Brain on stress: How the social environment gets under the skin

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Stress is a state of the mind, involving both brain and body as well as their interactions; it differs among individuals and reflects not only major life events but also the conflicts and pressures of daily life that alter physiological systems to produce a chronic stress burden that, in turn, is a factor in the expression of disease. This burden reflects the impact of not only life experiences but also genetic variations and individual health behaviors such as diet, physical activity, sleep, and substance abuse; it also reflects stable epigenetic modifications in development that set lifelong patterns of physiological reactivity and behavior through biological embedding of early environments interacting with cumulative change from experiences over the lifespan. Hormones associated with the chronic stress burden protect the body in the short run and promote adaptation (allostasis), but in the long run, the burden of chronic stress causes changes in the brain and body that can lead to disease (allostatic load and overload). Brain circuits are plastic and remodeled by stress to change the balance between anxiety, mood control, memory, and decision making. Such changes may have adaptive value in particular contexts, but their persistence and lack of reversibility can be maladaptive. However, the capacity of brain plasticity to effects of stressful experiences in adult life has only begun to be explored along with the efficacy of top-down strategies for helping the brain change itself, sometimes aided by pharmaceutical agents and other treatments.

brain structural plasticity | adverse childhood experiences | interventions

The brain is the central organ of stress and adaptation (Fig. 1). The social environment as well as the physical environment have powerful effects on the body and the brain through the neuroendocrine, autonomic, and immune systems (1–3). Two important processes are evident: The first process is the biological embedding of early experiences, the subject of this symposium, that determines operating ranges of physiological systems for the effects of later experiences, and the second process is the cumulative wear and tear of the physical and social environment on the brain and body acting through the neuroendocrine, autonomic, metabolic, and immune systems. This review focuses on the central role of the brain in both processes (2, 3) and the interaction of biological embedding with cumulative wear and tear over the life course; it considers the nature of interventions that can alter the predispositions and risks created by biological embedding as well as those interventions caused by life experiences and the health-damaging and -promoting behaviors by which individuals live their lives. In particular, increasing understanding of the plasticity of the mature brain offers some hope for finding better strategies to help those individuals whose lives have been burdened by adverse early-life experiences. At the same time, this view presents an encouraging and broader message as to the potential for experience—and pharmacologically regulated brain plasticity. Our current understanding in this area has been facilitated by advances in neuroendocrinology and neuroscience.

Historical Background

Neuroendocrinology, which developed and flourished beginning in the 1950s through the pioneering work of Geoffrey W. Harris (4) and many others (5) and led to the Nobel Prize recognition of Roger Guillemin (6) and Andrew V. Schally (7), focused on the hypothalamus and its connection with the pituitary gland. Hormonal feedback on these organs was part of the negative and positive feedback regulation of pituitary hormone secretion. Work on estradiol feedback (8, 9) called attention to hormone effects on mating behavior and defense of territory and brought in structures like the amygdala in addition to the hypothalamus. Glucocorticoid actions were focused on the hypothalamus until the discovery of glucocorticoid and mineralocorticoid receptors in the hippocampus (10) began to shift the focus from the feedback regulation of neuroendocrine function to other aspects of behavior, including cognition, mood, and self-regulatory behaviors.

Robert M. Sapolsky (11), studying the aging brain, developed the "glucocorticoid-cascade hypothesis" of stress and aging in the work by Sapolsky et al. (11), which focused on the deleterious effects of glucocorticoid feedback on the hippocampus, and this finding was reinforced by the elegant studies of Landfield et al. (12). Other than damage, however, there are now known to be many beneficial, adaptive actions of adrenal steroids on memory and immune function (13–15). Moreover, adrenal steroids do not work in a vacuum, but rather, they work in concert with other mediators of the autonomic, immune, and metabolic hormone systems (1); this work, together with the adaptive as well as potentially damaging aspects of these mediators, became part of the concepts of allostasis and allostatic load (16).

This notion of protection and damage as ends of possible outcomes of the actions of the mediators of allostasis was extended back to the brain by the finding of structural plasticity not only in hippocampus but in other brain regions, such as amygdala, prefrontal cortex, and nucleus accumbens (2). The concept of the plasticity of the adult brain is traceable to the enriched environment studies of the 1960s (17). Indeed, acute and chronic stress-induced plasticity is reversible, at least in young adult brains (18), and it does not constitute brain damage per se; however, the overstimulation of these systems (e.g., by seizures, head trauma, and ischemia) does cause permanent irreversible damage (19). Moreover, there is evidence that the aging brain loses its resilience [that is, its ability to recover from stress-induced changes (18) as well as those changes caused by isolation and an unhealthy lifestyle], which can be ameliorated by top-down interventions, such as physical activity and positive social interactions (20, 21). In this connection and others, modern imaging methods are enabling translation from animal models to the human brain.
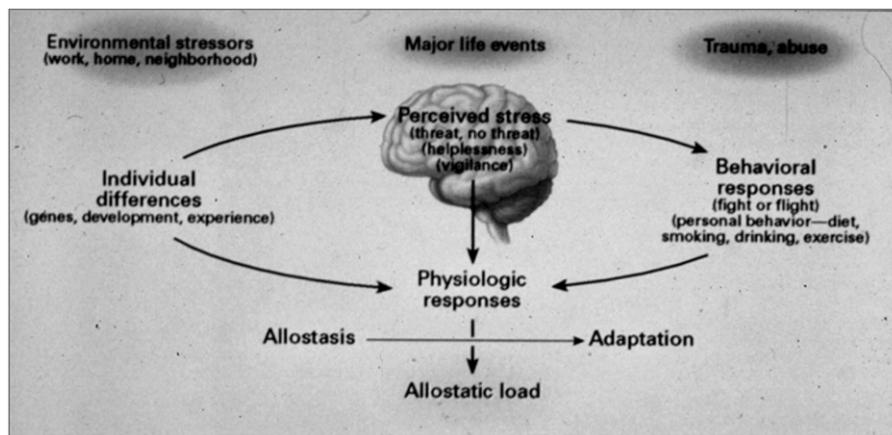
Fig. 1. Central role of the brain in the protective and damaging effects of the mediators of stress and adaptation operating through the process of allostasis that can lead to allostatic load and overload when overused and dysregulated. Reproduced from ref. 16, copyright (1998) Massachusetts Medical Society.

Concurrently, studies of rodent mother–infant interactions led to remarkable findings that are discussed in this symposium regarding the epigenetic effects of maternal care. These findings have been complemented by studies of the effects of prolonged maternal separation (22), novelty exposure and consistency of maternal care (23), prenatal stress (24), postnatal maternal abuse (25), and maternal anxiety (26) on subsequent brain and behavioral development. Again, modern imaging methods are enabling this information to be translated to the developing human brain (27), and indeed, imaging with neuropsychology is an area where rapid progress is being made and needs to be made to translate the growing basic neuroscience knowledge of mechanisms into clinical relevance and application.

The studies of effects of early-life adversity in children on later physical as well as cognitive and mental health disorders, pioneered by the Adverse Childhood Experiences study of Anda et al. (28) and the pioneering integration of social and biological factors for brain development in "From Neurons to Neighborhoods" (29), have highlighted the importance of nurturing early-life experiences for healthy brain and body function over the life course. Although prevention is clearly the best and most cost-effective and humane course, it is important to consider treatment for those individuals who have experienced abuse. The following discussion will amplify each of these points.

Cumulative Burden—Allostasis and Allostatic Load/Overload

The biphasic nature of actions of mediators of allostasis (i.e., the active processes of adaptation) is well-illustrated by acute and chronic glucocorticoid effects acting in concert with other mediators. For example, glucocorticoids and catecholamines work synergistically to acutely enhance acquired immunity (e.g., delayed-type hypersensitivity) and also, promote memory of aversive events (13, 14). Sympathetic stimulation increases inflammatory cytokine production (30), and this production, in turn, increases glucocorticoid production, which typically has antiinflammatory and immune modulatory actions (31) but can also exacerbate inflammation under some circumstances (32). Parasympathetic activation not only counterbalances effects of sympathetic activation but also has antiinflammatory actions (33). Likewise, low levels of inflammatory cytokines have neurotrophic and neuroprotective actions (34), whereas overproduction accompanies a wide range of diseases of brain and body (35). Finally, metabolic hormones (e.g., insulin, leptin, and ghrelin) interact both positively and negatively with these other mediators: They interact positively in mediating beneficial effects of physical activity and negatively for metabolic syndrome (36).

It should be emphasized that the consideration of multiple interacting mediators of allostasis is a fundamental concept that can be applied at many levels of analysis from molecules, cells, and brain circuits (systems biology) (37) to social interactions and societies, where social scientists have long recognized this complexity. Function at both levels occurs by multifactorial and often reciprocal interactions, with causation arising from the operation of the network of factors.

Batteries of biomarkers that measure allostatic load (also termed allostatic overload to highlight pathophysiology of the extreme) (38) tap into the major mediators of allostasis along with some key secondary outcomes, such as body mass index or waist–hip ratio and glycosylated hemoglobin (39), and provide a broad-based assessment of the dysregulation of these adaptive systems that has turned out to have predictive value in a variety of epidemiologic studies (40). However, the primary core of allostasis and allostatic load focuses on how individuals perceive and have or do not have confidence in their ability to cope with the burdens of life experiences (i.e., a sense of control as reflected in perceived stress) (41). This focus brings us to the brain.

Glucocorticoids and Hippocampus—Biphasic Effects and Plasticity

The discovery of receptors for glucocorticoids in the hippocampus 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 (42) and remodeling of dendrites and synapses in the major neurons of Ammon's horn (43). 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, BDNF, lipocalin-2, and tissue plasminogen activator (1, 44). 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 unidentified G protein-coupled membrane receptor related to endocannabinoid production (45, 46).

Studies of the human hippocampus have shown shrinkage of the hippocampus not only in mild cognitive impairment and Alzheimer's disease (47) but also in type 2 diabetes (48), prolonged major depression (49), Cushing disease (50), and posttraumatic stress disorder (PTSD) (51). Moreover, in nondisease conditions such as chronic stress (52), chronic inflammation (53), lack of physical activity (54), and jet lag (55), smaller hippocampal or temporal lobe volumes have been reported.

Thus far, there is no indication of whether these changes are caused by volume reduction in dentate gyrus because of inhibited neuronal replacement, dendritic shrinkage, glial cell loss, or a combination of all three factors. Autopsy studies on depression suicide have indicated loss of glial cells and smaller neuron soma size (56), 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, and leptin and that insulin-like growth factor-1 mediates exercise-induced neurogenesis (1). Thus, other than 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 (1).

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 (14), and acute stress causes a delayed formation of dendritic spines in basolateral amygdala neurons and an increase of anxiety after 10 d (57). Chronic stress of the same type, which impairs dentate gyrus neurogenesis and causes dendritic shrinkage and spine loss in Ammon's horn neurons, causes expansion of dendrites in the basolateral amygdala (58) while causing spine downregulation in the medial amygdala (59). The latter is dependent on tissue plasminogen activator, whereas the former is not (59).

Translating to the human brain, amygdala hyperactivity is reported in major depression as well as anxiety disorders, such as PTSD (60), and enlargement of the amygdala has been reported in acute depression (61). With respect to PTSD, an approach after acute trauma is the administration of glucocorticoids based on the counterintuitive findings that low normal glucocorticoid levels at the time of trauma predispose to development of PTSD symptoms (62). Increased amygdala reactivity to angry and sad faces is reported in individuals with early signs of cardiovascular disease (63), 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 (64) as well as after sleep deprivation (65).

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, whereas dendrites expand in the orbitofrontal cortex (66). Because the orbitofrontal cortex is involved in determining the saliency of reward or punishment (67), this finding 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 (66, 68, 69). Moreover, circadian disruption impairs cognitive flexibility and causes shrinkage of medial prefrontal cortical dendrites (70). These studies complement the studies on the hippocampus/temporal lobe noted above in flight crews suffering from chronic jet lag (55) 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 (18), and this finding harkens back to the glucocorticoid cascade hypothesis (11), because the mechanism for medial prefrontal cortical dendritic remodeling is likely to involve the same mechanisms

as in the hippocampus (namely, excitatory amino acids and glucocorticoids) (71, 72).

Biological Embedding—Effects of Stressful Experiences in Early Life

Early-life events related to maternal care in animals as well as parental care in humans play a powerful role in later mental and physical health, which was shown by the adverse childhood experiences (ACE) studies and recent work noted below. Animal models have contributed enormously to our understanding of how the brain and body are affected, starting with the "neonatal handling" studies of Levine et al. (73) and the recent elegant work by Meaney and Szyf (74). Epigenetic transgenerational effects transmitted by maternal care are central to these findings. Other than the amount of maternal care, the consistency over time of that care and the exposure to novelty are also very important not only in rodents (23, 75) but also, monkey models (76). Prenatal stress impairs hippocampal development in rats as does stress in adolescence (77). Abusive maternal care in rodents and the surprising attachment shown by infant rats to their abusive mothers seems to involve an immature amygdala (25), activation of which by glucocorticoids causes an aversive conditioning response to emerge. Maternal anxiety in the variable foraging demand model in rhesus monkeys leads to chronic anxiety in the offspring as well as signs of metabolic syndrome (26, 78).

In studies on ACE in human populations, there are reports of increased inflammatory tone not only in children but also in young adults related to early-life abuse, which includes chronic harsh language as well as physical and sexual abuse (79, 80). Chaos in the home is associated with development of poor self-regulatory behaviors as well as obesity (81). It should be noted that the ACE study was carried out in a middle class population (28), indicating that poverty is not the only source of early-life stressors.

Nevertheless, low socioeconomic status (SES) does increase the likelihood of stressors in the home and neighborhood, including toxic chemical agents such as lead and air pollution (82). Without a determination of exact causes, it has been reported that low SES children are found to be more likely to be deficient in language skills as well as self-regulatory behaviors and certain types of memory that are likely to be reflections of impaired development of parasylvian gyrus language centers, prefrontal cortical systems, and temporal lobe memory systems (83, 84). Low SES is reported to correlate with smaller hippocampal volumes (85). Lower subjective SES, an important index of objective SES, is associated with reduction in prefrontal cortical gray matter (86). Moreover, having grown up in lower SES environment is accompanied by greater amygdala reactivity to angry and sad faces (87), which as noted above, may be a predisposing factor for early cardiovascular disease that is known to be more prevalent at lower SES levels (88). Finally, depression is often associated with low SES; children of depressed mothers who were followed longitudinally have shown increased amygdala volume, whereas hippocampal volume was not affected (27).

However, on the positive side, there are the reactive alleles that, in nurturing environments, lead to beneficial outcomes and even better outcomes compared with less-reactive alleles, although those same alleles can enhance adverse outcomes in a stressful early-life environment (89–91). Regarding adverse outcomes and good and bad environments, it must be recognized, as stated in the Active Calibration Model (92), that allostatic processes are adjusted by epigenetic influences to optimize the individuals adaptation to and resulting fitness for a particular environment, whether more or less threatening or nurturing. However, there are trade-offs in terms of physical and mental health that, on the one hand, may increase the likelihood of passing on one's genes by improving coping with adversity and enhancing mental health

and overall reproductive success but on the other hand, may impair later health (e.g., by eating of comfort foods) (93).

Indeed, the Active Calibration Model and the concepts of allostasis and allostatic load are orthogonal and provide complementary ways of understanding individual developmental trajectories, which was suggested in the work by Rutter (94); this work called for studies on individual differences in vulnerability and resilience in person–environment interactions and a better understanding of the interplay between stressor exposure and later outcomes along a developmental and life-course trajectory (94, 95). In this connection, it should be noted that resilience means not only the ability to recover from stress-induced change but also the ability to show experience-related change (for example, when an individual from a safe environment is placed into a dangerous one or vice versa) (92, 96).

Interventions—How Far Can They Go?

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 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 (2, 3, 95). 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 (97). 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" (98, 99) independently of any notable disorder and within the range of normal behavior and physiology.

Moreover, interventions to change physiology and brain function may be useful when adaptation to a particular environment, as in the Active Calibration Model (92), 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 (100). However, it is perhaps premature to draw that conclusion, because the ultimate limits of adult brain plasticity are still unknown, which 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 (101). Moreover, regular physical activity, consisting of walking 1 h/d for 5 of 7 d/wk, increases hippocampal volume in previously sedentary adults (20). This finding complements work showing that fit individuals have larger hippocampal volumes than sedentary adults of the same age range (54). It is also well-known that regular physical activity is an effective antidepressant and protects again cardiovascular disease, diabetes, and dementia (102, 103). Moreover, intensive learning has also been shown to increase volume of the human hippocampus (104).

Social integration and support and finding meaning and purpose in life are known to be protective against allostatic load (105) and dementia (106). Programs such as the Experience Corps that promote these aspects along with increased physical activity have been shown to slow the decline of physical and mental health and improve prefrontal cortical blood flow in a similar manner to regular physical activity (21, 107).

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 (49, 108) and prefrontal cortex (109). Although there does not seem to be neuronal loss, there is evidence for glial cell loss and smaller neuronal cell nuclei (56, 110), 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 (111) and bipolar (112) 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 (28). 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 (113). However, there are other potential applications, such as the recently reported ability of fluoxetine to enhance recovery from stroke (114). However, a key aspect of this view (115) 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 intensive physiotherapy to promote neuroplasticity to counteract the effects of a stroke).

This finding 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 (116) and food restriction on the other hand (117), in which reducing inhibitory neuronal activity seems to play a key role (118). 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 (98).

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 (119) and amygdala in the case of chronic anxiety (120). This finding reinforces two important messages: (*i*) plasticity-facilitating treatments should be given within the framework of a positive behavioral or physical therapy intervention, and (*ii*) negative experiences during the window may even make matters worse (115). In that connection, it should be noted that BDNF also has the ability to promote pathophysiology like in seizures (121–123).

Conclusion

The ability of the brain and body to adapt to acute and chronic stress is an increasingly important topic in the modern world. What this overview has emphasized is the interplay between cumulative wear and tear (allostatic load/overload) facilitated by the same mediators that are essential for adaptation and survival. The brain is the central organ of the perception and the response to stressors, and it is a target of allostatic load/overload along with the rest of the body (Fig. 1). Biological embedding of early experiences interacts with influences of the chemical and physical environment and sets the course for the body, because it attempts to cope with challenges during the life course. This review has also noted that, as embodied in the Active Calibration Model, the individual adapts to particular environments and experiences to achieve reproductive success; however, these adaptations to one context may be maladaptive to another environment, and as a result, they may predispose the individual to greater allostatic load/overload.

In the case of adverse early-life experiences in which adaptation is directed to threat and danger, although prevention is the

best and most economical course of action, treatments after the problems with physical and mental health have developed are also necessary. This review has noted that top-down therapies, sometimes aided by pharmaceutical agents, have potential that must be explored farther, because neuroscience and now, clinical practice are beginning to recognize the potential of brain plasticity after the early developmental period (124).

Finally, although this review has emphasized the neurobiological underpinnings of toxic and tolerable stress and adverse early-life experiences, it has also noted many positive aspects of brain plasticity involving such activities as regular exercise and experiences that give meaning and purpose to life, such as in the concepts of eudamonia and positive health noted earlier. Thus, a future research goal should be to provide a neurobiological framework for understanding positive health, positive effect, and self-efficacy and self-esteem and how these components are biologically embedded in a nurturing environment by epigenetic influences, including effects on reactive alleles in the genome.

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Correction

The authors note that on page 17184, right column, first paragraph, line 4, "effect" should instead appear as "affect."

CORRECTION