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In pursuit of resilience: stress, epigenetics, and brain plasticity

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The brain is the central organ for adaptation to experiences, including stressors, which are capable of changing brain architecture as well as altering systemic function through neuroendocrine, autonomic, immune, and metabolic systems. Because the brain is the master regulator of these systems, as well as of behavior, alterations in brain function by chronic stress can have direct and indirect effects on cumulative allostatic overload, which refers to the cost of adaptation. There is much new knowledge on the neural control of systemic physiology and the feedback actions of physiologic mediators on brain regions regulating higher cognitive function, emotional regulation, and self-regulation. The healthy brain has a considerable capacity for resilience, based upon its ability to respond to interventions designed to open "windows of plasticity" and redirect its function toward better health. As a result, plasticity-facilitating treatments should be given within the framework of a positive behavioral intervention; negative experiences during this window may even make matters worse. Indeed, there are no magic bullets and drugs cannot substitute for targeted interventions that help an individual become resilient, of which mindfulness-based stress reduction and meditation are emerging as useful tools.

Keywords: hippocampus; amygdala; prefrontal cortex; allostasis; allostatic load/overload; self-regulation; mindfulness; meditation; physical activity; eudaimonia

Introduction

"Stress," so commonly used in daily discourse, refers to experiences that cause feelings of anxiety and frustration because they threaten one's security or push one beyond his/her ability to successfully cope ("There is so much to do and so little time!"). Besides time pressures and daily hassles in the workplace and at home, stressors have also been described in relation to economic insecurity; poor health; dangerous, toxic, and noisy neighborhoods; and interpersonal conflict. Much less frequently, situations arise that are life threatening—accidents, natural disasters, violence—and evoke the classical fight-or-flight response. In contrast to daily hassles, these stressors are acute and yet also usually lead to chronic stress, and may cause posttraumatic stress disorder (PTSD), in the aftermath of the tragic event.

The most common stressors are therefore life experiences that cause individuals to behave in certain ways; for example, being "stressed out" may cause anxious and/or depressed mood, a loss of sleep, ingestion of comfort foods and excess calories, and smoking or drinking alcohol excessively. Being "stressed out" may also cause individuals to neglect social activities or regular physical activity, as they, for example, sit at a computer and try to alleviate the burden of "too much to do in so little time." Often, individuals are tempted to cope with the use of medications, for example, anxiolytics and sleep-promoting agents, potentially leading over time to an increase in body weight and development of metabolic syndrome and heart disease.

The brain is the organ that decides which experiences are stressful and determines behavioral and physiological responses, which can be either health promoting or health damaging. Moreover, the brain is a biological organ that changes under acute and chronic stress and directs many systems of the body—neuroendocrine, autonomic, metabolic, cardiovascular, and immune—that are involved in the

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short- and long-term consequences of the daily experiences of living. What do these experiences do to the body and brain, whether or not they are called "stress"? This paper is directed toward promoting resilience to adverse events, defined as achieving a positive outcome in the face of adversity, and emphasizes how stress-related hormones can play both protective and damaging roles in the brain and body, depending on how tightly their release is regulated. Also discussed are some of the approaches for dealing with stress in a complex world by reviewing interventions aimed at setting the body and brain on a health trajectory. Among these interventions are meditation and mindfulness-based stress reduction (MBSR) that engage the brain–body interconnection while opening "windows of plasticity" that allow the brain to change itself. But before discussing interventions, first considered is how the body and brain adapt to daily experiences.

Definition of allostasis and allostatic load and overload

The word "stress" is ambiguous and has connotations that make it less useful in understanding how the body handles daily life events. To understand the balance between adaptation and maladaptation, we introduced a biologically oriented alternative that provides insight into the processes by which the body adapts to daily life, which, in turn, could lead to a better understanding of how best to intervene, a topic that will be discussed at the end of this article. There are two sides to this story: on the one hand, the body responds to almost any event or challenge by acutely releasing chemical mediators (e.g., catecholamines that increase heart rate and blood pressure and that help one cope with the situation); on the other hand, chronic elevation of these same mediators (e.g., chronically increased heart rate and blood pressure) produce chronic wear and tear on the cardiovascular system that can result, over time, in disorders such as strokes and heart attacks. For this reason, the term *allostasis* was introduced by Sterling and Eyer in 1988[1] to refer to the active process by which the body responds to daily events and maintains homeostasis (note that allostasis literally means achieving stability through change). Because sustained or inadequate allostasis can lead to disease, we introduced the term "allostatic load or overload"[2] to refer to the wear and tear that results from either too much stress or from inefficient management of allostasis (e.g., failure to turn off the response when no longer needed). Other forms of allostatic load involve not turning on an adequate (e.g., cortisol) response in the first place, to which other systems (e.g., inflammation) then overreact; habituating or failing to habituate to the recurrence of the same stressor and thus dampening the allostatic response, leading to more wear and tear on the brain and body.[3,4]

Classifying "stress" helps reduce ambiguity

The ambiguity of the word "stress" can be reduced by using the following classifications of types of stress: good stress, tolerable stress, and toxic stress. (The reader is referred to http://developingchild.harvard.edu/library/resources for a report related to toxic stress.) Good stress is a term used in popular language to refer to the experience of rising to a challenge, taking a risk, and feeling rewarded by an often positive outcome; a related term is "eustress." Healthy self-esteem and good impulse control and decision-making capability, all functions of a healthy brain architecture, are important in this scenario. Even adverse outcomes can function as growth experiences for individuals with such positive, adaptive characteristics.

Tolerable stress refers to situations where negative events occur, but the individual with healthy brain architecture is able to cope, often with the aid of family, friends, and other individuals who provide support. Here, "distress" refers to the uncomfortable feeling related to the nature of the stressor and the degree to which the individual feels a lack of ability to influence or control the stressor.[5]

Finally, toxic stress refers to situations in which negative events are experienced by an individual who has limited support and may also have brain architecture that reflects the effects of adverse early life events that have impaired the development of good impulse control and judgment and adequate self-esteem. Here, the degree and/or duration of distress may be greater. With toxic stress, the inability to cope is likely to have adverse effects on behavior and physiology, resulting in a higher degree of allostatic overload.

Circadian disruption, allostasis, and allostatic load

The circadian system, which is an essential component of allostasis that maintains homeostasis, is also a source of allostatic load and overload when

disrupted.[6] Based in the suprachiasmatic nucleus (SCN) of the hypothalamus, the brain's clock controls rhythms in the rest of the brain and body through both neural mechanisms and diffusible signals such as glucocorticoids. Biological clocks at the molecular level are present in every cell of the body and are synchronized by the SCN directly (by way of neural connections) or, in some organs such as the liver, indirectly through hormonal signals (e.g., cortisol, melatonin) or behavioral outputs (e.g., feeding). The SCN also regulates the timing of sleep and activity, so that circadian systems regulate rest–activity cycles and keep organisms in synchrony with their external environment. Indeed, disruption of these key homeostatic systems could clearly contribute to allostatic overload.

Reduced sleep duration has been associated with increased body mass and obesity in the National Health and Nutrition Examination Survey[6] and sleep restriction to 4 h of sleep per night increases blood pressure, decreases parasympathetic tone, increases inflammatory cytokines, elevates evening cortisol and insulin levels, and promotes increased appetite, possibly through the elevation of ghrelin, a proappetitive hormone, along with decreased levels of leptin.[6] Circadian disruption, as in shift work and jet lag, has often been overlooked as a separate yet related phenomenon to sleep deprivation but has been reported to contribute to obesity as well as cognitive impairment.[6–8]

Epigenetics: two meanings that are both important for prevention and treatment

Epigenetics refers to events "above the genome" that regulate expression of genetic information without altering the DNA sequence. Besides the CpG methylation described below, other epigenetic mechanisms include histone modifications that repress or activate chromatin unfolding[9] and the actions of noncoding RNAs,[10] as well as transposons and retrotransposons[11] and RNA editing.[12] For prevention and treatment, in the spirit of integrative medicine, it is important to let the "wisdom of the body" prevail and to focus on strategies that center around the use of targeted behavioral therapies along with treatments, including pharmaceutical agents, that open up windows of plasticity in the brain and facilitate the efficacy of the behavioral interventions.[13] This is because a major challenge throughout the life course is to find ways of redirecting future behavior and physiology in more positive and healthy directions.[14] In keeping with the original definition of epigenetics[15] as the emergence of characteristics not previously evident or even predictable from an earlier developmental stage (e.g., consider a fertilized frog or human egg, which look similar, and the events that occur as each develop), we do not mean reversibility as in "rolling back the developmental clock," but rather redirection.

One area of epigenetics relates to assessing the effects of childhood abuse, where increased methylation of CpG residues in the glucocorticoid receptor (GR) promotor results in lower GR expression and thus reduced capacity for glucocorticoid-mediated allostasis.[16] Histone methylation has been studied as a mediator of stress-induced repression of genes and the activity of retrotransposons,[17] whereas acetylation of histones mediates gene activation, as in the action of new, rapidly acting antidepressant candidates.[18]

Even in adulthood, gene expression in the brain continually changes with experience[19] and there is a loss of resilience of neural architecture with aging[20] that can be redirected by exercise[21] and potentially by pharmacological interventions.[22] Moreover, chronic anxiety, possibly resulting from adverse childhood experiences, can respond to a behavioral intervention in adulthood.[23] Indeed, MBSR and meditation increase functional connectivity within the brain and benefit fluid intelligence as well as improve function in aging,[24,25] and a sense of meaning and purpose in life has also been shown to benefit overall health and cognitive function.[26,27] This topic is revisited toward the end of the paper.

The brain as a target of stress

The response of the brain to stressors is a complex process involving multiple interacting mediators that utilize both epigenetic genomic and nongenomic mechanisms, from the cell surface to the cytoskeleton to epigenetic regulation via the cell nucleus. Resilience in the face of stress is a key aspect of a healthy brain, even though gene expression indicates that the brain continually changes with experience.[28] Therefore, recovery of stress-induced changes in neural architecture after stress is not a reversal but a form of neuroplastic adaptation that is impaired in mood disorders and reduced with aging. Resilience may be thought of as an active

process that involves ongoing adaptive plasticity without external intervention.[29]

On the other hand, resilience is decreased and vulnerability is increased by adverse childhood experiences that lead to "biological embedding" of trajectories of the response to stressful life events[30] throughout the life course,[14] which contribute disproportionately to allostatic overload in the form of physical and mental health disorders over the life span.[31] Evidence from CpG methylation of DNA indicates the embedded influence of early adversity.[16]

Interventions that change the brain and improve health

Can the effects of stress and adverse early life experiences on the brain be treated and compensated for even though there are no magic bullets, such as penicillin, for stress-related disorders?[14] Depression and anxiety disorders, including PTSD, need to be treated with targeted behavioral therapies, where pharmaceutical agents are used to open up windows of plasticity in the brain and facilitate the efficacy of the behavioral interventions.[13,32,33] Indeed, the goal of interventions for stress-related disorders is to mobilize internal and external coping resources that can lead to growth, adaptation, and learning in order to promote resilience and improved mental as well as physical health.[29,34]

Brain-derived neurotrophic factor (BDNF) is a mediator of plasticity, and while it can facilitate beneficial plasticity (e.g., see Ref. 35), it should be noted that BDNF also has the ability to promote pathophysiology, as in seizures.[36–38] BDNF is one of an increasing number of mediators that work with glucocorticoids and excitatory amino acids to regulate plasticity.[39] Overexpression of BDNF creates a ceiling that prevents further stress-induced change while underexpression of BDNF also creates a state of rigidity.[39–41] With the limits of too much and not enough BDNF, glucocorticoid actions both facilitate BDNF actions and are facilitated by BDNF in a feed-forward loop that facilitates plasticity.[42]

How the brain becomes "stuck"

Depression and anxiety disorders illustrate a loss of resilience, meaning 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[43,44] and prefrontal cortex (PFC).[45] While there appears to be no neuronal loss, there is evidence for glial cell loss and smaller neuronal cell nuclei,[46,47] which is consistent with a shrinking of the dendritic tree after chronic stress. As far as reversal of these changes, there are a few studies that indicate that pharmacological treatment reverses the decreased hippocampal volume in unipolar[48] and bipolar[49] depression, but the possible role of any concurrent cognitive behavioral therapy in these studies is unclear.

Aging is also an example of a loss of resilience to the effects of chronic stress, based on studies of the rodent PFC.[20] What is not clear yet is whether this loss of resilience can be reversed or prevented; pharmacological studies do, however, indicate some retardation of age-related changes in morphology, neurochemical markers, and cognitive function.[22,50] Although not directly addressing recovery of resilience, studies on the beneficial effects of physical activity on the aging brain are revealing the retention, with age, of the capacity for structural plasticity.

Opening windows with physical activity

Regular physical activity has effects not only on cardiovascular and metabolic systems but also on the brain, with improvements seen in the blood flow of prefrontal and parietal cortices and enhancement in executive function.[51] Moreover, regular physical activity, consisting of walking 1 h/day, 5 out of 7 days/week, increases hippocampal volume in previously sedentary elderly adults,[52] which complements another study showing that fit individuals have larger hippocampal volumes than sedentary adults of the same age range.[53] Regular physical activity is an effective antidepressant and protects against cardiovascular disease, diabetes, and dementia.[54,55] Moreover, intensive learning has also been shown to increase the volume of the human hippocampus, as shown in a study with medical students (Table 1).[56]

Redirecting biological embedding from early life experiences

Along with cardiovascular disease, obesity, and substance abuse, depression is more prevalent in individuals who have had adverse early life experiences.[57] Compensating for the biological embedding of adverse childhood experience is a huge challenge, and the reversal of amblyopia and

Table 1. Nonpharmacological interventions that change the brain

Regular physical activity
Increased hippocampal volume and PFC blood flow and improved executive function and memory (Erickson *et al.*[52])
Mindfulness-based stress reduction
Reducing anxiety decreases amygdala volume (Hölzel *et al.*[23])
Social support and integration
Experience Corps for elderly volunteers improved executive function, PFC blood flow, and overall health (Carlson *et al.*[26])
Meaning and purpose; eudaimonia (Ryff[81])

other conditions by "releasing the brakes" that retard structural and functional plasticity[32] has provided some hope. 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 central feature of successful treatment.[58] Yet, there are other potential applications, such as the recently reported ability of fluoxetine to enhance recovery from stroke.[59] However, an important aspect of this new view[33] is that the drug is opening a window of opportunity that may be capitalized by a positive behavioral intervention (e.g., behavioral therapy in the case of depression or the intensive physiotherapy to promote neuroplasticity to counteract the effects of a stroke).

Potential of fluoxetine, caloric restriction, and cortisol as regulators of neuroplasticity

The concept of opening a window of plasticity is consistent with studies in animal models that show that ocular dominance imbalance from early monocular deprivation can be reversed by patterned light exposure in adulthood, which can be facilitated by fluoxetine, on the one hand,[60] and caloric restriction, on the other hand,[61] in which reducing inhibitory neuronal activity appears to play a key role. 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.[32]

The caloric restriction study also showed that injestion of cortisol in drinking water instead of caloric restriction[61] was able to open a window of plasticity and enable binocular visual stimulation to correct amblyopia. This may be explained, at least in part, by the key role of physiologic levels of cortisol in promoting turnover of spine synapses and the importance of circadian patterns of glucocorticoid elevation in spine formation and elimination in relation to motor learning and possibly other forms of learning.[62,63]

Perception-based therapy

A new therapeutic approach[64] is based on training older adults in visual perceptual discrimination, using Gabor patches that had built-in animation for directed motion.[65] Ten hours of training were found to improve on-task perception, and the training also benefitted working memory for a delayed-recognition motion direction task. Moreover, electroencephalography showed that training produced more efficient sensory encoding of the stimuli, which correlated with gains in working memory performance. This finding fits with other evidence that perceptual training improves the ability to detect signal over noise and thus produces some generalized cognitive benefits. The authors suggested that there are two fundamental design elements that drive neuroplasticity in this type of intervention, because they personalize training to the capacity of each person and allow abilities to improve over time. To do so, the training incorporates continuous performance feedback to provide repeated cycles of reward to the subject. Moreover, training is designed to adapt to the trainee's ongoing performance using psychophysical staircase functions that enhance the challenge in response to accurate performance and reduce it for inaccurate performance.

Other top-down therapies that change the brain

Social integration and support, and finding meaning and purpose in life, are known to be protective against allostatic load[66] and dementia,[67] and programs such as the Experience Corps that promote these along with increased physical activity have been shown to slow the decline of physical and mental health and to improve PFC blood flow in a similar manner to regular physical activity.[26,68] It should be noted that many of these interventions that are intended to promote plasticity and slow age-related decline, such as physical activity and positive social interactions that give meaning and purpose, are also useful for promoting positive health and eudemonia,[69,70] independently of any notable

disorder and within the range of normal behavior and physiology (Table 1).

Mindfulness and meditation

Therapies addressing functional links between brain and body may be particularly effective in treating the range of symptoms associated with many chronic diseases.[71] Successful cognitive behavioral therapies, which are tailored to individual needs, can produce volumetric changes in both the PFC in the case of chronic fatigue[72] and in the amygdala in the case of chronic anxiety[23] (Table 1), and in brainstem areas associated with well-being.[73] MBSR has been shown to increase regional brain gray matter density in the hippocampus, cerebellum, and PFC, which are involved in learning and memory processes, emotion regulation, self-referential processing, and perspective taking.[74] Indeed, enhancing self-regulation of mood and emotion appears to be an important outcome.[25] More studies showing brain changes after MBSR have been reviewed very recently.[75]

In relation to MBSR effects on amygdala volume that accompany anxiety reduction in generalized anxiety disorder (GAD),[23] a follow-up study of symptom improvements followed GAD patients who were randomized to an 8-week MBSR or a stress management education (SME) active control program. In GAD patients, amygdala activation in response to neutral faces decreased following both interventions, whereas blood oxygen level–dependent responses in ventrolateral prefrontal regions showed greater increases in MBSR than in SME participants. Furthermore, functional connectivity between the amygdala and PFC increased significantly pre- to post-intervention within the MBSR subjects, but not in the SME group, at least not to a level that has clinical relevance, based on changes in Beck Anxiety Inventory scores. Amygdala–prefrontal connectivity turned from negative coupling, as typically seen in downregulation of emotions, to positive coupling, suggesting a unique mechanism of mindfulness involving other components of the complex PFC. These findings suggest that, in GAD, MBSR training leads to changes in frontolimbic areas crucial for the regulation of emotion and may do so in ways unique to MBSR.[76]

Meditation has been reported to enlarge hippocampal volume and to do so differently in men and women, suggesting to the authors that meditation practices and, most likely, MBSR, operate differently in males and females.[77] This suggestion is reminiscent of very recent work showing sex differences in rats that showed differing fear responses. During fear conditioning and extinction, this work revealed that, despite no overall sex differences in freezing behavior, the neural processes underlying successful or failed extinction maintenance were sex specific.[78] Given other work showing sex differences in stress-induced structural plasticity in PFC projections to the amygdala and other cortical areas,[79] these findings are relevant not only to sex differences in fear conditioning and extinction but "also to exposure-based clinical therapies, which are similar in their premises to those of fear extinction and which are primarily used to treat disorders that are more common in women than in men."[78]

Another domain where MBSR and meditation practices are reported to have positive effects on brain function is in age-related cognitive decline.[24] Fluid intelligence has been shown to decline slower in aging yoga practitioners and in aging MBSR practitioners than in controls.[25] Resting-state functional networks of yoga practitioners and meditators were more integrated and more resilient to simulated damage than those of controls. Furthermore, the practice of meditation was found to be positively correlated with fluid intelligence, resilience, and global network efficiency.[25] Moreover, gray matter volume is reported to be preserved in meditators compared to age-matched controls.[80]

Conclusions

The brain is the central organ for perceiving and adapting to experiences that are often called stressors and is, furthermore, a plastic and malleable organ that responds to interventions designed to redirect its function toward healthier behavior and physiology. There has been considerable expansion of knowledge regarding neural control of systemic physiology and the feedback actions of physiologic mediators on the brain regions regulating higher cognitive function, emotional regulation, and self-regulation.

The key is to use the wisdom of the body's mechanisms of allostasis to open a window for plasticity of brain architecture and then use a targeted intervention to change the brain in a desired direction, with resulting improvement in brain–body

interactions and health. This new view reinforces two important messages: first, that plasticity-facilitating treatments should be given within the framework of a positive behavioral or physical therapy intervention; and, second, that negative experiences during the window may even make matters worse. Indeed, there are no magic bullets and drugs cannot substitute for targeted interventions that help an individual become resilient. MBSR and meditation are among the new tools for promoting and benefiting physical and mental health. A major challenge is making this approach useful for individuals who have had adverse early life experiences that predispose them to an array of mental, cognitive, and physical health problems.

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Conflicts of interest

The author declares no conflicts of interest.

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