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Central role of the brain in stress and adaptation: Links to socioeconomic status, health, and disease

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The brain is the key organ of stress reactivity, coping, and recovery processes. Within the brain, a distributed neural circuitry determines what is threatening and thus stressful to the individual. Instrumental brain systems of this circuitry include the hippocampus, amygdala, and areas of the prefrontal cortex. Together, these systems regulate physiological and behavioral stress processes, which can be adaptive in the short-term and maladaptive in the long-term. Importantly, such stress processes arise from bidirectional patterns of communication between the brain and the autonomic, cardiovascular, and immune systems via neural and endocrine mechanisms underpinning cognition, experience, and behavior. In one respect, these bidirectional stress mechanisms are protective in that they promote short-term adaptation (*allostasis*). In another respect, however, these stress mechanisms can lead to a long-term dysregulation of allostasis in that they promote maladaptive wear-and-tear on the body and brain under chronically stressful conditions (*allostatic load*), compromising stress resiliency and health. This review focuses specifically on the links between stress-related processes embedded within the social environment and embodied within the brain, which is viewed as the central mediator and target of allostasis and allostatic load.

Keywords: allostasis; allostatic load; amygdala; autonomic nervous system; hippocampus; hypothalamic-pituitary-adrenal axis; immune system; neuroplasticity; prefrontal cortex; socioeconomic status; stress

Introduction

It is well established that life stress can presage ill health among vulnerable individuals.[1] This stress-related vulnerability is determined by genetic, biobehavioral, and environmental factors that interact over the lifespan to influence individual risk trajectories, particularly through neurobiological pathways. Conventionally, stress is defined as a transactional process arising from real or perceived environmental demands that can be appraised as threatening or benign, depending on the availability of adaptive coping resources to an individual.[2,3] In extension, the biological, behavioral, and social coping responses that ensue from stress perception and appraisal processes are held to specifically influence risk for and resilience against ill health.[1,4,5] These stress processes impacting health can be heuristically labeled as "good," "tolerable," and "toxic"—depending on the degree to which an individual has control over a given stressor and has support systems and resources in place for handling a given stressor over the lifespan.[6,7] For example, overcoming some stressful experiences can lead to growth, adaptation, and beneficial forms of learning that promote future resiliency. Other stressful experiences, however, can lead to a proliferation of interacting behavioral, cognitive, physiological, and neural changes that promote vulnerability to ill health.

The brain is a primary mediator and target of stress resiliency and vulnerability processes because it determines what is threatening and because it regulates the behavioral and physiological responses to a given stressor. The hippocampus, a particular brain system supporting memory and mood, was the first area besides the hypothalamus to be recognized specifically as a target of stress hormones.[8] Importantly, stressful experiences and associated changes in the release of stress hormones produce both adaptive and maladaptive effects on the

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hippocampus, hypothalamus, and other brain regions throughout life.[5] For example, the amygdala (important for detecting and responding to threats in the environment) and areas of the prefrontal cortex (important for decision making and regulating emotions, impulsivity, and autonomic and neuroendocrine function) are also targets of stress processes.

As reviewed here, early maltreatment, conflict-laden familial relationships, stressful life events, and adverse physical and social conditions—often occasioned by lower socioeconomic environments—during development and aging can influence the structural and functional plasticity of the hippocampus, amygdala, and prefrontal cortex—processes collectively referred to as neuroplasticity. In turn, alterations in the neuroplasticity of these brain systems can affect patterns of emotional expression and regulation, stress reactivity, recovery, and coping, and perhaps even the rate of bodily aging (see further).

Critically, however, the effects of stress on the brain do not necessarily constitute permanent "damage" *per se* and are amenable to recovery, preventative strategies, and interventions that include pharmaceutical agents and lifestyle factors (*e.g.*, exercise, dietary changes, and social support). Hence, because stress processes—particularly those that unfold in social environments—have powerful effects through the brain on the body, all public and private sector social policies will necessarily affect mental and physical health. As such, these policies can be considered as *top-down* intervention efforts to affect neuroplasticity and stress resiliency. In the following sections, we review emerging translational animal and human studies explicating the neurobiological pathways potentially linking stress-related processes and health. We note that this review is presented within the context of a conceptual framework and processes emphasizing the brain as the central mediator and target of two neurobiological processes. Key concepts include:

(1) *Allostasis*, defined as a dynamic regulatory process wherein homeostatic control is maintained by an active process of adaptation during exposure to physical and behavioral stressors, and

(2) *Allostatic load*, defined as the consequence of allodynamic regulatory wear-and-tear on the body and brain promoting ill health, involving not only the consequences of stressful experiences themselves, but also the alterations in lifestyle that result from a state of chronic stress.

Throughout, this review emphasizes a life course perspective—wherein the effects of early caregiving, maltreatment, and stressors encountered during development and aging are viewed as holding the potential to modify neuroplasticity and stress resiliency both in the short term and over the long term. Further, we will emphasize the brain as the central mediator of stress processes, insofar as distributed brain networks encode, filter, and store environmental information according to unique personal histories and life experiences to determine what is threatening and thus "stressful" to the individual. Moreover, we will emphasize the brain as the instrumental organ for regulating biological, behavioral, and social responses that are influenced by short-term (acute) and long-term (chronic) stress processes. Finally, we will emphasize the brain as a central *target* of stress processes, insofar as stressful experiences affect neuroplasticity through nonlinear feedforward and feedback mechanisms linking the central and peripheral nervous systems.

Complimenting other contributions to this volume, we will review the limited, but growing, evidence on the putative neurobiological pathways possibly linking socioeconomic status (SES) and health through such stress-related processes. This evidence is largely derived from the study of animal models that permit identifying stress mechanisms at the cellular level, as well as studying stress-related processes that unfold over the entire lifespan. These animal models are critical in that they permit causal inferences and in that they inform translational human experimental, epidemiological, and clinical intervention research. In addition, we review human neurobiological and neuroimaging studies of stress reactivity and the impact of SES on brain functionality and morphology.

Socioeconomic status, health, and stress-related processes center on the brain

There is cumulative evidence reviewed elsewhere in this volume that disparities in income, education, occupation, and other dimensions of SES account for appreciable variance in all-cause and disease-specific morbidity and mortality rates, as well as the prevalence of risk factors for chronic medical

conditions[9–11] and prevalent psychopathologies of mood and substance abuse.[12,13] That health and longevity track a socioeconomic gradient cannot be explained entirely by material deprivation, illiteracy, or restricted availability of quality health care among those occupying a lower socioeconomic position.[9,14,15] Hence, several conceptual models of SES-related health disparities posit that life experiences inherent to socioeconomic position at the individual, familial, and community levels could influence well-being and disease risk through stress-related pathways.[9,14,16,17] For example, the chronic experience of low SES at the individual level could involve enduring financial hardships, a sense of insecurity regarding future prosperity, and the possible demoralizing feelings of marginalization or social exclusion attributable to comparative social, occupational, or material disadvantage. Further, an individual's perception of her or his relative standing or ranking in a social hierarchy, formally termed subjective social status, may affect an individual's pattern of emotional, behavioral and physiological reactivity to and recovery from life stressors, consequently impacting risk for ill health.[18–23]

As reviewed further, these stress-related processes are mediated by and feedback to the brain, impacting its abilities to regulate peripheral physiology, engage in adaptive social and health behaviors, experience and control emotions, and support cognitive functioning. Hence, a person who develops, matures, and ages in a low socioeconomic position could become vulnerable to impairments in the functionality of stress regulatory systems of the brain and body important for health. Critically, such stress-related processes may unfold not only at the individual level, but also at the level of families and residential areas. For example, children who develop in lower SES households, in addition to being exposed to toxic substances and excessive noise and temperature variations, are more likely to live in unfavorable housing conditions and to be exposed to what have been termed "risky family" dynamics, characterized by conflict-laden relationships, aggressive and harsh parenting, and other forms of early life stress which may alter risk trajectories for ill health in later life.[24] Finally, individuals living in low SES neighborhoods may be more frequently exposed to stressful life events[25,26] in association with higher concerns over community crime, pollution, and crowding,[27] as well as unstable, effortful, and unrewarding employment opportunities related to persistent economic hardship (see Diez-Roux, this volume).

Yet despite epidemiological and population-based evidence linking low SES with health via purported stress processes, little is known about the neurobiological pathways linking stress and health in the context of SES. Next, we review available animal and human studies potentially bearing on this issue, focusing specifically on those brain systems instrumental for stress regulatory processes. Importantly, from a multilevel and translational perspective, the stress-related neurobiological pathways documented by these animal and human studies may be modifiable by interventions at the individual and population levels, and some of these will be discussed at the end of this chapter.

Protective and damaging effects of neurobiological stress processes

To the extent that low SES is a potential source of life stress associated with ill health, then the brain systems linking SES-related stress processes to health most plausibly include limbic brain areas that jointly (*i*) support social and emotional information processing; (*ii*) regulate neuroendocrine, immune, autonomic nervous system functions involved in both adaptation and pathophysiology, as embodied in the concepts of allostasis and allostatic load; and (*iii*) express well-characterized forms of neuroplasticity in association with conditions of chronic and acute stress in nonhuman animal models. Although several limbic areas meet one or more of these criteria, cumulative translational evidence from animal and human studies reviewed below implicates three in particular: the hippocampus, amygdala, and subdivisions of the prefrontal cortex (see Fig. 1). Next, we provide an overview of the role of these brain areas in their dual control of visceral, cognitive, and emotional processes after summarizing the concepts of allostasis and allostatic load.

Stress, allostasis, and allostatic load

The brain not only processes inputs from the external environment, but also controls adjustments of the body engendered by behavioral states like waking, sleeping, lying, standing, and exercising. These bodily adjustments promote adaptive

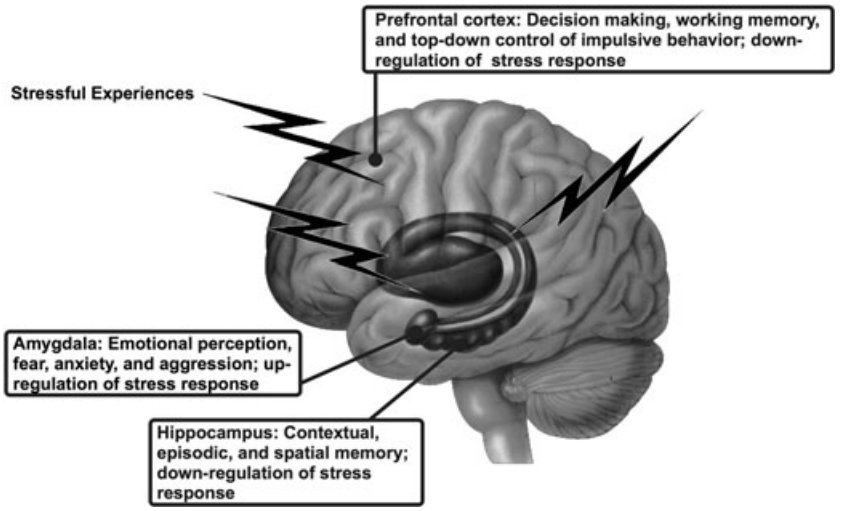

Figure 1. **Schematic illustration of the location and key functions of limbic brain areas that play an integrated role in cognitive, emotional, and visceral control processes important for allostasis, allostatic load, and stress responding. Each of the three brain areas is discussed in detail in the text in relation to both animal model studies that focus on what happens at the cellular and molecular levels and studies on the human brain using functional and structural imaging and neuropsychological and neuroendocrine assessments.**

activities, such as locomotion, and coping with aversive situations and discrete stimuli, such as noise, crowding, hunger, excessive heat or cold, and other threats to safety. Systems promoting adaptation include the hypothalamic-pituitary-adrenal (HPA) axis; the autonomic nervous system; the metabolic system (including the thyroid axis, insulin, other metabolic hormones); the gut; the kidneys; and the immune system (including the regulated network of cytokine producing cells throughout the body). The biomediators of these systems (*e.g.*, cortisol, sympathetic and parasympathetic transmitters, cytokines, metabolic hormones) operate as a nonlinear, interactive network in which mediators down- and up-regulate each other, depending on such factors as concentration, location in the body, and sequential temporal patterning.[28] Importantly, the activity of these mediating systems and mediators are closely coupled to the psychological and genetic make-up, developmental history, and behavioral state of the individual.

Adversity, including interpersonal conflicts, social instability, and other stressful experiences, can accelerate pathophysiological processes through adaptive systems of the body, increasing vulnerability for higher morbidity and mortality rates at the population level. For example, the cardiovascular system is one of the most susceptible systems to stress. Hence, blood pressure increases are sensitive to job stress in factory workers, in employees with repetitive jobs and time pressures,[29] and in British civil servants of departments undergoing privatization.[30] As further evidence, cardiovascular disease is a primary reason for the increased death rate in Eastern Europe amidst the social collapse after the fall of communism.[31] Finally, it is noteworthy that otherwise adaptive and brain-mediated stressor-evoked blood pressure surges have been linked to accelerated atherosclerosis,[32] as well as increased risk for myocardial infarction (MI).[33,34] Besides the cardiovascular system, there are indications that metabolic disorders and abdominal obesity—contributors to cardiovascular disease—are increased at the lower end of the socioeconomic gradient in Swedish males[35] and in the British Civil Service.[36] Finally, there is growing epidemiological evidence that impaired immune system function is also a likely target of stress processes within the context of socioeconomic position.[19,37–42]

Stress-related processes impacting health within the context of SES can be viewed and understood by appreciating the marked differences individuals

show in response to adverse acute and chronic stressors. In other words, individuals respond in different ways to adversity and threats (real or implied) to their safety and homeostasis. As also discussed in the chapter by Seeman *et al* (this volume), physiological responses of the autonomic nervous system, HPA axis, cardiovascular, metabolic and immune systems lead to protection and adaptation of the organism to these challenges. This process, referred to as allostasis,[43] is an essential component of maintaining homeostasis. However, adaptation to adversity has a price, and the cost of adaptation has been labeled as allostatic load.[44,45] *Hence, allostatic load is the wear-and-tear on the body and brain resulting from chronic dysregulation (i.e., over-activity or inactivity) of physiological systems that are normally involved in adaptation to environmental challenge.* While it is true that physiological parameters like blood oxygen and pH are maintained in a narrow range (homeostasis), the cardiovascular system, metabolic machinery, immune system and central nervous system all show a large range of activity as a function of the time of day and in response to external and internal demands (allostasis).

Mediators of allostasis, therefore, facilitate adaptation whereas the parameters associated with homeostasis do not vary as a means of promoting adaptation. Importantly, such variation in parameters associated with adaptation has long been appreciated, particularly beginning with the early work of Walter Cannon.[46] Allostatic systems are involved in coping and adaptation, and generally, they are most useful when they can be rapidly mobilized and terminated when not needed. It is when they are prolonged or not terminated promptly that these systems undermine health. Moreover, the inability to engage allostatic systems when needed also produces a load on the body, because the normal protection afforded by these systems is lacking.

An important aspect of allostasis and allostatic load is the notion of anticipation. Although originally introduced in relation to explaining the reflex that prevents us from blacking out when we get out of bed in the morning,[43] anticipation also implies psychological states, such as apprehension, worry, and anxiety, as well as cognitive preparation for a coming event. Because anticipation can drive the output of allostatic biomediators (this is particularly true of hormones like ACTH, cortisol, and adrenalin), it is likely that states of prolonged anxiety and anticipation can theoretically result in allostatic load.[47]

Other important aspects of individual responses in relation to allostasis and allostatic load are health damaging and health promoting behaviors, such as smoking, drinking, sleeping, eating a prudent diet, and regularly exercising, collectively called "lifestyle" behaviors. These may be embodied within the overall notion of allostasis—*i.e.*, how individuals cope with a challenge – and they also contribute in some ways to allostatic load (*e.g.*, a Western (high-fat) diet accelerates atherosclerosis and progression to Type II diabetes; smoking accelerates atherogenesis; exercise and restorative sleep promote cognitive functioning and health[28]).

Within the framework presented here and detailed elsewhere, there are four types of physiological response that may contribute to and reflect allostatic load. The first type is related to frequent stressors, for example, blood pressure surges that not only trigger MI in susceptible individuals, but accelerate atherosclerosis and prime the risk for MI when they are supposedly repeatedly expressed over the lifespan. Here, it is the frequency and intensity of the "hits" or events (*e.g.*, large blood pressure surges) that determines the level of allostatic load engendered by this type. Although, frequent stress may lead into the other types described below as the body responds to repeated events by either failing to terminate neural and endocrine responses or failing to respond adequately.

The second type of allostatic load involves a failure to habituate to repetition of the same stressor, leading to a persistent elevation of mediators like cortisol. This was first described for a subset of individuals in a repeated public speaking challenge who failed to habituate their cortisol response.[48] Later studies have shown that these individuals have low self esteem and a smaller hippocampus, stress-related behavioral, and neurobiological processes discussed later.[49,50]

The third type of allostatic load involves failure to terminate adaptive autonomic and neuroendocrine responses. Consider, for example, blood pressure elevations in repetitive, time pressured work[51] and the fact that chronic, elevated levels of glucocorticoids accelerate obesity and Type II diabetes. Moreover, we note below that persistent glucocorticoid elevation and/or excitatory activity in brain systems regulating glucocorticoid secretion causes dendritic

remodeling and neuronal death in the hippocampus and other limbic brain areas.

The fourth type of allostatic load is the failure to respond adequately to a challenge. Consider, for example, autoimmunity and inflammation that is associated with inadequate endogenous glucocorticoid responses, as in the Lewis rat[52] and possibly also in chronic fatigue syndrome and fibromyalgia.[53–55] Here, other biomediators of allostatic systems—such as inflammatory cytokines—show elevated activity, and this may increase allostatic load because of inadequate HPA regulation, which normally "constrains" their activity. Post-traumatic stress is also a form of psychopathology that is yet another example of how an acute, but traumatic event, leads to dysregulated HPA axis activity that may not respond adequately to acute challenge and promote comorbid physical disease.[56]

Joint roles of amygdala, hippocampus, and prefrontal cortex in visceral functions

The hippocampus and amygdala are limbic brain structures that process experiences by interfacing with lower vegetative brain areas, such as the hypothalamus and brainstem, and higher cortical areas, particularly within the prefrontal cortex. They also help to interpret, on the basis of current and past experiences, whether an event is threatening or otherwise stressful—thus influencing allostatic responses. The amygdala is an essential neural component of the memory system for fearful and emotionally laden events, whereas the hippocampus supports determining the context in which such events take place, as well as other aspects of episodic and declarative memory.[57–59] For example, whereas lesions to the central or lateral amygdala abolish conditioning of the freezing response of an animal to a tone paired with a shock, hippocampal lesions have no such effects. On the other hand, hippocampal lesions abolish conditioning of the freezing response to the "context," *i.e.*, to the environment of a particular conditioning chamber.[58]

As illustrated in Figure 1, the amygdala and hippocampus are linked to each other anatomically and functionally.[60–62] For example, lesions of the basolateral amygdaloid nucleus reduce long-term potentiation—a process underpinning memory—in the hippocampal dentate gyrus and stimulation of this nucleus facilitates dentate gyrus long-term potentiation.[63,64] The hippocampus and amygdala also regulate the HPA axis, with the hippocampus in general being inhibitory and the amygdala being excitatory.[62,65–67] However, this statement oversimplifies a great deal of complexity. For example, within the hippocampus, certain sites respond to electrical stimulation by increasing HPA activity.[68] Moreover, other brain areas are involved. For example, a recent brain lesion and steroid implant study—as well as emerging neuroimaging evidence reviewed below—indicate that the medial prefrontal cortex (mPFC) plays an important role in constraining the HPA axis under stress-related conditions.[69]

Further, glucocorticoid implants into the mPFC reduce the magnitude of the HPA response to stress, and they reduce plasma insulin levels in rodents.[69] In contrast, lesions of the dorsal and ventral areas of the prefrontal cortex differentially impair regulation of the HPA stress response via circuitry with the hypothalamus.[70,71] Among other implications, these findings point to the important role of steroid feedback to the brain in the control of HPA activity, particularly to sites outside of the hippocampus and hypothalamus. It is important to note that the HPA axis is dynamically regulated, and that steroid feedback operates at several levels in relation to neural control of the turning on and shutting off of the stress response.[72,73] Besides rate-sensitive and level-sensitive feedback, delayed feedback may be viewed as both a thermostat (steroid elevation turning down ACTH release) and a modulation by neural activity, which can be inhibitory (perhaps via the GABA system), as well as excitatory upon hypothalamic paraventricular nucleus (PVN) neurons.[67] Further, the bed nucleus of the stria terminalis—a basal forebrain structure involved in many motivational and stress-related processes—is reported to have both inhibitory and excitatory pathways to the PVN that regulate limbic system inputs to the HPA axis.[74] The demonstration that constant steroid feedback via corticosterone pellets implanted into adrenalectomized (ADX) rats normalizes ACTH levels, but allows for sustained ACTH secretion after stress, highlights the importance of neural control in the allostatic shut-off of the HPA stress response.[72,73] The fact that in the same study, diurnal exposure to CORT in the drinking water also normalized ACTH levels in ADX rats but allowed for a more rapid termination of the HPA stress response, even when no steroid was present, further highlights the

importance of understanding the role of diurnally varying levels of adrenal steroids in priming neural mechanisms subserving a shut-off of the HPA axis.[72,73] A further aspect of feedback regulation of HPA function is the ability of energy sources, such as sucrose, to reduce ACTH secretion independently of adrenal steroids.[75] We shall now examine the roles of hippocampus, amygdala and prefrontal cortex in cognitive functions and emotional regulation, particularly as they relate to allostatic processes mediated by and targeting the brain.

Brain systems mediating allostatic processes

As reviewed earlier, the hippocampus, amygdala, and prefrontal cortex are anatomically networked components of a neural circuitry that coordinates behavior with neuroendocrine, immune, and autonomic functions in the service of adaptively coping with environmental and psychosocial challenges. In the following sections, we review translational animal and human studies focusing on these areas, particularly within the context of their importance for mediating allodynamic processes important for health. To establish a context for this review, we present a conceptual model in Figure 2 that embodies the concepts of allostasis and allostatic load as mediated by and impacting brain systems important for stress regulation. Importantly, this model highlights specific stress-related dimensions of SES potentially linked to risk for ill health. The following discussion is accompanied by summary sections for those readers who do not want to read the details.

Hippocampus and stress processes

Functional neuroanatomy of the hippocampus

The hippocampus is located in the medial temporal lobe and—as reviewed above—plays instrumental roles in learning and remembering declarative and spatial information, processing the contextual aspects of emotional events, and regulating visceral functions, including the HPA axis. Also as summarized earlier, the hippocampus is interconnected with the amygdala and prefrontal cortex. The hippocampus contains receptors for adrenal steroids, and for major metabolic hormones that have functional effects on the hippocampus. Specifically, these biomediators can enhance cognitive processes, affect mood and motivation, and promote excitability and neuroprotection. Yet, these same biomediators can have deleterious effects on the hippocampus under conditions associated with chronic stress and allostatic load.[76]

Animal model studies of the hippocampus

A number of animal models demonstrate that chronic stressful experiences (*e.g.*, prolonged immobilization, housing in dominance hierarchies, early maternal separation) can remodel hippocampal neurons and result in changes in the gross morphology of the hippocampus. Notably, the hippocampus is one of the most sensitive and malleable regions of the brain, and it is very important for cognitive function. Within the hippocampus, input from the entorhinal cortex to the dentate gyrus is ramified by connections between the dentate gyrus and the CA3 pyramidal neurons. Hence, one granule neuron innervates, on average, 12 CA3 neurons, and each CA3 neuron innervates, on average, 50 other CA3 neurons via axon collaterals, as well as 25 inhibitory cells via other axon collaterals. The net result is a 600-fold amplification of excitation, as well as a 300-fold amplification of inhibition, that provides some degree of control of the system.[77]

As to why this type of circuitry exists, the dentate gyrus-CA3 system is believed to play a role in the memory of event sequences, although long-term storage of memory occurs in other brain regions.[78] But, because the DG-CA3 system is so delicately balanced in its function and vulnerability to damage, there is also adaptive structural plasticity: New neurons continue to be produced in the dentate gyrus throughout adult life, and CA3 pyramidal cells undergo a reversible remodeling of their dendrites in conditions such as hibernation and chronic stress.[77,79–81] The role of this plasticity may be to protect against permanent damage. As a result, the hippocampus undergoes a number of allostatic or adaptive changes in response to acute and chronic stress.

One type of change involves replacement of neurons via neurogenesis. The sub-granular layer of the dentate gyrus contains cells that have some properties of astrocytes (*e.g.*, expression of glial fibrillary acidic protein) and which give rise to granule neurons.[82,83] After Bromodeoxyuridine (5-bromo-2-deoxyuridine, BrdU) administration to label DNA of dividing cells, these newly born cells appear as clusters in the inner part of the granule cell layer,

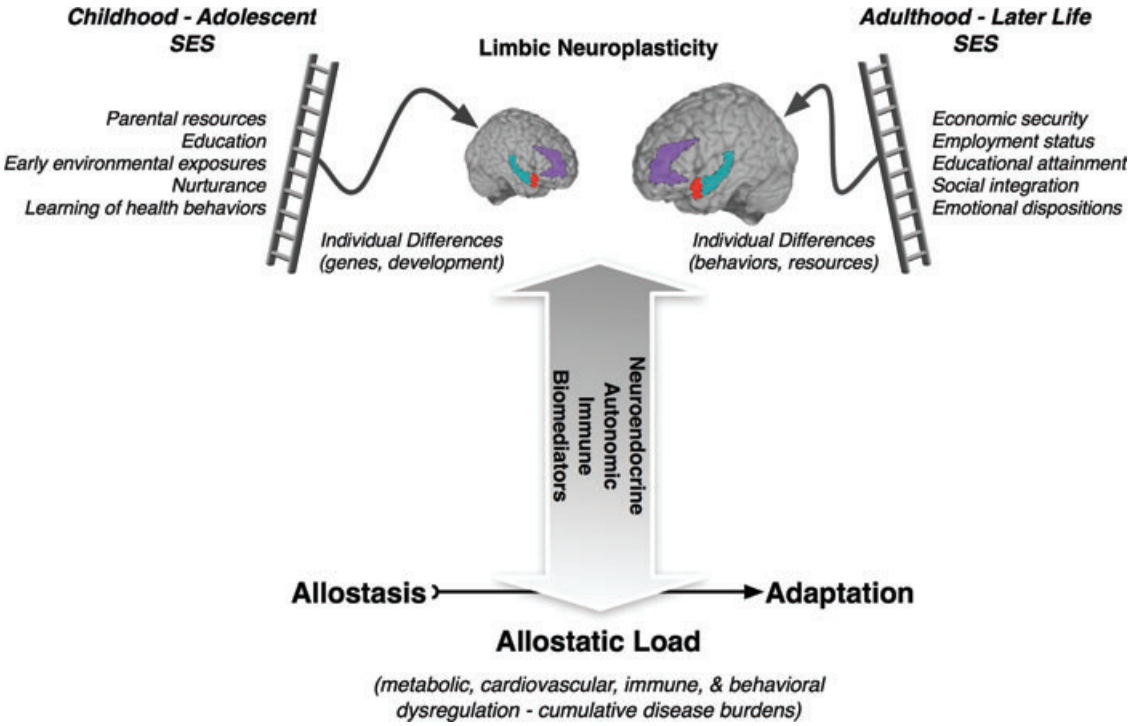

Figure 2. Neurobiological pathways of SES and allostatic load. A heuristic schematic illustrating the potential neurobiological pathways by which psychosocial factors related to SES may impact allostatic control systems underpinning allostatic load and disease risk. In childhood and adolescence, psychosocial factors related to SES and reviewed elsewhere in this volume (*e.g.*, parental resources and education) are likely to interact with genetic and dispositional individual differences to affect the neuroplasticity of limbic brain areas that regulate allostatic control systems. These brain areas include subdivisions of the prefrontal cortex (*e.g.*, the anterior cingulate cortex *in purple*), hippocampus (*in blue-green*), and the amygdala (*in red*). Importantly, these limbic areas regulate neuroendocrine, autonomic, and immune systems, which are involved in the bidirectional allodynamic control of central and peripheral physiology. In adulthood and later life, psychosocial factors related to SES (*e.g.*, meaningful employment and social integration) may similarly interact with individual difference and behavioral lifestyle factors to affect the neuroplasticity and aging of the same limbic systems mediating and targeted by allostatic control systems. To the extent that lower SES adversely affects limbic neuroplasticity via stress-related factors, then the regulation of key allostatic control systems may become impaired, leading to allostatic load on the body and brain and perhaps increased risk for ill health.

where a substantial number will subsequently differentiate into granule neurons within just 7 days. In the adult rat, 9000 new neurons are born per day and survive with a half-life of 28 days.[84] There are many hormonal, neurochemical and behavioral modulators of neurogenesis and cell survival in the dentate gyrus, including estradiol, insulin-like growth factor 1 (IGF-1), antidepressants, voluntary exercise, and hippocampal-dependent learning.[85–87] With respect to stress, certain types of acute stress and many chronic stressors suppress neurogenesis or cell survival in the dentate gyrus, and the mediators of these inhibitory effects include excitatory amino acids acting via *N*-methyl-D-aspartic acid (NMDA) receptors and endogenous opioids.[88]

Another form of neuroplasticity is the remodeling of dendrites in the hippocampus. Chronic restraint stress causes retraction and simplification of dendrites in the CA3 region of the hippocampus.[77,89] Such dendritic reorganization is found in

both dominant and subordinate rats undergoing adaptation of psychosocial stress in the visible burrow system, which is independent of adrenal size.[90] What this particular result emphasizes is that it is not adrenal size or presumed amount of physiological stress *per se* that determines dendritic remodeling, but a complex set of other interacting factors that modulate neuronal structure. Indeed, in species of mammals that hibernate, dendritic remodeling is a reversible process, and it occurs within hours of the onset of hibernation in European hamsters and ground squirrels. Moreover, it is reversible within hours of wakening of the animals from torpor.[79–81,91] This implies that reorganization of the cytoskeleton is taking place rapidly and reversibly and that changes in dendrite length and branching are not "damage" but a form of structural plasticity. Further, in humans, remarkable changes in hippocampal morphology—specifically volumetric changes—have been associated with the extent of expertise about the spatial layout of cities,[92,93] further suggesting dynamic experience-dependent neuroplasticity in the hippocampus.

Regarding the mechanism(s) of structural remodeling, adrenal steroids are important mediators of hippocampal neuroplasticity during repeated stress, and exogenous adrenal steroids can also mediate neuroplasticity in the absence of an external stressor. The mediating role of adrenal steroids depends on interactions with neurochemical systems, including serotonin, GABA and excitatory amino acids.[77,94] Perhaps the most important interactions are those with excitatory amino acids such as glutamate. Excitatory amino acids released by the hippocampal mossy fiber pathway play a key role in remodeling the CA3 region of the hippocampus, and regulation of glutamate release by adrenal steroids may play a particularly important role.[77,94]

Among the consequences of chronic stress, such as prolonged restraint, is the elevation of extracellular glutamate levels, leading to induction of glial glutamate transporters, as well as increased activation of a nuclear transcription factor, the phosphorylated form of cyclic AMP response element binding protein (phosphoCREB).[95] Moreover, 21d of chronic restraint stress (21d CRS) depletes clear vesicles from mossy fiber terminals and increases expression of presynaptic proteins involved in vesicle release.[96–98] Taken together with the fact that vesicles that remain in the mossy fiber terminal are near active synaptic zones and that there are more mitochondria in the terminals of stressed rats, this suggests that CRS increases the release of glutamate.[98]

Extracellular molecules also play a role in remodeling and neuroplasticity. Neural cell adhesion molecule (NCAM) and its polysialated-NCAM (PSA-NCAM), as well as L1 are expressed in the dentate gyrus and CA3 region and the expression of both NCAM, L1, and PSA-NCAM are regulated by 21d CRS.[99] Tissue plasminogen activator (tPA) is an extracellular protease and signaling molecule that is released with neural activity and is required for chronic stress-induced loss of spines and NMDA receptor subunits on CA1 neurons.[100]

Within the neuronal cytoskeleton, the remodeling of hippocampal neurons by chronic stress and hibernation alters the acetylation of microtubule subunits—consistent with a more stable cytoskeleton[101]—and alters microtubule associated proteins, including the phosphorylation of a soluble form of τ, which is increased in hibernation and reversed when hibernation is terminated.[91]

Neurotrophic factors also play a role in dendritic branching and length. For example, mice bred to show reduced levels of brain derived neurotrophic factor (BDNF±) show a less branched dendritic tree and do not show a further reduction of CA3 dendrite length with chronic stress, whereas wild-type mice show reduced dendritic branching (Magarinos, McEwen unpublished observations). However, there is contradictory information thus far concerning whether CRS reduces BDNF mRNA levels, with some studies reporting a decrease[102] and others reporting no change.[103–105] This may reflect the balance of two opposing forces, namely, that stress triggers increased BDNF synthesis to replace depletion of BDNF caused by stress.[106] BDNF and corticosteroids also appear to oppose each other—with BDNF reversing reduced excitability in hippocampal neurons induced by stress levels of corticosterone.[107]

Corticotrophin releasing factor (CRF) is another key mediator of many aspects of neuroplasticity related to stress.[108] CRF in the PVN regulates ACTH release from the anterior pituitary gland, whereas CRF in the central amygdala is involved in control of behavioral and autonomic responses to stress, including the release to tPA that is an essential part of stress-induced anxiety and structural plasticity in the medial amygdala.[109] CRF in the hippocampus

is expressed in a subset of γ-aminobutyric acid (GABA) neurons (Cajal-Retzius cells) in the developing hippocampus, and early life stress produces a delayed effect that reduces cognitive function and the number of CA3 neurons as well as decreased branching of hippocampal pyramidal neurons.[110,111] Indeed CRH inhibits dendritic branching in hippocampal cultures *in vitro*.[112]

Summary

Animal model studies on the hippocampus have revealed a mechanism by which repeated stress causes remodeling of hippocampal circuitry; namely, shortening of dendrites, loss of spine synapses and suppression of the neurogenesis that is ongoing in the young adult dentate gyrus region of the hippocampal formation. This is a reversible process for stressors lasting a number of weeks, and it involves as mediators not only circulating glucocorticoids but also excitatory amino acid neurotransmitters and other endogenous mediators and modulators. Because of these two inter-related roles of the hippocampus—supporting aspects of memory and regulating HPA activity—impairment of hippocampal function through changes in either excitability, reversible plasticity or permanent damage may be expected to have two effects: (1) The first is to impair hippocampal involvement in episodic, declarative, contextual and spatial memory; impairments of these functions are likely to debilitate an individual's ability to process information in new situations and to make decisions about how to deal with new challenges. (2) The second effect is to impair the hippocampal role in regulating HPA activity, particularly the termination of the stress response, leading to elevated HPA activity and further exacerbating the actions of adrenal steroids in the long-term effects of repeated stress. This concept, first called the "glucocorticoid cascade hypothesis" of hippocampal aging,[113] stands at the center of the notion of "allostasis" and "allostatic load" and the central role of the brain.

Human neuroimaging studies of the hippocampus

Complementing animal studies of stress-related processes mediated by and affecting neuroplasticity in the hippocampus, a growing number of human *structural* neuroimaging studies have begun to examine stress processes in association with aspects of gross hippocampal morphology. For example, individuals with stress-related psychiatric disorders, such as major depressive disorder and post-traumatic stress disorder, show volumetric reductions in the hippocampus.[114–128] Reduced hippocampal volume has also been found in Cushing's Disease.[129] Interestingly, in Cushing's, surgical correction of hypercortisolemia has been reported to at least partially reverse hippocampal volume reduction as well as mood and memory deficits.[130,131] In depression, there is evidence of volumetric increase in the hippocampus after antidepressant treatment,[120] suggesting that the deficits in depression are potentially reversible. Moreover, there is increasing support for the notion that targeting the plasticity of the hippocampus in depression and mood disorders may underpin pharmacological and nonpharmacological treatment efficacy.[132]

In addition to clinical studies, there is emerging evidence from otherwise healthy individuals for a relationship between chronic stressful experiences and changes in hippocampal morphology. Among post-menopausal women, for example, higher levels of chronic perceived stress, as measured over an approximate 20-year period of life, have been associated with reduced gray matter volume in the hippocampus in addition to the orbital prefrontal cortex.[133] Further, more than 3 years after the terrorist attacks on the World Trade Center buildings on September 11, 2001, otherwise healthy adults living in close proximity to the buildings showed a reduction in gray matter volume in the hippocampus, as well as in anatomically networked areas of the amygdala and mPFC.[134]

Although these structural neuroimaging findings are provocative, it is important to note that it has not yet been demonstrated that putatively stress-related variation in the morphology of the hippocampus or other brain regions in humans is invariably the permanent consequence of so-called "neurotoxic" stress-related mechanisms.[135–137] It is possible, for example, that pre-existing individual differences in hippocampal and regional brain morphology could partly increase vulnerability to and decrease resiliency against life stress.[138] These individual differences could emerge early in life, and could result from a combination of genetic and developmental influences. In line with this notion, there is recent evidence that individual differences in

self-esteem and locus of control, positive psychological attributes that emerge early in life and modify the appraisal of environmental stressors, are associated with hippocampal volume and related changes in HPA regulation in both young and elderly people.[50] Further, there is evidence that birth weight itself predicts hippocampal volume in adulthood, particularly among women reporting unfavorable maternal care—suggesting that the postnatal caregiving environment may affect the neurodevelopmental consequences of prenatal risk.[139]

In addition to these early life processes, recent human evidence shows that carriers of the methionine (met) allele of the valine(val)66met BDNF polymorphism express lower gray matter volume in the hippocampus and prefrontal cortex compared with carriers of the val/val allele.[140–142] As reviewed earlier, in animal models, chronic stress is known to down-regulate BDNF, possibly contributing to cellular remodeling in the hippocampus.[143–145] Thus, given that the m*et al*lele is associated with relatively reduced activity-dependent secretion and intracellular trafficking of pro-BDNF, this allele could plausibly affect the contribution of BDNF to signaling cascades mediating synaptic plasticity and, potentially, neurogenesis in response to stress. In further support of genetically mediated plasticity of the hippocampus possibly affecting stress resiliency, a recent twin study demonstrated that smaller hippocampal volume may predict vulnerability to the development of PTSD.[146] In aggregate, these structural neuroimaging studies of humans complement translational animal studies of stress processes in that they reveal both vulnerability and experience-dependent patterns of hippocampal morphology relevant to risk for and resilience against ill health.

Within the context of the allostatic load model presented in Figure 2, there are several additional immune-mediated mechanisms involving bidirectional brain–body and body–brain patterns of communication that may further account for individual differences in hippocampal morphology. More precisely, growing evidence supports an association between peripheral immune activation and behavioral, affective and cognitive disturbances. Peripheral proinflammatory cytokines, such as interleukin (IL)-6, represent plausible mediators of these effects, as they can penetrate the blood–brain barrier directly via active transport mechanisms[147,148] or indirectly via the vagus nerve[149,150] to stimulate the production of central proinflammatory cytokines, including IL-6, which are expressed in hippocampus along with their receptors.[151,152]

Moreover, this central inflammation may adversely affect learning and memory through processes related to neurodegeneration and structural remodeling of the hippocampus in particular. In humans, there is evidence for an inverse association between peripheral levels of IL-6, a relatively stable marker of systemic inflammation, and memory function in mid-life adults.[153] In an extension of this particular study,[154] a computational structural neuroimaging method (voxel-based morphometry) was used to test the relationship between plasma IL-6 levels and hippocampal gray matter volume. Results showed that peripheral levels of IL-6 covaried inversely with hippocampal gray matter volume. However, the exact mechanisms by which peripheral IL-6 relates to hippocampal gray matter volume and cognition in humans remain unclear, as do their implications for stress-related processes involved in mediating neuroplasticity, particularly within the hippocampus.

Interestingly, sleep disruption is associated with elevated plasma levels of IL-6.[155] The hippocampus is also affected by jet lag and circadian disruption, and a study using structural brain imaging on airline crews with short turn recovery times after international flights across multiple time zones revealed smaller volumes of the temporal lobe containing the hippocampus compared to air crews with a longer time between flights.[156] Related to inflammation are metabolic imbalance and oxidative stress[157] and the consequences of diabetes for cognitive function and the hippocampus. Studies of Type 2 diabetes have revealed reduced hippocampal volume that is larger in those subjects with the greatest elevations of glycosylated hemoglobin, indicative of elevated blood glucose levels.[158] Mild cognitive impairment in aging is also associated with hippocampal volume reduction that is also related to elevated glycosylated hemoglobin levels below the threshold for Type 2 diabetes.[159] One of the treatments that can prevent Type 2 diabetes is regular physical activity and a recent study shows that fit individuals have larger left and right hippocampal volumes than unfit individuals.[160]

In addition to structural neuroimaging studies of chronic stress and related processes, an increasing

number of functional neuroimaging studies in humans are beginning to link hippocampal activity with acute stressor-evoked changes in the HPA axis, as measured by salivary cortisol. As has been widely demonstrated in laboratory studies,[161] these functional neuroimaging studies have shown that the HPA axis is reliably engaged by stressors that involve completing demanding and uncontrollable cognitive challenges with added negative social evaluation. For example, using a modified version of the Trier Social Stress Test (TSST) administered during positron emission tomography (PET) scanning, significant associations between *increased* salivary cortisol levels and *decreased* activity in the hippocampus and networked brain areas, including the amygdala and hypothalamus have been documented.[162] These particular findings are notable in that the hippocampus is thought to exert an inhibitory control over the hypothalamus, and thus the HPA axis. When "deactivated" under stress, the hippocampus and other limbic areas innervating the hypothalamus may in turn *disinhibit* the HPA axis and the consequent release of cortisol. In a more recent study, associations between cortisol reactivity to the TSST and patterns of activation in brain areas other than the hippocampus during PET scanning have also been documented.[163] The results of this study extended those of Pruessner and colleagues to show that in response to the TSST, *increased* activation of areas of the mPFC covaried with decreased salivary cortisol reactivity. These particular findings are broadly consistent with the notion that the mPFC plays an integrative role in cognitive and affective processing[164,165] and with animal models demonstrating that subregions of the mPFC regulate the HPA axis through inhibitory control mechanisms.[69,166]

In view of these conceptualizations of the mPFC, Kern and colleagues interpreted their findings to suggest that social stressors such as the TSST engage the mPFC as part of a regulatory circuitry that modulates downstream stress reactivity and coping processes. Supporting this interpretation, Kern and colleagues used functional connectivity analyses to link *increased* activation in the mPFC with *decreased* activation in the hippocampal-amygdala complex, in addition to other limbic areas. These connectivity findings agreed with the notion developed from translational animal models that the mPFC may inhibit HPA activity via regulatory signaling with brain areas innervating the hypothalamus, as reviewed earlier on animal findings detailing the dual role of the amygdala, hippocampus, and prefrontal cortex in visceral and cognitive functions.[69,166] In view of these translational findings, an important direction of future research will be to link stress-related variation in hippocampal morphology and functionality to markers of SES, as SES may impact health in part via dysregulated HPA functioning. For example, open questions are whether dimensions of lower SES at the individual, family, or community levels are associated with hippocampal structural or functional plasticity over the lifespan, possibly in association with dysregulated allostatic control over the HPA axis and associated cognitive sequelae.

Summary

Studies on the human hippocampus with structural and functional imaging have produced provocative results that are consistent with the animal models showing a capacity for plasticity that should be followed up by longitudinal studies to demonstrate stress-related changes that are independent of preexisting individual differences in hippocampal volume and function.

Amygdala and stress processes

Functional neuroanatomy of the amygdala

The amygdala is comprised of distinct cell groups in the medial anterior temporal lobes, adjacent to the hippocampus (see Fig. 1). A critical function of the amygdala in stressor-related processing involves the rapid assignment of emotional and behavioral salience to environmental events[167–171] The amygdala supports such processing by integrating multimodal sensory inputs from distributed cortical, thalamic, and brainstem afferent relays. More precisely, sensory input is relayed through thalamic and cortical-thalamic pathways to the basolateral area via the lateral nucleus, basolateral nucleus, and accessory basal nucleus. From the basolateral nucleus, motivationally relevant sensory signals are relayed to the central nucleus. As a primary output nucleus, the central nucleus signals commands for adaptive changes in behavior and supporting physiological adjustments via the stria terminalis to lateral and paraventricular hypothalamic nuclei and to periaqueductal, medullary, and preautonomic nuclei. Importantly, the central nucleus

is also networked with cortical areas involved in stressor-related processing—principally, areas of the prefrontal cortex, including the anterior cingulate cortex (ACC), ventromedial prefrontal cortex, and orbital prefrontal cortex.[172–174] Hence, the amygdala is broadly viewed to interrelate cortical processes supporting the coordination of stressor-evoked changes in behavior and peripheral physiological reactivity, particularly within the context of adverse social environments affecting health.[5,24,175]

Animal studies of the amygdala

Chronic immobilization stress of the type that causes retraction of dendrites in CA3 region of the hippocampus produces dendritic growth in neurons in basolateral amygdala.[176] Moreover, chronic stress of this type not only impairs hippocampal-dependent cognitive function, but also enhances amygdala-dependent unlearned fear and fear conditioning processes[177,178] that are consistent with the opposite effects of stress on hippocampal and amygdala structure. Chronic stress also increases aggression between animals living in the same cage, and this is likely to reflect another aspect of hyperactivity of the amygdala.[178,179] Moreover, chronic corticosterone treatment in drinking water produces an anxiogenic effect in mice,[180] an effect that could be due to the glucocorticoid enhancement of CRF activity in the amygdala.[181,182]

As for mechanism(s) mediating forms of amygdala neuroplasticity, besides the possible role of glucocorticoids and excitatory amino acids, tPA is required for acute stress to activate not only indices of structural plasticity, but also to enhance anxiety.[183] These effects occur in the medial and central amygdala, but not in basolateral amygdala—with the release of CRF acting via CRF-1 receptors appearing to be responsible.[109] Furthermore, tPA plays a role in stress-induced decreases in spine density in medial amygdala neurons, but not in the stress-induced increase in spine density in basolateral amygdala neurons.[184] However, nothing is yet known about the role of tPA, if any, in the prefrontal cortex. Although, it is noteworthy that tPA does appear to play a role in stress-induced reductions of spine synapse number in the CA1 region of the mouse hippocampus.[100]

BDNF may also play a role in amygdala, because over-expression of BDNF, without any applied stressor, enhances anxiety in an elevated plus maze and increases spine density on basolateral amygdala neurons and this occludes the effect of immobilization stress on both anxiety and spine density.[185] As noted earlier for hippocampus, BDNF over-expressing mice also show reduced behavioral depression in the Porsolt forced-swim task and show protection against stress-induced shortening of dendrites in the CA3 region.[185]

Summary

Animal studies on the amygdala reveal stress-induced structural plasticity within major subdivisions of this brain region that relate to stress effects on aggression and anxiety.

Human neuroimaging studies of the amygdala

Complimenting the above animal work, the amygdala has been shown to be central to emotion and stress-related processes humans.[186–189] Specifically, there is human functional neuroimaging evidence that the amygdala is involved in mediating forms of peripheral stress reactivity that have been linked to physical health outcomes. For example, individual differences in amygdala reactivity to emotionally salient stimuli have been shown to covary with physiological parameters associated with cardiovascular disease risk, including basal levels of autonomic-cardiac control,[190] stressor-evoked changes in blood pressure,[191] and diurnal variations in the secretion of the stress hormone, cortisol.[165] Most recently, it has been demonstrated that individuals who express *greater* amygdala reactivity to threatening social cues (angry and fearful facial expressions) also exhibit *higher* levels of preclinical atherosclerosis, as determined noninvasively by a thickening of the intima-media layers of carotid artery vessel wall complex.[192] Moreover, in that study, individuals who showed *lower* levels of preclinical atherosclerosis exhibited a pattern of functional connectivity (correlated activity) between the amygdala and ACC that suggested a potentially greater down-regulation of the amygdala by this area of the prefrontal cortex during the processing of threatening social cues.

These findings are noteworthy from a clinical-translational perspective because the amygdala and its functional interactions with the ACC and other areas of the prefrontal cortex have long been implicated in conferring risk for psychopathologies of mood and anxiety,[193–195] which are highly co-morbid with atherosclerotic

cardiovascular disease.[196–199] Further, functional aspects of the ACC in particular have been recently implicated in atherogenesis in a primate model of comorbid depression and cardiovascular disease.[200] In synthesis, the ACC and other areas of the prefrontal cortex may not only plausibly protect against some forms of psychiatric syndromes, but also physical diseases (*e.g.*, atherosclerotic cardiovascular disease) by effectively regulating the amygdala and the peripheral expression of biomediators involved in allostatic load.

In addition to studies of stress reactivity and cardiovascular risk, there is emerging evidence suggesting that amygdala may be involved in linking stress-related processes to health within the context of childhood SES. In particular, social information processing models emphasizing a life course perspective have postulated that lower SES individuals may develop an early sensitivity to social threats in the environment, leading to dysregulated forms of emotional control and recurrent biobehavioral stress responses that increase risk for ill health in later life.[175,201,202] This postulate parallels the notion that risk trajectories for ill health may be developmentally "embedded" in the brain and in biobehavioral stress-response systems by early and unfavorable socioeconomic circumstances.[203,204]

Consistent with this notion, recent neuroimaging evidence has shown that a retrospective measure of lower perceived parental social standing, a putative indicator of socioeconomic disadvantage during childhood and adolescence, is uniquely associated with greater amygdala reactivity to threatening (angry) facial expressions (see Fig. 3).[205] Notably, this association was observed among healthy individuals who had not yet reached their adult SES, and it was not explained by several potential confounding factors, including sex, ethnicity, dispositional emotionality, recent symptoms of depression and anxiety, parental education, and participants' perceptions of their own social standing. Given that the amygdala is (*i*) instrumental for gauging the emotional salience of social and environmental information, (*ii*) critical for regulating the neuroendocrine and autonomic stress-response axes, and (*iii*) sensitive to early life stress, then increased amygdala reactivity to angry or otherwise threat-related facial expressions could represent a neural correlate of a so-called developmental "embedding" of early SES-related experiences that influence sensitivity to perceived social threats—possibly affecting stress regulatory peripheral allostatic systems influencing health or disease vulnerability.

Most recently, amygdala reactivity has been linked to concurrent changes in the neural representation of social hierarchies in humans.[206] In this study, functional magnetic resonance imaging (fMRI) was used to identify neural responses correlated with perceived social rank within the context of an interactive, simulated social context involving exposure to both stable and unstable social hierarchies.

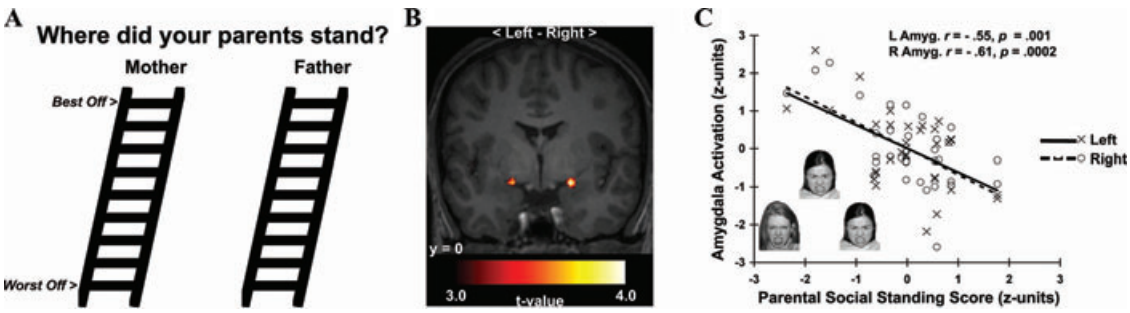

Figure 3. **Lower perceived parental social standing predicted greater amygdala reactivity to angry faces in a functional neuroimaging study of young adults. (A) Social ladders used to assess perceived parental social standing. (B) Statistical parametric maps projected onto an anatomical template. The maps profile amygdala areas where lower perceived parental social standing predicted greater reactivity to angry faces. (C) Plots depicting standardized perceived parental social standing scores (*x*-axis) and mean-centered, standardized reactivity values derived from left (L, *open circles, dashed line*) and right (R, *closed circles, solid line*) amygdala areas in B. Inset in C illustrates exemplar trial of angry faces used to elicit amygdala reactivity. From Gianaros *et al.* (2008), reprinted with permission.**

Interestingly, in the context of an unstable social hierarchy, viewing a superior ranking individual engaged the amygdala and areas of the mPFC involved in social cognition. These findings are important in that they are among the first to begin to translate animal studies on the role of the amygdala and networked corticolimbic areas in potentially linking stress processes to candidate neurobiological mechanisms mediating the impact of socioeconomic gradients on mental and physical health. Moreover, it is noteworthy that experimentally manipulating social standing—following an interpersonal paradigm similar to that employed by Zink and colleagues[206]—has recently been shown to increase the subjective experience of negative affect concurrent with elevations in systolic blood pressure.[207] In light of translational evidence on the role of the amygdala in mediating negative affect and blood pressure control, it is plausible that the amygdala supports key functions in stress and emotion processes related to SES and health, as speculated previously.[208]

Summary

Studies on the human amygdala reinforce a large body of animal studies demonstrating the importance of this region for emotion- and stress-related behavioral and physiological processes. Moreover, there is emerging neuroimaging evidence indicating that the functionality of the amygdala may be linked to socioeconomic factors, including childhood SES and the dynamic representation of relative social standing.

Prefrontal cortex and stress processes

Functional neuroanatomy of the prefrontal cortex

As shown in Figure 1, the prefrontal cortex occupies the anterior portion of the frontal lobes and is broadly involved in higher cognitive functions (*e.g.*, working memory and executive control). One such function is the *top-down* regulation of stress and threat-related responding and coping processes mediated by subcortical limbic areas, including the hippocampus, amygdala, and hypothalamus.[209] Importantly, several prefrontal areas send direct projections to the hypothalamus and other areas involved in regulating the peripheral stress-response axes important for health. These prefrontal areas primarily include the orbital and dorsal medial prefrontal cortex and the ACC.

Animal studies of the prefrontal cortex

Chronic stress also causes functional and structural changes in the medial prefrontal cortex, particularly in areas of anterior cingulate, prelimbic, infralimbic, and orbitofrontal regions—corresponding to conventional animal anatomical labeling. For example, CRS and chronic immobilization cause dendritic shortening in medial prefrontal cortex,[89,176,210–214] but also produce dendritic growth in orbitofrontal cortex.[215] Taken together with the differential effects of the same stressors on the hippocampus and amygdala, these actions of stress are reminiscent of recent work on experimenter versus self-administered morphine and amphetamine, in which different, and sometimes opposite, effects were seen on dendritic spine density in orbitofrontal cortex, medial prefrontal cortex, and hippocampus CA1.[216] For example, amphetamine self-administration increased spine density on pyramidal neurons in the medial prefrontal cortex and decreases spine density on orbitofrontal pyramidal neurons.[217]

Along with many other brain regions, the prefrontal cortex, as well as the amygdala discussed earlier, contain adrenal steroid receptors;[218,219] however, the role of adrenal steroids, excitatory amino acids and other mediators has not yet been studied in detail in these brain regions, in contrast to the hippocampus. Nevertheless, glucocorticoids do appear to play a role, since 3 weeks of chronic corticosterone treatment was shown to produce retraction of dendrites in medial prefrontal cortex,[210] although with subtle differences in the qualitative nature of the effect from what has been described after chronic restraint stress.[212] Another study determined the effect of adrenalectomy or chronic treatment for 4 weeks with corticosterone or dexamethasone on volume and neuron number in the prefrontal cortex.[220] Dexamethasone treatment at a dose that may have been high enough to enter the brain (although this was not directly measured) caused a loss of neurons in Layer II of the infralimbic, prelimbic, and cingulate cortex, whereas corticosterone treatment reduced the volume but not the neuron number of these cortical regions.[220] The dexamethasone treatment was particularly effective in impairing working memory and cognitive flexibility using working memory task in a Morris water maze.[220] Effects of

chronic stress were not investigated in this study. These data notwithstanding, the cautions expressed above concerning differences between chronic stress and chronic glucocorticoid treatment must be kept in mind for the prefrontal cortex, as well as the amygdala, which has not been studied yet in this regard.

Behavioral correlates of CRS-induced remodeling in the prefrontal cortex include impairment in attention set shifting, possibly reflecting structural remodeling in the medial prefrontal cortex.[215] Attention set shifting is a task in which a rat first learns that either odor or the digging medium in a pair of bowls predicts where food reward is to be found; then new cues are introduced and the rat needs to learn which ones predict the location of food.[221] There is also a report that chronic restraint stress impairs extinction of a fear conditioning task.[222] This is an important lead since the prefrontal cortex is involved in extinction, a type of learning,[223] but much more research is needed to explore the complex relationship between stress, fear conditioning, extinction, and possible morphological remodeling that may well accompany each of these experiences.

Summary

Animal studies on the prefrontal cortex reveal stress-induced changes in neuronal structure and connectivity. On the one hand, the medial prefrontal cortex shows reduced neuronal complexity and loss of synaptic connections as a result of repeated stress, whereas the orbitofrontal cortex shows greater neuronal complexity as a result of chronic stress.

Human studies of the prefrontal cortex

Most of the work on the prefrontal cortex and stress-related processes in humans, particularly within the context of SES research, has focused on areas of the ACC. The ACC is an evolutionally old cortical system common to mammals,[224] and it occupies much of the medial wall of the prefrontal cortex surrounding the corpus callosum. Within the ACC, there are regional differences in cellular architecture and efferent and afferent projections to other brain areas that largely correspond to putatively distinct subregions, which have been described in terms of a dorsal cognitive-motor division, a ventral visceral-motor division, and an intermediate affective division anterior to the genu of the corpus callosum, a major white matter tract connecting the two hemispheres of the brain.[225–227] Of these cingulate regions, the perigenual anterior cingulate cortex (pACC) has been specifically linked to several emotion and stress-related processes in neuroimaging studies and patient lesion studies. These processes include the appraisal of salient environmental and personal events, the experience of emotional states, and the regulation of behavioral and autonomic responses to emotional and stressful stimuli.[225,227–231] Further, there is growing evidence that the pACC is involved in mediating individual differences in stressor-evoked cardiovascular reactivity, which have long been associated with risk for cardiovascular disease.[232–234] For example, greater stressor-evoked pACC activity across individuals has been associated with larger magnitude blood pressure reactions to a variant of a Stroop color-word interference stressor,[235] particularly in interaction with the amygdala.[191] Such a role for the pACC in mediating stressor-evoked cardiovascular reactivity is instantiated through its reciprocal circuitry with adjacent areas of the orbital and medial prefrontal cortex, anterior insula, amygdala, and areas in the hypothalamus, periaqueductal gray (PAG), pons, medulla, and the pre-sympathetic intermediolateral (IML) cell column of the spinal cord.[227,236] As such, the pACC—along with other networked cingulate and prefrontal areas—may provide for an interface between stressor appraisal processes and concurrent allodynamic control.[237]

Furthermore and as detailed earlier, translational evidence from animal models has demonstrated that prelimbic and infralimbic areas of the rodent ACC, anatomically homologous areas of the human pACC, show pronounced changes in structural plasticity under conditions of chronic stress. Thus, from a translational perspective developed within the context of these animal findings, stress-related dimensions of low socioeconomic position could plausibly covary with changes in the morphology of the ACC in humans. In support of this speculation, there is structural neuroimaging evidence in humans that individuals who report holding a low social standing in the United States—as reflected by low subjective social status ladder rankings on the MacArthur scale of perceived social standing[18]—show a reduced gray matter volume in the pACC[238] (see Fig. 4). Notably, the relationship between low subjective social status and reduced

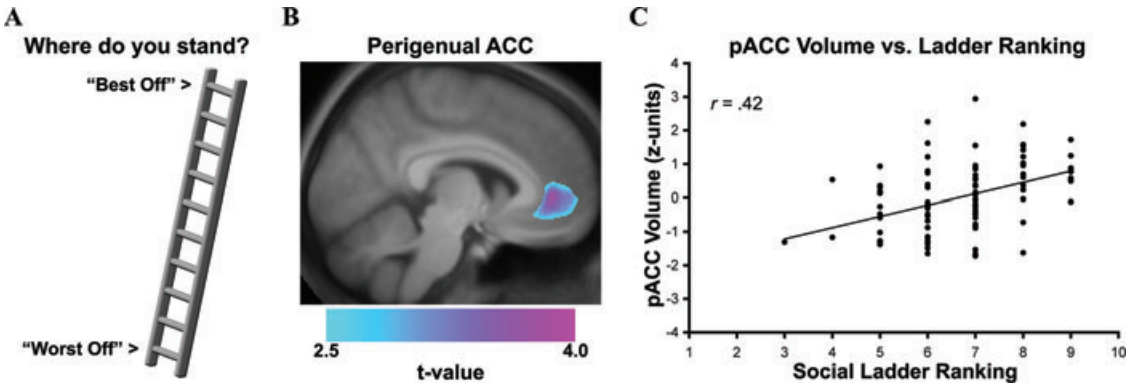

Figure 4. Lower subjective social status, as reflected by a lower self-reported ranking on a "social ladder", was associated with reduced gray matter volume in the perigenual area of the anterior cingulate cortex (pACC). (**A**) Illustration of 10-point social ladder scale used to assess subjective social status. (**B**) Overlaid on an anatomical template is a statistical parametric map of color-scaled *t*-values, which illustrate the pACC area where lower subjective social status was associated with reduced gray matter volume across individuals. (**C**) Plotted along the *y*-axis is the standardized (z-score) gray matter volume values for pACC area profiled in B. Plotted along the *x*-axis are social ladder rankings from the scale illustrated in A (1 = "Worst Off," 10 = "Best Off"). $^{*}P < 0.001$. From Gianaros *et al.* (2007), reprinted with permission.

pACC gray matter volume persisted in this study after accounting for several demographic and psychological factors (*e.g.*, subclinical depressive symptoms, dispositional forms of negative emotionality) and conventionally defined levels of personal and community SES. However, while these cross-sectional findings did not establish a causal direction of association, they do implicate reduced pACC gray matter volume as a structural neural correlate of low subjective social status, a presumptive stress-related dimension of socioeconomic position that has been linked to dysregulated neuroendocrine activity, adverse mental and physical health outcomes, and impaired immune functioning in prior epidemiological studies.[18,19,21–23,239]

Further, increasing evidence indicates that a compromised structural or functional coupling between the pACC and networked corticolimbic areas such as the amygdala—particularly in the context of environmental adversity and genetic risk—may increase vulnerability to psychiatric and medical syndromes characterized by dysregulated emotion-related behaviors and physiology.[240] Finally, there is recent *in vivo* imaging evidence in humans that reduced ACC volume is associated with HPA axis dysregulation, as indicated by a nonsuppressed cortisol response to a dexamethasone challenge.[241] Thus, it is plausible that volumetric or other morphological changes in the pACC could account in part for the dysregulated forms of emotional control and neuroendocrine functioning that have been found among individuals reporting a low subjective social status.

In addition to the pACC, human evidence also implicates *dorsal anterior cingulate* cortex (dACC) areas in emotion-related processes, particularly those associated with emotion regulation, stressor-evoked physiological reactivity, and subjective distress. Within the cognitive neuroscience literature, areas in the dACC are broadly viewed to support processes related to attention, effortful executive control, and conflict and error monitoring. These processes are instantiated by reciprocal circuitry with the lateral prefrontal cortex, motor and supplementary motor cortex, and posterior parietal cortex.[242] A conventional view is that dACC areas monitor for conflicts between competing streams of incompatible information, which foster the potential for behavioral error.[243–245] After conflict detection, dACC areas engage prefrontal, motor, and parietal cortices to resolve conflicts and minimize behavioral error by modulating attention, working memory, and motor control processes. In addition to these cognitive processes, dACC areas are also engaged by states of pain-related anxiety,[164,246] intentional regulation of autonomic activity,[247] and

awareness of subjective emotional experiences.[248] Based on an integrative translational account of both cognitive and affective neuroscience findings regarding dACC functionality, Critchley[228] posits that the dACC may be particularly important for generating autonomic and cardiovascular responses via projections to subcortical areas to support volitional, cognitive, and emotional behaviors. Consistent with this view, several forms of stress-related patterns of cardiovascular and neuroendocrine control have been linked to dCC activity in human neuroimaging studies. For example, stressor-evoked blood pressure reactivity has been shown to covary with heightened dACC activation to demanding cognitive challenges.[249,250]

There is also evidence that individual differences in dACC and prefrontal functionality are associated with the regulation of the HPA axis. For example, Eisenberger, *et al*[251] demonstrated that cortisol changes elicited by the Trier Social Stress Task (TSST) administered outside of an MRI scanner were correlated with dACC activation during a social rejection task performed inside of the scanner. Specifically, activation of the dACC, in addition to networked areas of the dorsal medial prefrontal cortex, were correlated with larger cortisol responses to TSST. Moreover, activity in these cortical areas statistically mediated the association between individual differences in perceived social support and cortisol responses. An intriguing conclusion drawn by the authors was that a person's level of social support may modulate how specific brain areas, including the dACC, regulate social stress-related cortisol reactivity.

In extension of this work, Taylor and colleagues[252] provided recent evidence that individuals who express lesser TSST-evoked cortisol reactivity also express lesser threat-related amygdala reactivity and greater regulatory activity in the ventral portion of the orbitofrontal prefrontal cortex; moreover, these neural activity patterns were observed specifically in association with higher levels of social resources—operationally defined as "personal dispositions that may help people to perceive potentially threatening events as less threatening and/or help them to manage their responses to events perceived to be threatening."[253] In aggregate, there is sufficient human evidence that the availability of social resources, which are often taxed and chronically depleted in the context of lower socioeconomic position, impact neural dynamics important for allostatic control and possibly disease risk.

Summary

Studies on the human prefrontal cortex have revealed an important role for this region and its functional subdivisions, particularly within the anterior cingulate cortex, in mediating stress-related behavioral and biological reactivity and regulation. Translational neuroimaging findings also reveal an association between low subjective social standing, a purported stress-related dimension of low SES, and reduced gray matter volume in the perigenual area of the ACC, an area important for regulating the autonomic and HPA stress-response axes.

Interventions for allostatic load and brain–body interactions

The notion that the brain is the central organ of stress may be used to argue for interventions that are top down and "holistic," insofar as such interventions stimulate the entire body to help itself and function normally by affecting the neurobiological circuitries detailed above. Importantly, such interventions can be aimed at the individual, in terms of targeting a person's behavioral habits and lifestyle. Moreover, they can be aimed at the level of social organization, in terms of addressing policies of the government and private sector that provide groups of individuals with access to and control over environmental, social, and material resources important for health and well-being.

Interventions for the individual

For the individual, two of the most important interventions are physical activity and arguably social integration. It is well established that a sedentary lifestyle is a major risk factor for many of the diseases of modern life including obesity, diabetes, cardiovascular disease, depression, and dementia. Moreover, recent studies have shown that moderate physical activity can be beneficial for the brain and cardiovascular and metabolic systems.[254–258] Voluntary physical activity has been shown to increase neurotrophin expression in cortex and hippocampal regions of the brain,[259] as well as to increase neurogenesis in the dentate gyrus of young and even aging animals.[260] One mechanism for these effects involves the actions of circulating IGF-1, which is

taken up by the brain and acts via receptors found in the hippocampus, as summarized early in this article. Moreover, increased neurogenesis in dentate gyrus has been linked to the actions of antidepressant drugs, providing a potential parallel with the antidepressant actions of physical activity.[261] Increased neurogenesis improves memory,[262] and new neurons are believed to participate in learning of hippocampal dependent tasks.[263] Although the precise role of neurogenesis in dentate gyrus is still controversial, new neurons appear to be more excitable and may contribute to greater cognitive flexibility.[262,264] Related to effects of exercise on neurogenesis is the effect of dietary restriction, that also increases neurogenesis and elevates BDNF levels in hippocampus.[265] BDNF is an important factor in current thinking about the actions of antidepressant treatments,[128] including the consequences for hippocampal volume, memory and mood disorders apparently related to having the Val66Met allele of the BDNF gene.[266–269]

Physical activity and the human brain

Extending prior work on exercise, physical activity, and neuroplasticity in animal models, an increasing number of neuroimaging studies are beginning to examine these processes in relation to human cognition and brain structure and function.[270] Colcombe *et al.*,[271] for example, investigated changes in brain activity using fMRI over the course of a 6-month aerobic exercise program. In this study, older adults performed a cognitive task that places demands on executive control and attention before and after exercise training interventions. Interestingly, adults assigned to an aerobic training group involving brisk, regular walking showed improved cognitive performance and postintervention patterns of fMRI activation in the prefrontal and parietal cortices that were comparable to those displayed by a much younger control group. In contrast, participants assigned to a control group involving toning and stretching showed no such changes in performance or fMRI activity. In a more recent structural neuroimaging study, Colcombe *et al.*[272] demonstrated that older adults who engaged in a 6 month aerobic walking program displayed an increase in the volume gray matter in the prefrontal and temporal cortices. Further, in this study, no such volumetric changes were observed in a nonaerobic control group or in a younger group of control participants. These particular structural neuroimaging findings were extended by Pereira *et al.*,[273] who reported increases in cerebral blood volume—an imaging correlate of neurogenesis—in the dentate gyrus of the hippocampus among middle-aged individuals who completed a 3 month aerobic exercise program. Interestingly, CBV changes in the hippocampus covaried with improved cardiorespiratory fitness and verbal learning and memory. Moreover, as noted earlier, fit individuals are reported to have larger left and right hippocampal volumes than unfit individuals.[160] Collectively, these human studies suggest that providing opportunities for voluntary aerobic exercise—which are generally limited in lower SES environments[274]—are likely to have beneficial effects on the neuroplasticity of prefrontal and hippocampal brain systems important for cognition, stress regulation, and resiliency against ill health.

Social integration

Dimensions of social relationships have long been linked to longevity and aspects of physical and mental health.[275–278] These dimensions include social network composition,[279] social support,[280] social interaction frequency and quality[281,282] and the experience of isolation and loneliness accompanying deficient or broken social relationships.[283] Importantly, cumulative evidence from social epidemiological studies has repeatedly demonstrated that different dimensions of social relationships can affect longevity and health via unique neurobehavioral pathways.[276,277,284] One dimension of social relationships that has been most consistently linked to longevity and health is *social integration*, a multidimensional construct referring to an individual's (1) effortful behavioral engagement in wide ranging social activities and relationships and (2) cognitive construal of her or his communality and identification with diverse social roles.[279] Epidemiological studies have specifically linked measures of social integration (*e.g.*, measures of the number of self-reported social positions or roles, as well as the frequency of participating in social activities) with lifespan,[275,278,285,286] trajectories of cognitive aging and risk for dementia,[287] severity of subclincial cardiovascular disease,[288] risk for stroke,[289] survival times in patients with cardiovascular disease,[290] and the recurrence of cancer.[291]

At present, social integration is understood to affect health and longevity through two dissociable pathways.[276] One pathway operates by affecting behavioral and biological factors associated with being socially isolated, as opposed to holding a minimum quantity of beneficial social contacts. The other pathways presumably operates by factors associated with the beneficial effects of incremental increases in social network diversity. Critically, the health beneficial effects of being more socially integrated may differ between men and women, depending on the health outcomes of interest.[292] Further, social integration may impact longevity and aspects of health through pathways and processes that are fundamentally different from those ascribed to other stress- and health-protective dimensions of social relationships that have also received much attention in epidemiological and laboratory studies of health and aging. For example, social support, which broadly refers to psychological and material resources provided by one's social ties, may enable individuals to cope more adaptively with acute and chronic stressors, *specifically when they are encountered*. Hence, the protective effects of social support may be context specific rather than health protective in general, as is thought to be the case for social integration.[276,293] Thus, social support provided by family or health professionals, who offer emotional support and provide useful information, has been shown to reduce the allostatic load score, which measures key physiological markers related to chronic stress and a potentially health damaging lifestyle.[294] Social support also ameliorates reported levels of chronic stress in caregivers, who show a reduced length of telomeres in white blood cells.[295]

So far, however, little to nothing is known about how social integration, social support, or other social factors may benefit human brain circuits that are affected by chronic stress and allostatic load, although it is clear that these factors are linked to mood, overall mental health, and related brain-based processes.[276,296–299] In this regard, there is intriguing translational evidence from animal models that social interactions and social isolation (a possible analog of deficient social integration in humans) have differential effects on neurogenesis and neuroplasticity in the amygdala and hypothalamus, brain systems important for allodynamic regulation.[300,301] Further, there is recent neuroimaging evidence that human individual differences in perceived social isolation are associated with regional brain activation to social stimuli, particularly in circuitries involved in the processing of reward (ventral striatum) and in visual attention (occipital cortex and temporo-parietal junction).[302] In view of the earlier discussion, an important direction for future research will be to delineate the unique pathways by which dimensions of social relationships and networks affect brain and bodily aging and health, and to design novel interventions impacting health-related aspects of social ties.

Pharmaceutical interventions

For the individual, life-long habits may be hard to change, and it is often necessary to turn to pharmacological interventions: sleeping pills, anxiolytics, β-blockers, and antidepressants are all drugs that are used to counteract some of the problems associated with the accumulation of allostatic overload. Likewise, drugs that reduce oxidative stress or inflammation, block cholesterol synthesis or absorption and treating insulin resistance or chronic pain can help deal with the metabolic and neurological consequences of chronically stressful experiences. All of these agents have value, and yet each one has side effects and limitations that are based in part on the fact that all of the systems that are dysregulated in allostatic overload are also systems that interact with each other and perform normal functions when properly regulated. Because of the nonlinearity of the systems of allostasis, the consequences of any pharmaceutical treatment may be either to inhibit the beneficial effects of the systems in question or to perturb other systems in a direction that promotes an unwanted side effect. Examples of the former include the problems with Cox 2 inhibitors, for example, Vioxx,[303] and examples of the latter include the obesity inducing effects of some of the atypical antipsychotics that are widely used to treat schizophrenia and bipolar disorder.[304]

Can the brain change with therapy?

In light of the potential adverse side effects and limitations of many pharmaceutical treatments, it is important to note that the human brain does appear to change functionally and structurally as a result of experience. Animal models teach us that experiences, including stress-induced changes in brain

structure are largely reversible and that resilience in both brain structure and behavior is the name of the game in adapting to changing environments.[76] A corollary of this is that failure to show resilience is a feature of maladaptation and pathophysiology, including anxiety and depressive disorders and the downstream effects that these have on the rest of the body via the autonomic, neuroendocrine, and immune systems. But how plastic is the human brain in response to interventions that effectively treat disorders that effect the brain as well as the rest of the body? Cognitive behavioral therapy has been demonstrated to be as efficacious as several medication regimens aimed at treating disorders of mood, particularly depression; moreover, cognitive therapy and medication appear to affect many of the same or overlapping neural mechanisms.[305] Moreover, there is recent evidence that successful cognitive therapy can even result in changes in brain morphology that parallel those of physical activity, particularly within the context of chronic fatigue syndrome—a brain–body disorder characterized by unabating or recurrent fatigue adversely affecting allostatic control systems.[306] Further, a recent cross-sectional study reports thicker cortical volume in right anterior insula and prefrontal cortex of subjects who had meditated for many years compared to matched controls.[307] Therefore, further studies of how the brain is changed by behavioral, as well as by pharmaceutical therapies, are important future directions.

Top-down effects of policies

At the level of social organization, the private sector has a powerful role. Businesses that encourage healthy lifestyle practices among their employees are likely to gain reduced health insurance costs and possibly a more loyal workforce.[308,309] Moreover, governmental policies are important, and the Acheson Report[310] from the United Kingdom in 1998 recognized that no public policy should be enacted without considering the implications for health of all citizens. Thus basic education, housing, taxation, setting of a minimum wage, and addressing occupational health and safety and environmental pollution regulations are all likely to affect the brain and health via a myriad of mechanisms. In young children, for example, the effects of developing in a low SES environment have been shown to modulate functional neural activity in brain areas important for reading—possibly impacting cognitive development, future academic achievement, and other contributors to adult SES.[311–314] At the same time, providing higher quality food and making it affordable and accessible in poor, as well as affluent neighborhoods, is necessary for people to eat better, providing they also learn what types of food to eat and can afford them. Likewise, making neighborhoods safer and more congenial and supportive[315] can improve opportunities for positive social interactions and increased recreational physical activity. For the elderly population, community centers and activities that promote social interactions and physical activity have been demonstrated to be beneficial.[258,316]

Finally, there are programs that combine some of the key elements just described; namely, education, physical activity, and social integration, along with one other ingredient that is hard to quantify: finding meaning and purpose in life. One example is the Experience Corps which takes elderly volunteers and trains them as teachers' assistants for younger children in the neighborhood schools.[317] Not only does this program improve the education of the children, it also benefits the elderly volunteers and improves their physical and mental health.[318]

Conclusions

To conclude, we reiterate the following key points embodied within this translational review of animal and human neurobiological evidence bearing on the health-related impact of stress processes—particularly those that may be important for understanding SES gradients in well-being and longevity:

(1) The brain is the most important organ mediating stress processes: it determines what is "stressful" to the individual by supporting conscious and unconscious appraisal processes; it determines the health-damaging or health promoting behaviors that result from this appraisal; and it regulates peripheral allodynamic control systems that feed back to the brain to affect functional and structural neuroplasticity.
(2) The brain is arguably the least studied and most important organ in human stress and socioeconomic research on health. Brain imaging measures can be easily incorporated into

large scale, longitudinal and cross-sectional studies. Importantly, these measures can help to define the neurobiological and mechanistic pathways by which stress and socioeconomic factors affect health and longevity.

(3) Animal models offer an opportunity to study causal relationships and lifespan processes that can inform translational research in human health neuroscience.

(4) Interventions should focus on top-down strategies intended to alter brain function in ways that will improve allostasis and minimize allostatic load. Instilling optimism, a sense of control and self-esteem, and finding a meaning and purpose in life should be among the chief goals of such interventions. Indeed, virtually all policies of the public and private sector are, in fact, health policies.

(5) Future work in this promising area will require interdisciplinary collaborations between neuroscientists, behavioral geneticists, social and biological psychologists, epidemiologists, policy and intervention researchers focusing on stress and health processes at multiple levels of analysis.

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Conflicts of interest

The authors declare no conflicts of interest.

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