Correction

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Correction for "Brain on stress: How the social environment gets under the skin," by Bruce S. McEwen, which appeared in supplement 2, October 16, 2012, of *Proc Natl Acad Sci USA* (109:17180–17185; first published October 8, 2012; 10.1073/pnas.1121254109).

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

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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.

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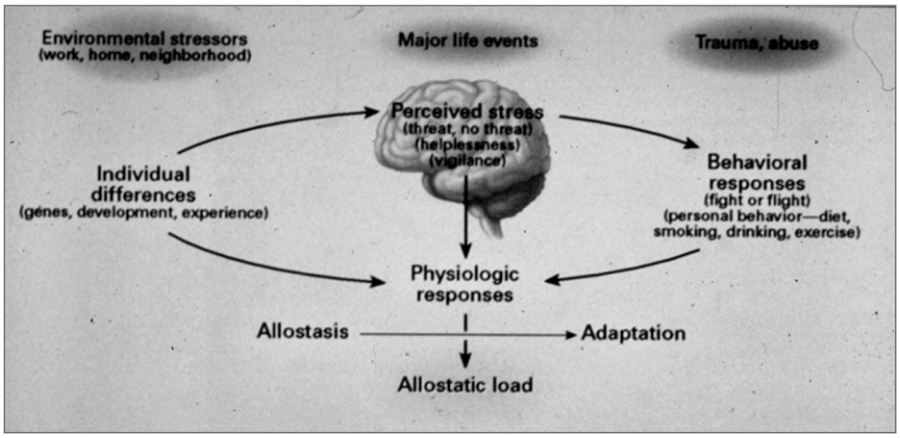

Fig. 1. Central role of the brain in the protective and damaging effects of the mediators of stress and adaptation operating through the process of allostasis that can lead to allostatic load and overload when overused and dysregulated. Reproduced from ref. 16, copyright (1998) Massachusetts Medical 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 down-regulation 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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1. McEwen BS (2007) Physiology and neurobiology of stress and adaptation: Central role of the brain. *Physiol Rev* 87:873–904.
2. McEwen BS, Gianaros PJ (2011) Stress- and allostasis-induced brain plasticity. *Annu Rev Med* 62:431–445.
3. Ganzel BL, Morris PA, Wethington E (2010) Allostasis and the human brain: Integrating models of stress from the social and life sciences. *Psychol Rev* 117:134–174.
4. Harris GW (1948) Electrical stimulation of the hypothalamus and the mechanism of neural control of the adenohypophysis. *J Physiol* 107:418–429.
5. Meites J (1992) Short history of neuroendocrinology and the International Society of Neuroendocrinology. *Neuroendocrinology* 56:1–10.
6. Guillemin R (1978) Peptides in the brain: The new endocrinology of the neuron. *Science* 202:390–402.
7. Schally AV, Arimura A, Kastin AJ (1973) Hypothalamic regulatory hormones. *Science* 179:341–350.
8. Pfaff DW, Keiner M (1973) Atlas of estradiol-concentrating cells in the central nervous system of the female rat. *J Comp Neurol* 151:121–158.
9. Stumpf WW, Sar M (1978) Anatomical distribution of estrogen, androgen, progestin, corticosteroid and thyroid hormone target sites in the brain of mammals: Phylogeny and ontogeny. *Am Zool* 18:435–445.
10. McEwen BS, Weiss JM, Schwartz LS (1968) Selective retention of corticosterone by limbic structures in rat brain. *Nature* 220:911–912.
11. Sapolsky RM, Krey LC, McEwen BS (1986) The neuroendocrinology of stress and aging: The glucocorticoid cascade hypothesis. *Endocr Rev* 7:284–301.
12. Landfield PW, Waymire JC, Lynch G (1978) Hippocampal aging and adrenocorticoids: Quantitative correlations. *Science* 202:1098–1102.
13. Dhabhar FS, McEwen BS (1999) Enhancing versus suppressive effects of stress hormones on skin immune function. *Proc Natl Acad Sci USA* 96:1059–1064.
14. Roozendaal B, Hahn EL, Nathan SV, de Quervain DJ-F, McGaugh JL (2004) Glucocorticoid effects on memory retrieval require concurrent noradrenergic activity in the hippocampus and basolateral amygdala. *J Neurosci* 24:8161–8169.
15. Joëls M (2006) Corticosteroid effects in the brain: U-shape it. *Trends Pharmacol Sci* 27:244–250.
16. McEwen BS (1998) Protective and damaging effects of stress mediators. *N Engl J Med* 338:171–179.
17. Bennett EL, Diamond MC, Krech D, Rosenzweig MR (1964) Chemical and anatomical plasticity of brain. *Science* 146:610–619.
18. Bloss EB, Janssen WG, McEwen BS, Morrison JH (2010) Interactive effects of stress and aging on structural plasticity in the prefrontal cortex. *J Neurosci* 30:6726–6731.
19. Sapolsky R (1992) *Stress, the Aging Brain and the Mechanisms of Neuron Death* (MIT Press, Cambridge, MA).
20. Erickson KI, et al. (2011) Exercise training increases size of hippocampus and improves memory. *Proc Natl Acad Sci USA* 108:3017–3022.
21. Carlson MC, et al. (2009) Evidence for neurocognitive plasticity in at-risk older adults: The experience corps program. *J Gerontol A Biol Sci Med Sci* 64:1275–1282.
22. Plotsky PM, Meaney MJ (1993) Early, postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. *Brain Res Mol Brain Res* 18:195–200.
23. Akers KG, et al. (2008) Social competitiveness and plasticity of neuroendocrine function in old age: Influence of neonatal novelty exposure and maternal care reliability. *PLoS One* 3:e2840.
24. Maccari S, Morley-Fletcher S (2007) Effects of prenatal restraint stress on the hypothalamus-pituitary-adrenal axis and related behavioural and neurobiological alterations. *Psychoneuroendocrinology* 32(Suppl 1):S10–S15.
25. Moriceau S, Sullivan RM (2006) Maternal presence serves as a switch between learning fear and attraction in infancy. *Nat Neurosci* 9:1004–1006.
26. Coplan JD, et al. (2001) Variable foraging demand rearing: Sustained elevations in cisternal cerebrospinal fluid corticotropin-releasing factor concentrations in adult primates. *Biol Psychiatry* 50:200–204.
27. Lupien SJ, et al. (2011) Larger amygdala but no change in hippocampal volume in 10-year-old children exposed to maternal depressive symptomatology since birth. *Proc Natl Acad Sci USA* 108:14324–14329.
28. Anda RF, Butchart A, Felitti VJ, Brown DW (2010) Building a framework for global surveillance of the public health implications of adverse childhood experiences. *Am J Prev Med* 39:93–98.
29. Shonkoff JP (2003) From neurons to neighborhoods: Old and new challenges for developmental and behavioral pediatrics. *J Dev Behav Pediatr* 24:70–76.
30. Bierhaus A, et al. (2003) A mechanism converting psychosocial stress into mononuclear cell activation. *Proc Natl Acad Sci USA* 100:1920–1925.
31. Sapolsky RM, Romero LM, Munck AU (2000) How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocr Rev* 21:55–89.
32. Munhoz CD, Sorrells SF, Caso JR, Scavone C, Sapolsky RM (2010) Glucocorticoids exacerbate lipopolysaccharide-induced signaling in the frontal cortex and hippocampus in a dose-dependent manner. *J Neurosci* 30:13690–13698.
33. Borovikova LV, et al. (2000) Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. *Nature* 405:458–462.
34. Penkowa M, et al. (2003) Astrocyte-targeted expression of IL-6 protects the CNS against a focal brain injury. *Exp Neurol* 181:130–148.
35. Campbell IL, Stalder AK, Akwa Y, Pagenstecher A, Asensio VC (1998) Transgenic models to study the actions of cytokines in the central nervous system. *Neuroimmunomodulation* 5:126–135.
36. Kahle EB, Zipf WB, Lamb DR, Horswill CA, Ward KM (1996) Association between mild, routine exercise and improved insulin dynamics and glucose control in obese adolescents. *Int J Sports Med* 17:1–6.
37. Geschwind DH, Konopka G (2009) Neuroscience in the era of functional genomics and systems biology. *Nature* 461:908–915.
38. McEwen BS, Wingfield JC (2003) The concept of allostasis in biology and biomedicine. *Horm Behav* 43:2–15.
39. Seeman T, et al. (2010) Modeling multisystem biological risk in young adults: The Coronary Artery Risk Development in Young Adults Study. *Am J Hum Biol* 22: 463–472.
40. Seeman T, Epel E, Gruenewald T, Karlamangla A, McEwen BS (2010) Socio-economic differentials in peripheral biology: Cumulative allostatic load. *Ann N Y Acad Sci* 1186:223–239.
41. Lazarus RS, Folkman S, eds (1984) *Stress, Appraisal and Coping* (Springer Verlag, New York).
42. Cameron HA, Gould E (1996) The control of neuronal birth and survival. *Receptor Dynamics in Neural Development*, ed Shaw C (CRC, Boca Raton, FL), pp 141–157.
43. McEwen BS (1999) Stress and hippocampal plasticity. *Annu Rev Neurosci* 22:105–122.
44. Mucha M, et al. (2011) Lipocalin-2 controls neuronal excitability and anxiety by regulating dendritic spine formation and maturation. *Proc Natl Acad Sci USA* 108: 18436–18441.
45. Hill MN, McEwen BS (2010) Involvement of the endocannabinoid system in the neurobehavioural effects of stress and glucocorticoids. *Prog Neuropsychopharmacol Biol Psychiatry* 34:791–797.
46. Du J, McEwen BS, Manji HK (2009) Glucocorticoid receptors modulate mitochondrial function: A novel mechanism for neuroprotection. *Commun Integr Biol* 2:350–352.
47. de Leon MJ, et al. (1997) Frequency of hippocampus atrophy in normal elderly and Alzheimer's disease patients. *Neurobiol Aging* 18:1–11.
48. Gold SM, et al. (2007) Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes. *Diabetologia* 50:711–719.
49. Sheline YI (2003) Neuroimaging studies of mood disorder effects on the brain. *Biol Psychiatry* 54:338–352.
50. Starkman MN, et al. (1999) Decrease in cortisol reverses human hippocampal atrophy following treatment of Cushing's disease. *Biol Psychiatry* 46:1595–1602.
51. Gurvits TV, et al. (1996) Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. *Biol Psychiatry* 40: 1091–1099.
52. Gianaros PJ, et al. (2007) Prospective reports of chronic life stress predict decreased grey matter volume in the hippocampus. *Neuroimage* 35:795–803.
53. Marsland AL, Gianaros PJ, Abramowitch SM, Manuck SB, Hariri AR (2008) Interleukin-6 covaries inversely with hippocampal grey matter volume in middle-aged adults. *Biol Psychiatry* 64:484–490.
54. Erickson KI, et al. (2009) Aerobic fitness is associated with hippocampal volume in elderly humans. *Hippocampus* 19:1030–1039.
55. Cho K (2001) Chronic 'jet lag' produces temporal lobe atrophy and spatial cognitive deficits. *Nat Neurosci* 4:567–568.
56. Stockmeier CA, et al. (2004) Cellular changes in the postmortem hippocampus in major depression. *Biol Psychiatry* 56:640–650.
57. Mitra R, Jadhav S, McEwen BS, Vyas A, Chattarji S (2005) Stress duration modulates the spatiotemporal patterns of spine formation in the basolateral amygdala. *Proc Natl Acad Sci USA* 102:9371–9376.
58. Vyas A, Mitra R, Shankaranarayana Rao BS, Chattarji S (2002) Chronic stress induces contrasting patterns of dendritic remodeling in hippocampal and amygdaloid neurons. *J Neurosci* 22:6810–6818.

59. Bennur S, et al. (2007) Stress-induced spine loss in the medial amygdala is mediated by tissue-plasminogen activator. *Neuroscience* 144:8–16.
60. Drevets WC (2000) Neuroimaging studies of mood disorders. *Biol Psychiatry* 48: 813–829.
61. Frodl T, et al. (2003) Larger amygdala volumes in first depressive episode as compared to recurrent major depression and healthy control subjects. *Biol Psychiatry* 53: 338–344.
62. Zohar J, et al. (2011) High dose hydrocortisone immediately after trauma may alter the trajectory of PTSD: Interplay between clinical and animal studies. *Eur Neuropsychopharmacol* 21:796–809.
63. Gianaros PJ, et al. (2009) Preclinical atherosclerosis covaries with individual differences in reactivity and functional connectivity of the amygdala. *Biol Psychiatry* 65: 943–950.
64. Ganzel BL, Kim P, Glover GH, Temple E (2008) Resilience after 9/11: Multimodal neuroimaging evidence for stress-related change in the healthy adult brain. *Neuroimage* 40:788–795.
65. Yoo S-S, Gujar N, Hu P, Jolesz FA, Walker MP (2007) The human emotional brain without sleep—a prefrontal amygdala disconnect. *Curr Biol* 17:R877–R878.
66. Liston C, et al. (2006) Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. *J Neurosci* 26:7870–7874.
67. Schoenbaum G, Roesch M (2005) Orbitofrontal cortex, associative learning, and expectancies. *Neuron* 47:633–636.
68. Liston C, McEwen BS, Casey BJ (2009) Psychosocial stress reversibly disrupts prefrontal processing and attentional control. *Proc Natl Acad Sci USA* 106:912–917.
69. Dias-Ferreira E, et al. (2009) Chronic stress causes frontostriatal reorganization and affects decision-making. *Science* 325:621–625.
70. Karatsoreos IN, Bhagat S, Bloss EB, Morrison JH, McEwen BS (2011) Disruption of circadian clocks has ramifications for metabolism, brain, and behavior. *Proc Natl Acad Sci USA* 108:1657–1662.
71. Cerqueira JJ, et al. (2005) Morphological correlates of corticosteroid-induced changes in prefrontal cortex-dependent behaviors. *J Neurosci* 25:7792–7800.
72. Martin KP, Wellman CL (2011) NMDA receptor blockade alters stress-induced dendritic remodeling in medial prefrontal cortex. *Cereb Cortex* 21:2366–2373.
73. Levine S, Haltmeyer G, Kara G, Denenberg V (1967) Physiological and behavioral effects of infantile stimulation. *Physiol Behav* 2:55–59.
74. Meaney MJ, Szyf M (2005) Environmental programming of stress responses through DNA methylation: Life at the interface between a dynamic environment and a fixed genome. *Dialogues Clin Neurosci* 7:103–123.
75. Tang AC, Akers KG, Reeb BC, Romeo RD, McEwen BS (2006) Programming social, cognitive, and neuroendocrine development by early exposure to novelty. *Proc Natl Acad Sci USA* 103:15716–15721.
76. Parker KJ, Buckmaster CL, Sundlass K, Schatzberg AF, Lyons DM (2006) Maternal mediation, stress inoculation, and the development of neuroendocrine stress resistance in primates. *Proc Natl Acad Sci USA* 103:3000–3005.
77. Isgor C, Kabbaj M, Akil H, Watson SJ (2004) Delayed effects of chronic variable stress during peripubertal-juvenile period on hippocampal morphology and on cognitive and stress axis functions in rats. *Hippocampus* 14:636–648.
78. Kaufman D, et al. (2005) Early appearance of the metabolic syndrome in socially reared bonnet macaques. *J Clin Endocrinol Metab* 90:404–408.
79. Danese A, et al. (2009) Adverse childhood experiences and adult risk factors for age-related disease: Depression, inflammation, and clustering of metabolic risk markers. *Arch Pediatr Adolesc Med* 163:1135–1143.
80. Miller GE, Chen E (2010) Harsh family climate in early life presages the emergence of a proinflammatory phenotype in adolescence. *Psychol Sci* 21:848–856.
81. Evans GW, Gonnella C, Marcynyszyn LA, Gentile L, Salpekar N (2005) The role of chaos in poverty and children's socioemotional adjustment. *Psychol Sci* 16:560–565.
82. McEwen BS, Tucker P (2011) Critical biological pathways for chronic psychosocial stress and research opportunities to advance the consideration of stress in chemical risk assessment. *Am J Public Health* 101(Suppl 1):S131–S139.
83. Farah MJ, et al. (2006) Childhood poverty: Specific associations with neurocognitive development. *Brain Res* 1110:166–174.
84. Hart B, Risley TR (1995) *Meaningful Differences in the Everyday Experience of Young American Children* (Brookes Publishing Company, Baltimore), p 304.
85. Hanson JL, Chandra A, Wolfe BL, Pollak SD (2011) Association between income and the hippocampus. *PLoS One* 6:e18712.
86. Gianaros PJ, et al. (2007) Perigenual anterior cingulate morphology covaries with perceived social standing. *Soc Cogn Affect Neurosci* 2:161–173.
87. Gianaros PJ, et al. (2008) Potential neural embedding of parental social standing. *Soc Cogn Affect Neurosci* 3:91–96.
88. Adler NE, Boyce WT, Chesney MA, Folkman S, Syme SL (1993) Socioeconomic inequalities in health. No easy solution. *JAMA* 269:3140–3145.
89. Boyce WT, Ellis BJ (2005) Biological sensitivity to context: I. An evolutionary-developmental theory of the origins and functions of stress reactivity. *Dev Psychopathol* 17:271–301.
90. Suomi SJ (2006) Risk, resilience, and gene x environment interactions in rhesus monkeys. *Ann N Y Acad Sci* 1094:52–62.
91. Caspi A, et al. (2003) Influence of life stress on depression: Moderation by a polymorphism in the 5-HTT gene. *Science* 301:386–389.
92. Del Giudice M, Ellis BJ, Shirtcliff EA (2011) The Adaptive Calibration Model of stress responsivity. *Neurosci Biobehav Rev* 35:1562–1592.
93. Jackson JS, Knight KM, Rafferty JA (2010) Race and unhealthy behaviors: Chronic stress, the HPA axis, and physical and mental health disparities over the life course. *Am J Public Health* 100:933–939.
94. Rutter M (1983) *Stress, Coping and Development: Some Issues and Some Questions* (McGraw-Hill, New York).
95. Ganzel BL, Morris PA (2011) Allostasis and the developing human brain: Explicit consideration of implicit models. *Dev Psychopathol* 23:955–974.
96. Karatsoreos IN, McEwen BS (2011) Psychobiological allostasis: Resistance, resilience and vulnerability. *Trends Cogn Sci* 15:576–584.
97. Bavelier D, Levi DM, Li RW, Dan Y, Hensch TK (2010) Removing brakes on adult brain plasticity: From molecular to behavioral interventions. *J Neurosci* 30:14964–14971.
98. Ryff CD, Singer B (1998) The contours of positive human health. *Psychol Inq* 9:1–28.
99. Singer B, Friedman E, Seeman T, Fava GA, Ryff CD (2005) Protective environments and health status: Cross-talk between human and animal studies. *Neurobiol Aging* 26(Suppl 1):113–118.
100. Caldji C, et al. (1998) Maternal care during infancy regulates the development of neural systems mediating the expression of fearfulness in the rat. *Proc Natl Acad Sci USA* 95:5335–5340.
101. Colcombe SJ, et al. (2004) Cardiovascular fitness, cortical plasticity, and aging. *Proc Natl Acad Sci USA* 101:3316–3321.
102. Rovio S, et al. (2005) Leisure-time physical activity at midlife and the risk of dementia and Alzheimer's disease. *Lancet Neurol* 4:705–711.
103. Babyak M, et al. (2000) Exercise treatment for major depression: Maintenance of therapeutic benefit at 10 months. *Psychosom Med* 62:633–638.
104. Draganski B, et al. (2006) Temporal and spatial dynamics of brain structure changes during extensive learning. *J Neurosci* 26:6314–6317.
105. Seeman TE, Singer BH, Ryff CD, Dienberg Love G, Levy-Storms L (2002) Social relationships, gender, and allostatic load across two age cohorts. *Psychosom Med* 64: 395–406.
106. Boyle PA, Buchman AS, Barnes LL, Bennett DA (2010) Effect of a purpose in life on risk of incident Alzheimer disease and mild cognitive impairment in community-dwelling older persons. *Arch Gen Psychiatry* 67:304–310.
107. Fried LP, et al. (2004) A social model for health promotion for an aging population: Initial evidence on the Experience Corps model. *J Urban Health* 81:64–78.
108. Sheline YI (1996) Hippocampal atrophy in major depression: A result of depression-induced neurotoxicity? *Mol Psychiatry* 1:298–299.
109. Drevets WC, et al. (1997) Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 386:824–827.
110. Rajkowska G (2000) Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. *Biol Psychiatry* 48:766–777.
111. Vythilingam M, et al. (2004) Hippocampal volume, memory, and cortisol status in major depressive disorder: Effects of treatment. *Biol Psychiatry* 56:101–112.
112. Moore GJ, Bebchuk JM, Wilds IB, Chen G, Manji HK (2000) Lithium-induced increase in human brain grey matter. *Lancet* 356:1241–1242.
113. Duman RS, Monteggia LM (2006) A neurotrophic model for stress-related mood disorders. *Biol Psychiatry* 59:1116–1127.
114. Chollet F, et al. (2011) Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): A randomised placebo-controlled trial. *Lancet Neurol* 10:123–130.
115. Castrén E, Rantamäki T (2010) The role of BDNF and its receptors in depression and antidepressant drug action: Reactivation of developmental plasticity. *Dev Neurobiol* 70:289–297.
116. Maya Vetencourt JF, et al. (2008) The antidepressant fluoxetine restores plasticity in the adult visual cortex. *Science* 320:385–388.
117. Spolidoro M, et al. (2011) Food restriction enhances visual cortex plasticity in adulthood. *Nat Commun* 2:320.
118. Southwell DG, Froemke RC, Alvarez-Buylla A, Stryker MP, Gandhi SP (2010) Cortical plasticity induced by inhibitory neuron transplantation. *Science* 327:1145–1148.
119. de Lange FP, et al. (2008) Increase in prefrontal cortical volume following cognitive behavioural therapy in patients with chronic fatigue syndrome. *Brain* 131: 2172–2180.
120. Hölzel BK, et al. (2010) Stress reduction correlates with structural changes in the amygdala. *Soc Cogn Affect Neurosci* 5:11–17.
121. Heinrich C, et al. (2011) Increase in BDNF-mediated TrkB signaling promotes epileptogenesis in a mouse model of mesial temporal lobe epilepsy. *Neurobiol Dis* 42:35–47.
122. Kokaia M, et al. (1995) Suppressed epileptogenesis in BDNF mutant mice. *Exp Neurol* 133:215–224.
123. Scharfman HE (1997) Hyperexcitability in combined entorhinal/hippocampal slices of adult rat after exposure to brain-derived neurotrophic factor. *J Neurophysiol* 78: 1082–1095.
124. Tough P (March 21, 2011) The Poverty Clinic. *The New Yorker*, p 25.