.

## 1.3 Brain Response to Stressors

The discovery of receptors for glucocorticoids in the hippocampus (McEwen et al. 1968) has led to many investigations in animal models and translation to the human brain using modern imaging methods. The most striking findings from animal models have identified structural plasticity in the hippocampus, consisting of ongoing neurogenesis in the dentate gyrus (Cameron and Gould 1996) and remodeling of dendrites and synapses in the major neurons of Ammon's horn (McEwen 1999). The mediators of this plasticity include excitatory amino acids and glucocorticoids, along with a growing list of other mediators, such as oxytocin, corticotrophin releasing factor, brain-derived neurotrophic factor (BDNF), lipocalin-2 and tissue plasminogen activator (tPA) (McEwen 2007; Mucha et al. 2011). Moreover, glucocorticoid actions involve both genomic and nongenomic mechanisms that implicate mineralocorticoid, as well as glucocorticoid receptors and their translocation to mitochondria, as well as cell nuclei, and, an as-yet unidentified G-protein coupled membrane-associated glucocorticoid receptor related to endocannabinoid production (Du et al. 2009a, Hill and McEwen 2010).

Studies of the human hippocampus have demonstrated shrinkage of the hippocampus not only in mild cognitive impairment and Alzheimer's (de Leon et al. 1997), but also in type 2 diabetes (Gold et al. 2007), prolonged major depression (Sheline 2003), Cushing's disease (Starkman et al. 1999), and posttraumatic stress disorder (PTSD) (Gurvits et al. 1996). Moreover, in nondisease conditions, such as chronic stress (Gianaros et al. 2007), chronic inflammation (Marsland et al. 2008), lack of physical activity (Erickson et al. 2009), and jet lag (Cho 2001), smaller hippocampal or temporal lobe volumes have been reported. As noted above, smaller hippocampal volumes are also reported in individuals with low self-esteem and locus of control (Pruessner et al. 2005).

So far there is no indication as to whether these changes are due to volume reduction in dentate gyrus due to inhibited neuronal replacement or to dendritic shrinkage or glial cell loss, or a combination of all three. Autopsy studies on depression-suicide have indicated loss of glial cells and smaller neuron soma size (Stockmeier et al. 2004), which is indicative of a smaller dendritic tree. With regard to type 2 diabetes, it should be emphasized that the hippocampus has receptors for, and the ability to take up and respond to insulin, ghrelin, insulin-like growth factor-1 (IGF1) and leptin, and that IGF1 mediates exercise-induced neurogenesis (McEwen 2007). Thus, besides its response to glucocorticoids, the hippocampus is an important target of metabolic hormones that have a variety of adaptive actions in the healthy brain which is perturbed in metabolic disorders, such as diabetes (McEwen 2007).

## 1.4 Structural Plasticity in Other Brain Regions

The discovery and implications of stress and glucocorticoid effects in the hippocampus have led to exploration of other brain regions involved in cognition, mood, and behavioral self-regulation. The amygdala shows quite different responses to acute and chronic stress than the hippocampus. The amygdala responds to glucocorticoids in the formation of emotionally charged memories (Roozendaal et al. 2004), and acute stress causes a delayed formation of dendritic spines in basolateral amygdala neurons and an increase of anxiety after 10 days (Mitra et al. 2005). Chronic stress of the same type that impairs dentate gyrus neurogenesis and causes dendritic shrinkage and spine loss in Ammon's horn neurons, also causes expansion of dendrites in the basolateral amygdala (Vyas et al. 2002), while inducing spine downregulation in the medial amygdala (Bennur et al. 2007). The latter is dependent on tPA while the former is not (Bennur et al. 2007).

Translating to the human brain, amygdala hyperactivity is reported in major depression, as well as in anxiety disorders, such as PTSD (Drevets 2000) and enlargement of the amygdala has been reported in acute depression (Frodl et al. 2003). With respect to PTSD, a novel approach after acute trauma is the administration of glucocorticoids, based on the counter-intuitive findings that low normal glucocorticoid levels at the time of open heart surgery, as well as accident trauma, predispose towards development of PTSD symptoms (Schelling et al. 2004; Zohar et al. 2011).

It is, therefore, of interest that glucocorticoid administration before, during, or right after trauma protects against PTSD-like symptoms in animal models and PTSD symptoms in people (Rao et al. 2012; Schelling et al. 2004; Zohar et al. 2011).

Increased amygdala reactivity to angry and sad faces is reported in individuals with early signs of cardiovascular disease (Gianaros et al. 2009), suggesting that the increased sympathetic activity and blood pressure reactivity may be a cause of allostatic load resulting from increased reactivity to daily experiences over time. Increased amygdala reactivity to faces has also been reported in individuals traumatized by 9/11 (Ganzel et al. 2008), as well as after sleep deprivation (Yoo et al. 2007).

The prefrontal cortex is another, now well-studied, target of chronic stress. In the same chronic stress models that lead to amygdala neuronal hypertrophy and shrinkage of dendrites in hippocampus, there is shrinkage of dendrites and loss of spines throughout the medial prefrontal cortex while dendrites expand in the orbitofrontal cortex (OFC) (Liston et al. 2006). Because the OFC is involved in determining the saliency of reward or punishment (Schoenbaum and Roesch 2005), this may reinforce the changes in the basolateral amygdala. For the medial prefrontal cortex, stress-induced impairment has been linked to poor cognitive flexibility in both animal and human studies (Dias-Ferreira et al. 2009; Liston et al. 2009; Liston et al. 2006). Moreover, circadian disruption impairs cognitive flexibility and causes shrinkage of medial prefrontal cortical dendrites (Karatsoreos et al. 2011). These studies complement those on the hippocampus/temporal lobe noted above in flight crews suffering from chronic jet lag (Cho 2001) and raise important questions about how the brain handles shift work, jet lag, and chronic sleep deprivation. Furthermore, aging in rats is associated with loss of recovery of stress-induced shrinkage of dendrites of medial prefrontal cortical dendrites (Bloss et al. 2010), and this harkens back to the glucocorticoid cascade hypothesis (Sapolsky et al. 1986), since the mechanism for medial prefrontal cortical dendritic remodeling is likely to involve the same mechanisms as those in the hippocampus, namely, excitatory amino acids and glucocorticoids (Cerqueira et al. 2005; Martin and Wellman 2011).

## 1.5 Deleterious Effects of Early Life Adversity

Lifetime experiences have a profound impact on the brain, both as a target of stress and allostatic load and as a determinant of physiological and behavioral response to stressors. Animal models have taught us that prenatal stress of the mother can impair features of normal brain development (Maccari and Morley-Fletcher 2007) and that prolonged separation of infant from mother also impairs other aspects of brain development and function (Eiland and McEwen 2012; Francis et al. 2002; Plotsky et al. 2005). On the positive side, good maternal care and consistency of that care is a powerful determinant of life-long patterns of reduced anxiety and efficient stress reactivity, as well as social, physical, and cognitive development (Akers et al. 2008; Caldji et al. 2000; Tang et al. 2011, 2012). Moreover, there are transgenera-

tional effects that appear to be behaviorally transmitted by the mother to the female offspring (Francis et al. 1999). In contrast, inconsistent maternal care and maternal anxiety, for example, from food insecurity, produce anxiety in offspring and appear to contribute to metabolic syndrome and predisposition to diabetes, which itself has adverse effects on the brain (Kaufman et al. 2007, 2005). Thus, the behavioral and physiological consequences of early life abuse and neglect are profound, and the epigenetic concept of behavioral transmission of abuse and its effects on human brain function are being explored at the level of epigenetic regulation of gene expression (McGowan et al. 2009).

Genotype is an important factor in determining the response to experiences (Caspi et al. 2002, 2003). An important addition to the new emphasis on gene x environment interactions is the notion of reactive alleles, as opposed to "bad genes," since alleles that can lead to pathophysiology under adverse conditions can also lead to superior outcomes when the individual with that reactive allele experiences a nurturing environment (Boyce and Ellis 2005; Suomi 2006).

During the last 10–15 years, a number of studies have documented that stress becomes bodily inscribed also in human fetuses and children, with major implications for health throughout the lifespan (e.g., Entringer et al. 2011). Allostatic overload and epigenetic mechanisms shape the developing brain and body's biological vulnerability to disease, as well as its responsiveness to potential interventions (McEwen 1998). Of particular relevance for children are experiences of abuse and neglect (Anda et al. 2010). On the physiological level, adverse childhood experiences are associated with dysregulated cardiovascular, metabolic, and immunological function, which in turn feed into numerous disease conditions both in the somatic and psychiatric domains (Anda et al. 2010). Chaos in the home and inconsistent parenting impairs brain development. This can lead to disturbed cognitive function, instable mood, low self-esteem, and numerous unhealthy activities, including overeating, substance abuse, sexual acting-out, and other forms of legal or illegal risk-taking (Evans et al. 2004).

As to the mechanisms of effects of stressful and other experiences, it is clear from the discussion above and from Fig. 1.3, that there are many interacting mediators. However, glucocorticoids stand out as having particularly important roles in the middle of all of these interactions, both positive and negative.

## 1.6 Diverse Role of Glucocorticoids

Glucocorticoid actions may be classified as direct genomic, indirect genomic, and nongenomic (Popoli et al. 2012; Yamamoto 1985), and all of these mechanisms may be involved in these two studies (see Fig. 1.4). Glucocorticoid and mineralocorticoid receptors are found in membrane-associated sites and are associated with release of glutamate (Karst et al. 2005; Popoli et al. 2012; Prager and Johnson 2009), translocation to mitochondria where calcium sequestration and free radical balance is regulated (Du et al. 2009b), and stimulation of the release of endocannabinoids

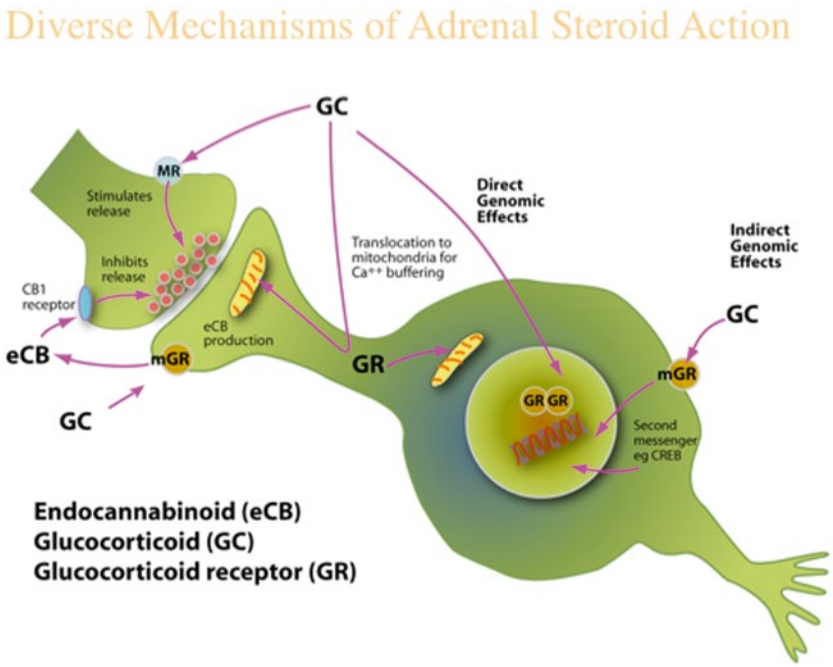


**Fig. 1.4** Adrenal steroids produce multiple effects, both rapid and delayed, via multiple mechanisms. Besides direct genomic effects via classical glucocorticoid receptors (*GR*), there are also indirect genomic effects with other transcription factors. Glucocorticoids also translocate GR to mitochondria, and there are membrane-associated forms of both GR and mineralocorticoid receptors (*MR*) that effect glutamate release and stimulate endocannabinoid synthesis

(eCB) (Hill and McEwen 2010; Tasker et al. 2006). There are trophic actions by low physiological levels of glucocorticoids to maintain turnover of spine synapses (Liston and Gan 2011) and dendritic growth (Gould et al. 1990), suggesting a previously unappreciated role in maintaining a dynamic brain architecture. And glucocorticoids have been shown to promote plasticity induced by binocular visual stimulation in reversing amblyopia in adult life produced by monocular deprivation during development (Spolidoro et al. 2011). Moreover, glucocorticoid actions on processes such as neurogenesis in the dentate gyrus and contextual learning involve concurrent activity of other mediator systems, such as oxytocin for neurogenesis (Leuner et al. 2012) and adrenergic mechanisms for contextual learning (Okuda et al. 2004).

Thus a key aspect of this view of glucocorticoid action is their dependence on other mediators and ongoing cellular processes. For example, glucocorticoid stimulation of direct release of glutamate, on the one hand, is counterbalanced by glucocorticoid induction of eCB formation which can feedback from postsynaptic sites to inhibit presynaptic glutamate release in a homeostatic manner, although *gamma-aminobutyric acid* (GABA) release is also a target of eCB inhibition and can lead to a disinhibition when cannabinoid (CB1) receptors are expressed on inhibitory termi-

nals (Hill and McEwen 2010; Popoli et al. 2012). Glucocorticoid (GC) action at the primary genomic levels also can involve synergy with other transcription regulation machinery, e.g., as in the case of GC-mediated activation of the mitogen-activated protein kinase (MAPK) pathway leading to phosphorylation of extracellular-signal-regulated kinases (ERKs) that then involves induction of protein mediators, such as Ras and Raf-1 along with indirect interactions with Stat5, Fos, Jun, Creb, and NF-kB (Revest et al. 2005). Clearly, our understanding of the complex and widespread actions of adrenal steroid hormones throughout the developing and adult nervous system is just beginning, and plasticity of neurons is emerging as a major topic of investigation, with considerable therapeutic potential!

## 1.7 Reactivation of Plasticity

What can be done to remediate the effects of chronic stress, as well as the biological embedding associated with early life adversity? Interventions may involve pharmaceutical, as well as behavioral, or "top-down," interventions (i.e., interventions that involve integrated central nervous system (CNS) activity, as opposed to pharmacological agents) that include cognitive-behavioral therapy, physical activity, and programs that promote social support and integration and meaning and purpose in life (McEwen and Gianaros 2011). More targeted interventions for emotional and cognitive dysfunction may arise from fundamental studies of such developmental processes as the reversal of amblyopia and other conditions by "releasing the brakes" that retard structural and functional plasticity (Bavelier et al. 2010). It should be noted that many of these interventions that are intended to promote plasticity and slow decline with age, such as physical activity and positive social interactions that give meaning and purpose, are also useful for promoting "positive health" and "eudamonia" (Ryff and Singer 1998; Singer et al. 2005) independently of any notable disorder and within the range of normal behavior and physiology.

Moreover, interventions towards changing physiology and brain function may be useful when adaptation to a particular environment, as in the Active Calibration Model (Del Giudice et al. 2011), has resulted in an individual who then chooses, or is forced, to adapt to a different, e.g., more or less threatening or nurturing, environment. Concerning biological embedding in neural architecture and the balance of neurochemical systems, in the case of adversity or shifting environments, one can hope at least to compensate, even if one cannot reverse, those effects of early life adversity (Caldji et al. 1998). However, it is perhaps premature to draw that conclusion, since the ultimate limits of adult brain plasticity are still unknown, as will be discussed below.

A powerful "top down" therapy (i.e., an activity, usually voluntary, involving activation of integrated nervous system activity, as opposed to pharmacological therapy which has a more limited target) is regular physical activity, which has actions that improve prefrontal and parietal cortex blood flow and enhance executive function (Colcombe et al. 2004). Moreover, regular physical activity, consisting of

walking an hour a day, 5 out of 7 days a week, increases hippocampal volume in previously sedentary adults (Erickson et al. 2011). This finding complements work showing that fit individuals have larger hippocampal volumes than sedentary adults of the same age-range (Erickson et al. 2009). It is also well known that regular physical activity is an effective antidepressant and protects against cardiovascular disease, diabetes, and dementia (Babyak et al. 2000; Snyder et al. 2010). Moreover, intensive learning has also been shown to increase volume of the human hippocampus (Draganski et al. 2006).

Social integration and support, and finding meaning and purpose in life, are known to be protective against allostatic load (Seeman et al. 2002) and dementia (Boyle et al. 2010), and programs such as the Experience Corps that promote these along with increased physical activity, have been shown to slow the decline of physical and mental health and to improve prefrontal cortical blood flow in a similar manner to regular physical activity (Carlson et al. 2009; Fried et al. 2004).

Depression and anxiety disorders are examples of a loss of resilience, in the sense that changes in brain circuitry and function, caused by the stressors that precipitate the disorder, become "locked" in a particular state and thus need external intervention. Indeed, prolonged depression is associated with shrinkage of the hippocampus (Sheline 1996, 2003) and prefrontal cortex (Drevets et al. 1997). While there appears to be no neuronal loss, there is evidence for glial cell loss and smaller neuronal cell nuclei (Rajkowska 2000; Stockmeier et al. 2004), which is consistent with a shrinking of the dendritic tree described above after chronic stress. Indeed, a few studies indicate that pharmacological treatment may reverse the decreased hippocampal volume in unipolar (Vythilingam et al. 2004) and bipolar (Moore et al. 2000) depression, but the possible influence of concurrent cognitive-behavioral therapy in these studies is unclear.

Depression is more prevalent in individuals who have had adverse early life experiences (Anda et al. 2010). BDNF may be a key feature of the depressive state and elevation of BDNF by diverse treatments ranging from antidepressant drugs to regular physical activity may be a key feature of treatment (Duman and Monteggia 2006). Yet, there are other potential applications, such as the recently reported ability of fluoxetine to enhance recovery from stroke (Chollet et al. 2011). However, a key aspect of this new view (Castren and Rantamaki 2010) is that the drug is opening a "window of opportunity" that may be capitalized by a positive behavioral intervention, e.g., behavioral therapy in the case of depression or the intensive physiotherapy to promote neuroplasticity to counteract the effects of a stroke.

This is consistent with animal model work that shows that ocular dominance imbalance from early monocular deprivation can be reversed by patterned light exposure in adulthood that can be facilitated by fluoxetine, on the one hand (Vetencourt et al. 2008) and food restriction or intermittent glucocorticoid treatment, on the other hand (Spolidoro et al. 2011). Investigations of underlying mechanisms for the reestablishment of a new window of plasticity are focusing on the balance between excitatory and inhibitory transmission and removing molecules that put the "brakes" on such plasticity (Bavelier et al. 2010; Espinosa and Stryker 2012).

In this connection it is important to reiterate that successful behavioral therapy, which is tailored to individual needs, can produce volumetric changes in both prefrontal cortex in the case of chronic fatigue (de Lange et al. 2008), and in amygdala, in the case of chronic anxiety (Holzel et al. 2010). This reinforces two important messages: (1) that plasticity-facilitating treatments should be given within the framework of a positive behavioral or physical therapy intervention; and (2) that negative experiences during the window may even make matters worse (Castren and Rantamaki 2010). In that connection, it should be noted that BDNF also has the ability to promote pathophysiology, as in seizures (Heinrich et al. 2011; Kokaia et al. 1995; Scharfman 1997).

## 1.8 Conclusions

The ability of the brain and the body to adapt successfully to acute and chronic stress is an increasingly important topic in the modern world. This overview has emphasized the interplay between the good and the bad, namely, the cumulative wear and tear (allostatic load/overload) facilitated by the same mediators that are essential for adaptation and survival. The role of glucocorticoids deserves emphasis because of the multiple mechanisms and effects that they have throughout the brain and the body, both good and bad. The brain has a central role in the perception and the response to stressors, as well as being the target of allostatic load/overload along with the rest of the body (Fig. 1.1). Biological embedding of early experiences interacts with influences of the chemical and physical environment and sets the course for the body as it attempts to cope with challenges during the life course. All experiences in adult, as well as early life, leave an imprint via epigenetic influences and altered patterns of gene expression, as well as brain architecture and function that are modifiable. This review has noted that "top down" therapies, sometimes aided by pharmaceutical agents, have potential to treat disorders due to stressful and traumatic experiences because of an increased recognition that the mature brain is more malleable than previously believed. In this regard, there is growing awareness of the need to understand what constitutes optimal health, and, thus, a future research goal should be to provide a neurobiological framework for understanding underlying mechanisms for developing and maintaining positive affect and self-efficacy and self-esteem and how these are biologically embedded in a nurturing environment via epigenetic influences, including effects upon reactive alleles in the genome.

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