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## Central effects of stress hormones in health and disease: understanding the protective and damaging effects of stress and stress mediators

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### Abstract

Stress begins in the brain and affects the brain, as well as the rest of the body. Acute stress responses promote adaptation and survival via responses of neural, cardiovascular, autonomic, immune and metabolic systems. Chronic stress can promote and exacerbate pathophysiology through the same systems that are dysregulated. The burden of chronic stress and accompanying changes in personal behaviors (smoking, eating too much, drinking, poor quality sleep; otherwise referred to as “lifestyle”) is called allostatic overload. Brain regions such as hippocampus, prefrontal cortex and amygdala respond to acute and chronic stress and show changes in morphology and chemistry that are largely reversible if the chronic stress lasts for weeks. However, it is not clear whether prolonged stress for many months or years may have irreversible effects on the brain. The adaptive plasticity of chronic stress involves many mediators, including glucocorticoids, excitatory amino acids, endogenous factors such as brain neurotrophic factor (BDNF), polysialated neural cell adhesion molecule (PSA-NCAM) and tissue plasminogen activator (tPA). The role of this stress-induced remodeling of neural circuitry is discussed in relation to psychiatric illnesses, as well as chronic stress and the concept of top-down regulation of cognitive, autonomic and neuroendocrine function. This concept leads to a different way of regarding more holistic manipulations, such as physical activity and social support as an important complement to pharmaceutical therapy in treatment of the common phenomenon of being “stressed out”. Policies of government and the private sector play an important role in this top-down view of minimizing the burden of chronic stress and related lifestyle (i.e. allostatic overload).

### 1. Introduction

The brain is the central organ of the stress response and determines what is stressful, as well as the behavioral and physiological responses to potential and actual stressors. The brain is also a target of stress and it changes structurally and chemically in response to both acute and chronic stressors. Glucocorticoids play a role in these changes, but there are other mediators as well. Although glucocorticoids and catecholamines are the two defining hormones of the “fight or flight” stress response, there are many other mediators, such as pro- and anti-inflammatory cytokines and the parasympathetic nervous system, that are also involved in the

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adaptation to stressors, as well as in the negative impact of chronic stress, known in every day language as being “stressed out”.

Indeed, there are important differences in the effects of acute and chronic stress, as well as differences in the consequences of acute and chronic treatment with glucocorticoids. This review explores these topics in the context of discussing the concepts of allostasis and allostatic load and overload and what they say about brain and body adaptation to acute and chronic stressors, as well as what can be done to reduce the negative aspects of allostatic overload. The principal theme of the discussion of interventions is how to take advantage of the central role that the brain plays in perceiving, responding to and adapting or not adapting efficiently to experiences and events throughout the lifecourse.

### 1.1 Defining stress, allostasis and allostatic load

“Stress” is an ambiguous term and has connotations that make it less than useful in understanding how the body can adapt or fail to adapt efficiently to experiences in daily life, including both daily hassles as well as major life events and abuse or trauma (Fig. 1). Insight into the biological and behavioral processes can lead to a better understanding of ways to intervene, a topic that will be discussed at the end of this article. There are two sides to this story (McEwen, 1998): on the one hand, the body responds to almost any sudden, unexpected event by releasing chemical mediators – e.g. catecholamines that increase heart rate and blood pressure – and help the individual 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 stroke 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” and is not intended to replace “homeostasis”).

Because chronically increased or dysregulated 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 (McEwen and Stellar, 1993; McEwen, 1998; McEwen and Wingfield, 2003). Other forms of allostatic overload involve not turning on an adequate response in the first place or not habituating to the recurrence of the same stressor and thus dampening the allostatic response. The advantage of the terminology “allostatic load/overload” over terms such as “the burden of chronic stress” is that there are changes in behavior (poor sleep, eating or drinking too much, smoking, lack of physical activity) that are part of the allostatic load/overload concept which are not so obvious in the use of the word “stress”.

### 1.2 Multiple mediators and multiple systems

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”. Glucocorticoids produced by the adrenal cortex in response to ACTH from the pituitary gland is the other major “stress hormone” besides adrenalin that we usually think of in connection with “stress”. However, there are other important hormones/mediators, as noted in Figure 2. 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. Whereas catecholamines can increase pro-inflammatory cytokine production, glucocorticoids are known to inhibit this production (Sapolsky et al., 2000). Yet, there are exceptions – pro-inflammatory effects of glucocorticoids that depend on dose and cell or tissue type (Dinkel et al., 2003; MacPherson et al., 2005). The parasympathetic nervous system also plays an important regulatory role in this non-linear network of allostasis, since it generally opposes the

sympathetic nervous system and slows the heart. Parasympathetic activity also has anti-inflammatory effects (Thayer and Lane, 2000; Borovikova et al., 2000).

These interactions are non-linear and very complex. What this non-linearity 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 non-linearity must be kept in mind in interpreting the results of any investigation that measures the biomarkers of allostasis.

The concepts of allostasis and allostatic load/overload emphasize the existence of multiple interacting mediators and the almost inevitable consequences of wear and tear on the body and brain from adapting to demands of daily life over time. These concepts also include the behavioral and physiological consequences of how an individual responds to chronic stressors, large or small, in terms of eating, sleeping, drinking alcohol, smoking, physical activity, social interactions. This condition is often referred to as being “stressed out” and behavioral patterns (sometime called “lifestyle”) are a large part of allostatic overload.

The common experience of being “stressed out” has as its core the elevation of some of the key systems that lead to allostatic overload – e.g., cortisol, sympathetic activity and pro-inflammatory cytokines, with a decline in parasympathetic activity. Nowhere is this better illustrated than for sleep deprivation, which is a frequent result of being “stressed out”. Sleep deprivation produces an allostatic overload that can have deleterious consequences (McEwen, 2006; McEwen, 2007). The effects include elevated evening cortisol, insulin and blood glucose, elevated blood pressure, reduced parasympathetic activity and elevated levels of proinflammatory cytokines, as well as the gut hormone, ghrelin, which increases appetite. Hunger for comfort foods and increased caloric intake are one result, along with depressed mood and cognitive impairment (Dallman, 2003; McEwen, 2006). In contrast to these potentially maladaptive consequences, the same mediators are involved in the natural world in adaptation to environmental changes (McEwen and Wingfield, 2003).

### 1.3 Stress in the natural world

Allostasis and allostatic load are very important for animals in the natural world, which use these adaptive responses for their own benefit or for the benefit of the species. Here, the term allostatic load is used (as opposed to allostatic overload) to refer to cumulative effects of responding to environmental demands that have an adaptive value for the survival of the species. Regarding allostasis, in Spring, a sudden snowstorm is an acute stressor to birds and disrupts mating, and elevated cortisol is pivotal in directing the birds to suspend reproduction, to find a source of food and to relocate to a better mating site or at least to delay reproduction until the weather improves (Wingfield and Romero, 2000). For allostatic load, bears preparing to hibernate for the winter eat large quantities of food and put on body fat to act as an energy source during the winter (Nelson, 1980). This anticipatory accumulation of fat is used, then, to survive the winter and provide food for gestation of young.

This is in contrast to fat accumulation that occurs in bears that are captive in zoos and eating too much, partially out of boredom, while not exercising (McEwen and Wingfield, 2003). The accumulation of fat under these latter conditions can be called “allostatic overload” referring to a condition that is associated with pathophysiology. Yet, some types of allostatic overload can also have a useful purpose for the preservation of the species, such as in migrating salmon or the marsupial mouse, which die of excessive stress after mating – the stress, and allostatic load, being caused for salmon, in part, by the migration up the rapidly flowing rivers but also because of physiological changes that represent accelerated aging (Maule et al., 1989; Farrell,

2002; Gotz et al., 2005). The result is freeing up food and other resources for the next generation. In the case of the marsupial mouse, it is only the males that die after mating, due apparently to a response to mating that reduces the binding protein, corticosteroid binding globulin (CBG), for glucocorticoids and renders them much more active throughout the body (Cockburn and Lee, 1988).

## 2. Central role of the brain

The brain is the key organ of the stress response because it determines what is threatening and, therefore, potentially stressful, and also controls the behavioral and physiological responses, and resulting lifestyle, discussed earlier in this article, which are as important to development of allostatic load and overload as the stressful experiences themselves (Fig. 1).

There are enormous individual differences in the response to stress, based upon the experience of the individual early in life and in adult life. Positive or negative experiences in school, at work or in romantic and family interpersonal relationships can bias an individual towards either a positive or negative response in a new situation. For example, someone who has been treated badly in a job by a domineering and abusive supervisor and/or has been fired will approach a new job situation quite differently than someone who has had positive experiences in employment. How the individual reacts may carry over into habits such as smoking, drinking excessively, eating too much, poor sleep, lack of exercise and interaction with friends and family, all of which contribute to allostatic overload.

Early life experiences perhaps carry an even greater weight in terms of how an individual reacts to new situations. Early life physical and sexual abuse carry with it a life-long burden of behavioral and pathophysiological problems (Felitti et al., 1998; Heim and Nemeroff, 2001). Cold and uncaring families produce long-lasting emotional problems in children (Repetti et al., 2002). Some of these effects are seen on brain structure and function and in the risk for later depression and post-traumatic stress disorder (Kaufman and Charney, 1999; Kaufman et al., 2000; Vermetten et al., 2006).

Animal models have been useful in providing insights into behavioral and physiological mechanisms. Early life maternal care in rodents is a powerful determinant of life-long emotional reactivity and stress hormone reactivity and increases in both are associated with earlier cognitive decline and a shorter lifespan (Francis et al., 1999; Cavigelli and McClintock, 2003). Effects of early maternal care are transmitted across generations by the subsequent behavior of the female offspring as they become mothers, and methylation of DNA on key genes appears to play a role in this epigenetic transmission (Weaver et al., 2004). Furthermore, in rodents, abuse of the young is associated with an attachment, rather than an avoidance, of the abusive mother, an effect that increases the chances that the infant can continue to obtain food and other support until weaning (Sullivan et al., 2000). Moreover, other conditions that affect the rearing process can also affect emotionality in offspring. For example, uncertainty in the food supply for rhesus monkey mothers leads to increased emotionality in offspring and possibly an earlier onset of obesity and diabetes (Coplan et al., 2001).

So far, we have emphasized the important role of the environment and experiences of individuals in the health outcomes, but clearly genetic differences also play an important role. Different alleles of commonly occurring genes determine how individuals will respond to experiences. For example, the short form of the serotonin transporter is associated with a number of conditions such as alcoholism, and individuals who have this allele are more vulnerable to respond to stressful experiences by developing depressive illness (Caspi et al., 2003). In childhood, individuals with an allele of the monoamine oxidase A gene are more vulnerable to abuse in childhood and more likely to themselves become abusers, and to show antisocial behaviors compared to individuals with another commonly occurring allele (Caspi

et al., 2002). Yet another example is the consequence of having the Val66Met allele of the BDNF gene on hippocampal volume, memory and mood disorders (Hariri et al., 2003; Pezawas et al., 2004; Jiang et al., 2005; Szeszko et al., 2005).

## 2.1 Stress and glucocorticoid effects on the hippocampus

**2.1.1 Types of structural plasticity**—One of the ways that stress hormones modulate function within the brain is by changing the structure of neurons. The hippocampus is one of the most sensitive and malleable regions of the brain and is also very important in cognitive function. Within the hippocampus, the input from the entorhinal cortex to the dentate gyrus is ramified by the connections between the dentate gyrus and the CA3 pyramidal neurons. One granule neuron innervates, on the average, 12 CA3 neurons, and each CA3 neuron innervates, on the average, 50 other CA3 neurons via axon collaterals, as well as 25 inhibitory cells via other axon collaterals. The net result is a 600-fold amplification of excitation, as well as a 300-fold amplification of inhibition, that provides some degree of control of the system (McEwen, 1999).

As to why this type of circuitry exists, the dentate gyrus-CA3 system is believed to play a role in the memory of sequences of events, although long-term storage of memory occurs in other brain regions (Lisman and Otmakhova, 2001). But, because the dentate gyrus-CA3 system is so delicately balanced in its function and vulnerability to damage, there is also adaptive structural plasticity, in that new neurons continue to be produced in the dentate gyrus throughout adult life, and CA3 pyramidal cells undergo a reversible remodeling of their dendrites in conditions such as hibernation and chronic stress (Popov et al., 1992; Popov and Bocharova, 1992; McEwen, 1999). The role of this plasticity may be to protect against permanent damage. As a result, the hippocampus undergoes a number of adaptive changes in response to acute and chronic stress.

One type of change involves replacement of neurons. The sub-granular layer of the dentate gyrus contains cells that have some properties of astrocytes (e.g. expression of glial fibrillary acidic protein) and which give rise to granule neurons (Kempermann and Gage, 1999; Seri et al., 2001). After bromodeoxy uridine administration to label DNA of dividing cells, these newly born cells appear as clusters in the inner part of the granule cell layer, where a substantial number of them will go on to differentiate into granule neurons within as little as 7 days. In the adult rat, 9000 new neurons are born per day and survive with a half-life of 28 days (Cameron and McKay, 2001). There are many hormonal, neurochemical and behavioral modulators of neurogenesis and cell survival in the dentate gyrus including estradiol, insulin-like growth factor-1, antidepressants, voluntary exercise and hippocampal-dependent learning (Aberg et al., 2000; Trejo, Carro et al., 2001; Czeh et al., 2001). With respect to stress, certain types of acute stress and many chronic stressors suppress neurogenesis or cell survival in the dentate gyrus, and the mediators of these inhibitory effects include excitatory amino acids acting via NMDA receptors and endogenous opioids (Gould et al., 1997).

Another form of structural plasticity is the remodeling of dendrites in the hippocampus. Chronic restraint stress causes retraction and simplification of dendrites in the CA3 region of the hippocampus (McEwen, 1999; Sousa et al., 2000). Such dendritic reorganization is found in both dominant and subordinate rats undergoing adaptation of psychosocial stress in the visible burrow system and it is independent of adrenal size (McKittrick et al., 2000).

What this result emphasizes is that it is not adrenal size or presumed amount of physiological stress per se that determines dendritic remodeling, but a complex set of other factors that modulate neuronal structure. Indeed, in species of mammals that hibernate, dendritic remodeling is a reversible process and occurs within hours of the onset of hibernation in European hamsters and ground squirrels, and it is also reversible within hours of waking of

the animals from torpor (Popov et al., 1992; Popov and Bocharova, 1992; Arendt et al., 2003). This implies that reorganization of the cytoskeleton is taking place rapidly and reversibly and that changes in dendrite length and branching are not “damage” but a form of structural plasticity.

**2.1.2 Glucocorticoids do not work alone**—Regarding the mechanism of structural remodeling, adrenal steroids are important mediators of remodeling of hippocampal neurons during repeated stress, and exogenous adrenal steroids can also cause remodeling in the absence of an external stressor. The role of adrenal steroids involve many interactions with neurochemical systems in the hippocampus, including serotonin, GABA and excitatory amino acids (McEwen, 1999; McEwen and Chattarji, 2004). Probably the most important interactions are those with excitatory amino acids such as glutamate. Excitatory amino acids released by the mossy fiber pathway play a key role in the remodeling of the CA3 region of the hippocampus, and regulation of glutamate release by adrenal steroids may play an important role (McEwen, 1999).

Among the consequences of restraint stress is the elevation of extracellular glutamate levels, leading to induction of glial glutamate transporters, as well as increased activation of the nuclear transcription factor, phosphoCREB (Wood et al., 2004). Moreover, 21d chronic restraint stress (21d chronic restraint stress) leads to depletion of clear vesicles from mossy fiber terminals and increased expression of presynaptic proteins involved in vesicle release (Magarinos et al., 1997) (Grillo et al., 2005). Taken together with the fact that vesicles that remain in the mossy fiber terminal are near active synaptic zones and that there are more mitochondria in the terminals of stressed rats, this suggests that chronic restraint stress increases the release of glutamate (Magarinos et al., 1997).

**2.1.3 Variable glucocorticoid involvement in structural plasticity**—Because glucocorticoids do not work alone, other mediators play a role in affecting the response to glucocorticoids. For neurogenesis in dentate gyrus, elevated glucocorticoid levels in an enriched environment or during physical activity are associated with increased neurogenesis and/or cell survival, even though there are other conditions in which glucocorticoids suppress neurogenesis (Mirescu and Gould, 2006). Chronicity of glucocorticoid elevation may play a role, with acute glucocorticoid elevation suppressing cell proliferation and prolonged glucocorticoid exposure ceasing to have this effect (Mirescu and Gould, 2006). Chronic restraint stress is known to reduce dentate gyrus proliferation whereas acute restraint does not have any measurable effect (Pham et al., 2003). In contrast, the ability of physical activity to elevate neurogenesis depends on the social housing environment: that is, individual housing of rats that results in elevated corticosterone levels prevented running from acutely increasing neurogenesis. Yet, reducing corticosterone levels by adrenalectomy and supplementation with corticosterone in the drinking water reinstated the positive effect of exercise on neurogenesis (Stranahan et al., 2006).

This implies a shift in glucocorticoid sensitivity and a possible factor may be excitatory neurotransmission. NMDA receptors play a role in regulation of neurogenesis, having both positive and negative effects in different experimental settings (Nacher and McEwen, 2006), and blocking NMDA receptors prevents acute glucocorticoid effects on neurogenesis (Cameron et al., 1998) indicating that the role of excitatory amino acids is a primary one. In this connection, it is important to recall the different effects of stress on memory that depend on the state of arousal and the timing with the learning situation (Joels et al., 2006). Moreover, the possible involvement of non-genomic effects of adrenal steroids must be considered (see below).

One of the consequences of the involvement of multiple mediators along with adrenal steroids in brain function is the conditional nature of adrenal steroid actions on memory. Emotional arousal for a rodent by being placed in a novel environment is required for adrenal steroids to enhance object recognition memory, that involves the hippocampus; the effects of adrenal steroids on this memory show an inverted U shaped dose response (Okuda et al., 2004). Moreover, spatial memory in a Morris water maze, a stressful behavioral task, is facilitated by adrenal steroids in wild type mice, but this facilitation is lacking in mice with a dimerization deficient glucocorticoid receptor (Oitzl et al., 1997). In the study involving novelty-induced emotional arousal, the dose range of corticosterone is such that both glucocorticoid receptor and mineralocorticoid occupancy are involved (Okuda et al., 2004). Yet, prior habituation to the novel environment, thus removing the emotional arouse of novelty, abolishes the facilitation (Okuda et al., 2004). Moreover, corticosterone doses that facilitate memory at 24h post training, inhibit memory retention at 1h post training (Okuda et al., 2004). The inhibition of memory retrieval by acute corticosteroid administration is a phenomenon that has also been reported (Newcomer et al., 1994; Newcomer et al., 1999; de Quervain et al., 2000; Roozendaal et al., 2003), and biphasic effects of corticosteroids on working memory have been described (Lupien et al., 2005). Joels and colleagues (Joels et al., 2006) propose a very plausible unifying theory that notes the importance of context and timing.

#### **2.1.4 Effects of chronic glucocorticoid administration on morphology and memory**

—In spite of the fact that glucocorticoids do not work alone, chronic corticosterone treatment by injection or by passive administration in the drinking water are both able to cause dendrites to retract in CA3 hippocampus (Woolley et al., 1990; Magarinos et al., 1999; Sousa et al., 2000). Moreover, the effects of injected corticosterone are known to be blocked by Dilantin, an inhibitor of ion channels that has anti-epileptic effects, a result that is consistent with the evidence that glutamate is involved in remodelling (Watanabe et al., 1992). Yet, there is an important difference between the effects of repeated stress and chronic glucocorticoid exposure, in that chronic corticosterone treatment was reported to reduce the volume fraction occupied by mitochondria in the CA3 region (Coburn-Litvak et al., 2004) while, as noted earlier, 21d chronic restraint stress increases mitochondrial profiles in mossy fiber terminals (Magarinos et al., 1997). This suggests that somewhat different mechanisms may be involved in effects of chronic restraint stress and corticosterone in hippocampus, a possibility that is supported by the finding that, while corticosterone treatment in the drinking water and 21d chronic restraint stress both caused CA3 remodeling when given alone, the combination of chronic restraint stress plus corticosterone treatment abolished the morphological change (Magarinos et al., 1998). These mechanistic differences remain to be determined.

In spite of the possible differences in mechanism, chronic corticosterone treatment and chronic restraint or immobilization stress both cause impairment of hippocampal dependent memory tasks, although there are differences in magnitude of effect that appear to be dependent on dose of corticosterone, duration of treatment, age of rat being treated and whether or not the cognitive task is a demanding one (Dachir et al., 1993; Arbel et al., 1994; Bardgett et al., 1994; Bodnoff et al., 1995; Endo et al., 1996; Bardgett et al., 1996; Mclay et al., 1998; Coburn-Litvak et al., 2003). These studies indicate that only more prolonged treatment by higher glucocorticoid doses are able to impair performance on more demanding tasks involving hippocampal function and that they do so under conditions in which there is no neuronal loss but there are reductions in volume of hippocampal neuropil that may be due to loss of glia cells or reduction of dendritic length and branching. Given these results with rodents, it is not so surprising that a relatively modest regimen of cortisol treatment for 12 months did not cause outright neuronal loss in the pigtail macaque hippocampus (Leverenz et al., 1999).

**2.1.5 Role of genomic and non-genomic mechanisms**—The hippocampus expresses both Type I (mineralocorticoid, mineralocorticoid receptor) and Type II (glucocorticoid,

glucocorticoid receptor) receptors, and these receptors mediate a biphasic response to adrenal steroids in the CA1 region although not in the dentate gyrus (Joels, 2006), which, nevertheless, shows a diminished excitability in the absence of adrenal steroids (Margeanu et al., 1994). Other brain regions, such as the paraventricular nucleus, lacking in mineralocorticoid receptors but having glucocorticoid receptors, show a monophasic response (Joels, 2006). Adrenal steroids exert biphasic effects on excitability of hippocampal neurons in terms of long-term potentiation and primed burst potentiation (Diamond et al., 1992; Pavlides et al., 1994; Pavlides et al., 1995) and show parallel biphasic effects upon memory (Pugh et al., 1997).

In considering possible mechanisms for the biphasic responses, the co-expression of mineralocorticoid receptors and glucocorticoid receptors in the same neurons could give rise to heterodimer formation and a different genomic activation from that produced by either mineralocorticoid receptor or glucocorticoid receptor homodimers (Joels, 2006). In addition, deletion of the Type I (mineralocorticoid receptors) receptor by genetic means has revealed that MR are required for non-genomic regulation of glutamatergic transmission by glucocorticoids (Karst et al., 2005), a phenomenon that involved glucocorticoid enhancement of extracellular levels of glutamate (Venero and Borrell, 1999) that plays an important role in both modulatory and excitotoxic effects of glucocorticoids (see subsection below: "Mechanisms of structural remodeling"). Although beyond the scope of this review, the subject of non-genomic actions of adrenal steroids has taken on increasing importance in view of the discovery of adrenal steroid receptors that are G protein coupled in the amphibian brain (Orchinik et al., 1991), as well as glucocorticoid receptor immunoreactivity in post-synaptic and other non-nuclear regions of neurons in the rodent brain (Liposits and Bohn, 1993; Johnson et al., 2005) and a large number of reported rapid, non-genomic actions of adrenal steroids (Borski, 2000; Makara and Haller, 2001). Hence it is perhaps not surprising that there are conditions involving neural transmission that favor either rapid positive or negative actions of adrenal steroids on processes such as learning and memory.

Although much of the work on mineralocorticoid receptors and glucocorticoid receptors has been done on rat and mouse brains, it is important to note that the rhesus monkey hippocampus has a predominance of mineralocorticoid receptors and relatively less glucocorticoid receptors compared to rodent species (Sanchez et al., 2000). This finding may have important implications for the effects of adrenal steroids on learning and vulnerability to stress and excitotoxicity, as well as age-related changes discussed earlier.

## 2.2 Prefrontal cortex and amygdala

Repeated stress also causes changes in other brain regions such as the prefrontal cortex and amygdala. Repeated stress causes dendritic shortening in medial prefrontal cortex (Sousa et al., 2000; Wellman, 2001; Vyas et al., 2002; Kreibich and Blendy, 2004; Cook and Wellman, 2004; Radley et al., 2004; Brown et al., 2005; Radley et al., 2005) but produces dendritic growth in neurons in amygdala (Vyas et al., 2002), as well as in orbitofrontal cortex (Liston et al., In Press). Along with many other brain regions, the amygdala and prefrontal cortex also contain adrenal steroid receptors; however, the role of adrenal steroids, excitatory amino acids and other mediators has not yet been studied in these brain regions. Nevertheless, in the amygdala, there is some evidence regarding mechanism, in that tissue plasminogen activator (tPA) is required for acute stress to activate not only indices of structural plasticity but also to enhance anxiety (Melchor et al., 2003). These effects occur in the medial and central amygdala and not in basolateral amygdala and the release of CRH acting via CRH1 receptors appears to be responsible (Matys et al., 2004).

Acute stress induces spine synapses in CA1 region of hippocampus (Shors et al., 2001) and both acute and chronic stress also increases spine synapse formation in amygdala (Vyas et al., 2002) but chronic stress decreases it in hippocampus (Pawlak et al., 2005). Moreover, chronic

stress for 21 days or longer impairs hippocampal-dependent cognitive function (McEwen, 1999) and enhances amygdala-dependent unlearned fear and fear conditioning (Conrad et al., 1999), which are consistent with the opposite effects of stress on hippocampal and amygdala structure. Chronic stress also increases aggression between animals living in the same cage, and this is likely to reflect another aspect of hyperactivity of the amygdala (Wood et al., 2003). Behavioral correlates of remodeling in the prefrontal cortex include impairment in attention set shifting, possibly reflecting structural remodeling in the medial prefrontal cortex (Liston et al., In Press).

### 2.3 Role of other modulators in structural remodeling

Extracellular molecules play a role in remodeling in the hippocampus and amygdala. Neural cell adhesion molecule (NCAM) and its polysialated-NCAM (PSA-NCAM), as well as L1 are expressed in the dentate gyrus and CA3 region and the expression of both NCAM, L1, and PSA-NCAM are regulated by 21d chronic restraint stress (Sandi, 2004). Tissue plasminogen activator (tPA) is an extracellular protease and signalling molecule that is released with neural activity and is required for chronic stress-induced loss of spines and NMDA receptor subunits on CA1 neurons (Pawlak et al., 2005).

Within the neuronal cytoskeleton, the remodeling of hippocampal neurons by chronic stress and hibernation alters the acetylation of microtubule subunits that is consistent with a more stable cytoskeleton (Bianchi et al., 2003) and alters microtubule associated proteins, including the phosphorylation of a soluble form of tau, which is increased in hibernation and reversed when hibernation is terminated (Arendt et al., 2003).

Neurotrophic factors also play a role in dendritic branching and length in that BDNF +/- mice show a less branched dendritic tree and do not show a further reduction of CA3 dendrite length with chronic stress, whereas wild-type mice show reduced dendritic branching (Magarinos, McEwen, unpublished). However, there is contradictory information thus far concerning whether chronic restraint stress reduces BDNF mRNA levels, some reporting a decrease (Smith and Cizza, 1996) and other studies reporting no change (Kuroda and McEwen, 1998; Isgor et al., 2004). This may reflect the balance of two opposing forces, namely, that stress triggers increased BDNF synthesis to replace depletion of BDNF caused by stress (Marmigere et al., 2003). BDNF and corticosteroids appear to oppose each other – with BDNF reversing reduced excitability in hippocampal neurons induced by stress levels of corticosterone (Hansson et al., 2006).

Corticotrophin releasing factor (CRF) is a key mediator of many aspects related to stress (Koob, 1999). CRF in the paraventricular nucleus regulates ACTH (adrenocorticotrophic hormone) release from the anterior pituitary gland, whereas CRF in the central amygdala is involved in control of behavioral and autonomic responses to stress, including the release to tPA that is an essential part of stress-induced anxiety and structural plasticity in the medial amygdala (Matys et al., 2004). CRF in the hippocampus is expressed in a subset of GABA neurons (Cajal-Retzius cells) in the developing hippocampus, and early life stress produces a delayed effect that reduces cognitive function and the number of CA3 neurons as well as decreased branching of hippocampal pyramidal neurons (Brunson et al., 2001; Brunson et al., 2005). Indeed, CRF inhibits dendritic branching in hippocampal cultures *in vitro* (Chen et al., 2004).

## 3. Translation to the human brain

### 3.1 Depression, Cushing's Disease and Anxiety Disorders

Much of the impetus for studying the effects of stress on the structure of the human brain has come from the animal studies summarized thus far. Although there is very little evidence

regarding the effects of ordinary life stressors on brain structure, there are indications from functional imaging of individuals undergoing ordinary stressors, such as counting backwards that there are lasting changes in neural activity (Wang et al., 2005). Another study, using voxel-based morphometry, has uncovered a relationship between shrinkage of grey matter volume in the hippocampus and orbitofrontal cortex and prospective reports of chronic life stress over a 20 year period (Gianaros et al., 2007).

Moreover, the study of depressive illness and anxiety disorders has also provided some insights. Life events are known to precipitate depressive illness in individuals with certain genetic predispositions (Kessler, 1997; Kendler, 1998; Caspi et al., 2003). Moreover, brain regions such as the hippocampus, amygdala and prefrontal cortex show altered patterns of activity in PET (positron emission tomography) and fMRI (functional magnetic resonance imaging) and also demonstrate changes in volume of these structures with recurrent depression: decreased volume of hippocampus and prefrontal cortex and amygdala (Drevets et al., 1997; Sheline et al., 1999; Sheline et al., 2003).

Interestingly, amygdala volume has been reported to increase in the first episode of depression, whereas hippocampal volume is not decreased (MacQueen et al., 2003; Frodl et al., 2003). It has been known for some time that stress hormones, such as cortisol, are involved in psychopathology, reflecting emotional arousal and psychic disorganization rather than the specific disorder *per se* (Sachar et al., 1973). We now know that adrenocortical hormones enter the brain and produce a wide range of effects upon it.

In Cushing's disease, there are depressive symptoms that can be relieved by surgical correction of the hypercortisolemia (Starkman and Scheingart, 1981; Murphy, 1991). Both major depression and Cushing's disease are associated with chronic elevation of cortisol that results in gradual loss of minerals from bone and abdominal obesity. In major depressive illness, as well as in Cushing's disease, the duration of the illness and not the age of the subjects predicts a progressive reduction in volume of the hippocampus, determined by structural magnetic resonance imaging (Starkman et al., 1992; Sheline et al., 1999). Moreover, there are a variety of other anxiety-related disorders, such as post-traumatic stress disorder (PTSD) (Bremner, 2002) (Pitman, 2001) and borderline personality disorder (Driessen et al., 2000), in which atrophy of the hippocampus has been reported, suggesting that this is a common process reflecting chronic imbalance in the activity of adaptive systems, such as the HPA (hypothalamo-pituitary-adrenal axis) axis, but also including endogenous neurotransmitters, such as glutamate.

Another important factor in hippocampal volume and function is glucose regulation. Outright Type 2 diabetes and poor glucose control as measured by glycosylated hemoglobin is associated with reduced hippocampal volume (Gold et al., 2007). Furthermore, poor glucose regulation is associated with smaller hippocampal volume and poorer memory function in individuals in their 60's and 70's who have "mild cognitive impairment" (mild cognitive impairment) (Convit et al., 2003), and both mild cognitive impairment and Type 2, as well as Type 1, diabetes are recognized as risk factors for dementia (Ott et al., 1996; de Leon et al., 2001; Haan, 2006).

### 3.2 Positive affect, self esteem and social support

Having a positive outlook on life and good self esteem appear to have long-lasting health consequences (Pressman and Cohen, 2005), and good social support is also a positive influence on the measures of allostatic load (Seeman et al., 2002). Positive affect, assessed by aggregating momentary experiences throughout a working or leisure day, was found to be associated with lower cortisol production and higher heart rate variability (showing higher parasympathetic activity), as well as a lower fibrinogen response to a mental stress test (Steptoe et al., 2005).

On the other hand, poor self esteem has been shown to cause recurrent increases in cortisol levels during a repetition of a public speaking challenge in which those individuals with good self esteem are able to habituate, i.e., attenuate their cortisol response after the first speech (Kirschbaum et al., 1995). Furthermore, poor self esteem and low internal locus of control have been related to 12–13% smaller volume of the hippocampus, as well as higher cortisol levels during a mental arithmetic stressor (Pruessner et al., 1999; Pruessner et al., 2005).

Related to both positive affect and self esteem is the role of friends and social interactions in maintaining a healthy outlook on life. Loneliness, often found in people with low self esteem, has been associated with larger cortisol responses to wakening in the morning, and higher fibrinogen and natural killer cell responses to a mental stress test, as well as sleep problems (Steptoe et al., 2004). On the other hand, having 3 or more regular social contacts, as opposed to 0 to 2 such contacts, is associated with lower allostatic load scores (Seeman et al., 2002).

#### 4. Interventions: conventional vs top down

If being “stressed out” has such pervasive long-term effects on the brain as well as the body, what are the ways to reduce the negative consequences? The answers are simple and obvious but often difficult to achieve and they involve not only individual behaviors but also the ways in which people’s lives are shaped by policies of government and the private sector.

From the standpoint of the individual, it seems obvious that a major goal should be to try to improve sleep quality and quantity, to have good social support and a positive outlook on life, to have positive self-esteem, to maintain a healthy diet, to avoid smoking and to engage in regular moderate physical activity. Concerning physical activity, it is not necessary to become an extreme athlete, and seemingly any amount of moderate physical activity helps (Bernadet, 1995; Rovio et al., 2005).

From the standpoint of organization of society, the goal should be to create incentives at home and in work situations and build community services and opportunities that encourage the development of the beneficial individual lifestyle practices. The Acheson Report (Acheson, 1998) from the United Kingdom in 1998 recognized that no public policy should be enacted without considering the implications for health of all citizens. Thus basic education, housing, taxation, setting of a minimum wage, and addressing occupational health and safety and environmental pollution regulations are all likely to affect health via a myriad of mechanisms. At the same time, providing higher quality food and making it affordable and accessible in poor as well as affluent neighborhoods is necessary for people to eat better, providing they also learn what types of food to eat. Likewise, making neighborhood safer and more congenial and supportive (Sampson et al., 1997) can improve opportunities for positive social interactions and increased recreational physical activity. However, governmental policies are not the only way to reduce allostatic load. For example, businesses that encourage healthy lifestyle practices among their employees are likely to gain reduced health insurance costs and possibly a more loyal workforce (Aldana, 2001; Pelletier, 2001; Whitmer et al., 2003).

These are the “top down” strategies that are likely to work via higher cognitive brain areas and their downstream effects on many processes. As simple as the solutions seem to be, changing behavior and solving problems that cause stress at work and at home is often difficult and may require professional help on the personal level, or even a change of job or profession. Yet these are important goals because the prevention of later disease is very important for full enjoyment of life and also to reduce the financial burden on the individual and on society.

Nevertheless, many people often lack the proactive, long term view of themselves and/or feel that they must maintain a stressful lifestyle and, if they deal with these issues at all, they want to treat their problems with a pill. Are there any medications to treat being stressed out? In fact,

there are many useful pharmaceutical agents: sleeping pills, anxiolytics, beta blockers and antidepressants are all drugs that are used to counteract some of the problems associated with being stressed out. Likewise, drugs that reduce oxidative stress or inflammation, block cholesterol synthesis or absorption and treat insulin resistance or chronic pain and can help deal with the metabolic and neurologic consequences of being stressed out. All are valuable to some degree, and yet each one has its side effects and limitations that are based in part on the fact that all of the systems that are dysregulated in allostatic overload are also systems that interact with each other and perform normal functions when properly regulated. Because of the non-linearity of the systems of allostasis, the consequences of any drug treatment may be either to inhibit the beneficial effects of the systems in question or to perturb other systems that interact with it in a direction that promotes an unwanted side effect. So the best solution would seem to be not to rely solely on such medications and find ways to change personal behaviors in a positive direction. Motivation and decision making and perseverance are all functions of the brain!

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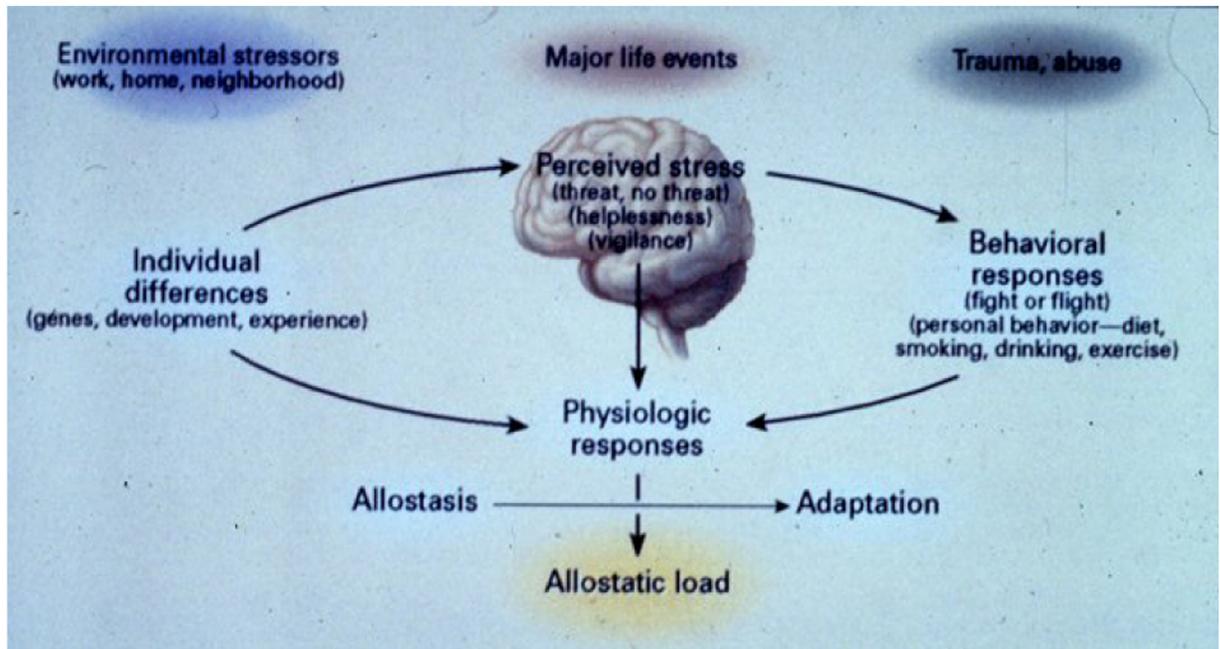
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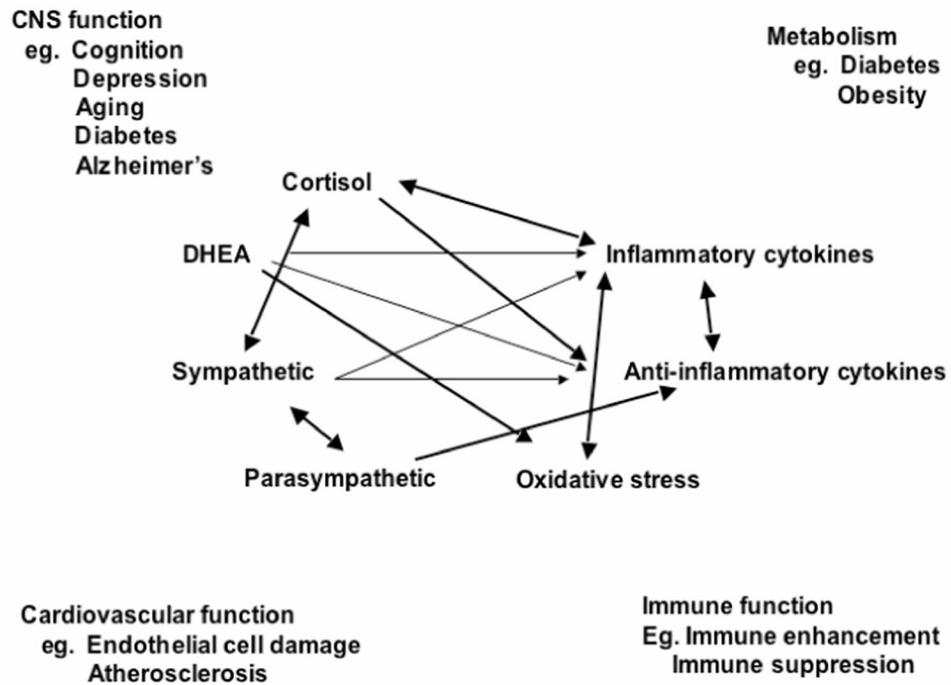
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**Fig. 1. Brain is the central organ of the stress response**

The brain is the central organ of perceiving and responding to stressors and determines both the behavioral and physiological responses.

The response to acute stress is adaptive (allostasis) whereas the response to chronic stress can lead to dysregulation of the mediators and exacerbate pathophysiology (allostatic load or overload). Early life experiences and genetic constitution play a major role in determining both acute and chronic responses. Besides major life events and trauma and abuse, ordinary stressors from the family, neighborhood and work are major contributors to allostatic load. Reprinted from McEwen 1998, by permission.



**Fig. 2. Mediators of stress and allostasis operate in a non-linear network**  
 Non-linear network of mediators of allostasis involved in the stress response. Arrows indicate that each system regulates the others, creating a non-linear network. Note that many body systems are influenced by the same mediators.