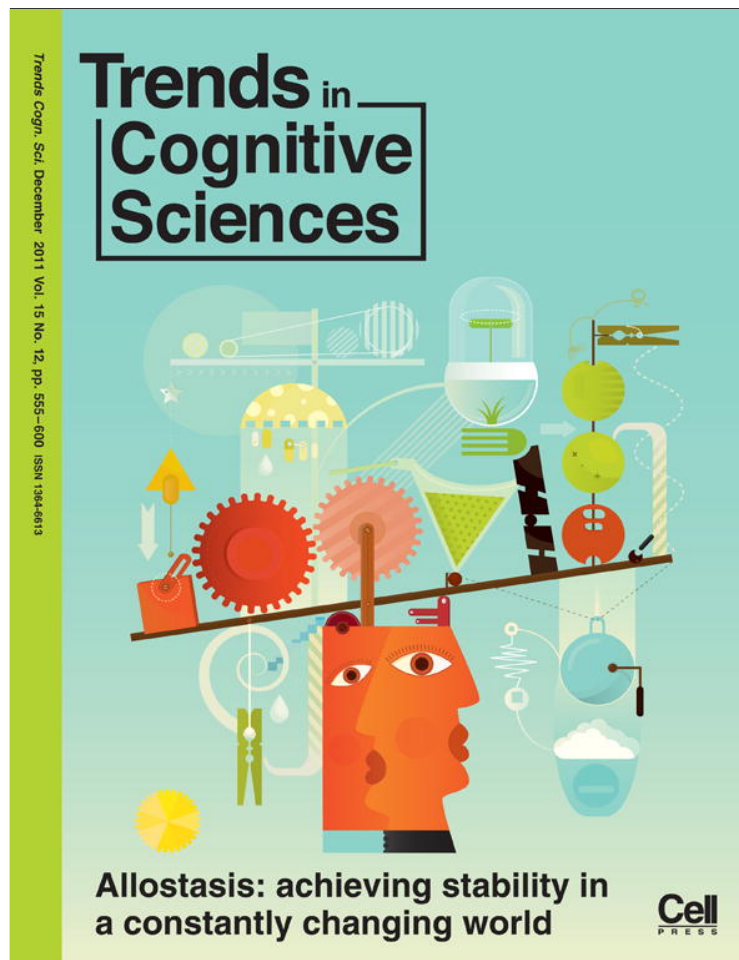


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Psychobiological allostasis: resistance, resilience and vulnerability

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The brain and body need to adapt constantly to changing social and physical environments. A key mechanism for this adaptation is the 'stress response', which is necessary and not negative in and of itself. The term 'stress', however, is ambiguous and has acquired negative connotations. We argue that the concept of allostasis can be used instead to describe the mechanisms employed to achieve stability of homeostatic systems through active intervention (adaptive plasticity). In the context of allostasis, resilience denotes the ability of an organism to respond to stressors in the environment by means of the appropriate engagement and efficient termination of allostatic responses. In this review, we discuss the neurobiological and organismal factors that modulate resilience, such as growth factors, chaperone molecules and circadian rhythms, and highlight its consequences for cognition and behavior.

Brain adaptation, resilience and vulnerability

The brain and body constantly adapt. Indeed, the brain may be considered the primary organ allowing for adaptation to changing environments. The brain constantly sorts relevant from irrelevant environmental inputs and engages body systems to respond to these changes. However, it is only in the past few decades that the brain has been recognized as an adaptable and resilient organ not only in development but also in adulthood [1]. It is also in recent decades that we have started recognizing the price that the body and brain have to pay in a '24/7' society, where the social and physical environment has an enormous impact on physical and mental well-being [2].

The notion of emotional or psychological resilience (see [Glossary](#)) has been a cornerstone of psychiatric thinking in responses to trauma for many years [3]. Resilience or susceptibility to trauma can be explored at the level of the individual through to the level of organizations, and even whole populations [4]. Although much attention has been paid to the psychological or organizational factors promoting resilience and minimizing susceptibility for individuals or populations, much less work has focused on understanding resilience and vulnerability in the brain, despite the fact that it influences several aspects of health. In this review, we discuss our current understanding of what factors render the brain vulnerable or resilient to

effects of stress, paying particular attention to how factors that mediate plasticity affect resilience or vulnerability. We also explore how modern industrialized society has produced an environment that pushes the limit of our physiology, and how this may in turn restrict the capacity of the brain and the body to respond to further stressors.

Stress, allostasis and allostatic load

The term 'stress' was borrowed from engineering ('a measure of the internal forces acting within a deformable body') by Hans Selye in the 1930s. In his translation to biology, Selye defined stress as the result of an organism's failed attempt to respond appropriately to a physical challenge [5]. Since then, this definition has been further elaborated

Glossary

Stress: a term that carries with it a mostly negative connotation. In Lazarus and Folkman's model, stress occurs when environmental demands exceed one's perception of their ability to cope [100]. In popular usage, there can be 'good stress' (e.g. stresses that increase function and performance), as well as 'tolerable stresses', (e.g. stress that is accompanied by resilience or resistance, as well as recovery; see below). Finally, there is what can be more broadly defined as 'toxic stress': stress that becomes so extreme or unpredictable that the system can no longer adequately respond (see: National Scientific Council For the Developing Child 'Excessive Stress Disrupts the Architecture of the Developing Brain: Working Paper No.3').

Allostasis: The biological responses that promote adaptation, using systemic mediators (sympathetic, parasympathetic activity, cortisol, pro- and anti-inflammatory cytokines, and metabolic hormones), forming a non-linear network in which each mediator regulates other mediators (Figure 1) [12]. Allostatic mediators can contribute to pathophysiology when these responses are over-used or dysregulated. Allostasis can also incorporate the effects of health-related behaviors such as diet, exercise, physical activity, smoking and substance use that also activate the same mediators.

Allostatic load and overload: the cumulative 'wear and tear' seen on body systems after prolonged or poorly regulated allostatic responses. In the wild, allostatic load can have an adaptive role (for instance, bears putting on fat for the winter), whereas allostatic overload can be observed, for example, in migrating salmon dying after mating. In more artificial environments, allostatic load and overload occur in non-adaptive ways. For instance, bears in a zoo are often overfed, inactive, and develop obesity, cardiovascular disease and diabetes (allostatic overload) [10].

Resilience: the ability to 'rebound' from adversity when one's ability to function has been to some degree impaired.

Resistance: the notion of being able to withstand or adapt to adversity [15], perhaps best thought of as a form of 'psychological immunity', where appropriate responses exist to resist the effects of a psychological stressor, just as one's body mounts immune responses to fight off an infection before it becomes a full blown illness. Importantly, resistance is scalable, and is relevant for individuals, groups, communities, and even nations.

Recovery: an individuals' internally driven return to baseline functioning following stress. The term also denote treatment and rehabilitation from stressful experiences or disorders.

Vulnerability: a state of heightened sensitivity to a stressor by mounting inappropriate or ineffective defense mechanisms that also implies a lack of resistance and absent or impaired resilience, often requiring external intervention.

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to include psychological threats, including both anticipation or ideation of impending threats, not just those actually present in the current environment [6]. The pioneering work of John Mason on psychological stress was seminal in this regard [7], and these ideas have permeated both modern psychology and neuroscience.

A more recent, alternative view of stress is encapsulated in the concept of allostasis and allostatic load and overload [8–11]. Allostatic responses are those physiological changes that occur in response to environmental perturbations. These responses are not negative in-and-of-themselves, but instead play an important positive role in helping an organism adapt to a changing environment. As such, the term allostasis should not be considered a replacement of the term ‘stress’, but rather a term that better reflects the fact that stress responses are essential for survival. Importantly, the concept of allostasis focuses on the mediators of adaptation, such as cortisol, the autonomic nervous system, metabolic hormones and immune system mediators that promote adaptation to stressors, but also participate in pathophysiology when they are overused or dysregulated with respect to their normal, balanced non-linear network (Figure 1) [12]. For instance, inflammatory cytokines can stimulate the production of corticosteroids, which in turn can suppress inflammatory cytokine production. Similarly, the sympathetic and parasympathetic systems exert differential effects on inflammatory cytokines, with the former stimulating their production and the latter inhibiting them (see [13,14] for a review). If these systems become unbalanced, for instance, when corticosteroid levels are too high, they can inhibit an appropriate inflammatory response during immune challenge. Conversely, if corticosteroid levels are too low, a ‘normal’ immune response can become uncontained

and result in rampant inflammation out of scale with the initial challenge.

It is important to emphasize that allostasis and allostatic load and overload apply not only to the body but also to the brain, where neural activity in response to new experiences drives adaptive plasticity, mediated in part by systemic hormones but also by endogenous excitatory amino acids, neurotrophic factors and other mediators. Changes in how such mediators respond possibly explain changes in vulnerability, both mental and physical, to stressors in the environment. Vulnerability, resilience and resistance in the face of stressful challenges are concepts that have emerged in the study and treatment of trauma resulting from war, natural disasters and accidents [15]. They are also relevant to how individuals handle stressors of everyday life that can precipitate depression and the development of cardiovascular disease [16]. A key factor in resilience is plasticity, and the brain is capable of considerable neural remodeling in which the mediators of that plasticity, for example, excitatory amino acids and glucocorticoids, are also capable of causing damage when not tightly regulated. This is the essence of allostatic load/overload as it applies to the brain.

Mediators of resilience and plasticity

In the brain, corticosteroids (CORT) play a key role in adaptive plasticity, as well as in the damage resulting from allostatic overload (e.g., ischemic or seizure damage [17,18]), and there are modulators that work synergistically to promote adaptation over damage, including the mineralocorticoid and glucocorticoid receptors and the molecular chaperones, such as BAG1 (see Box 1).

Acting in concert with CORT, neurotrophins, such as brain derived neurotrophic factor (BDNF), play a key role

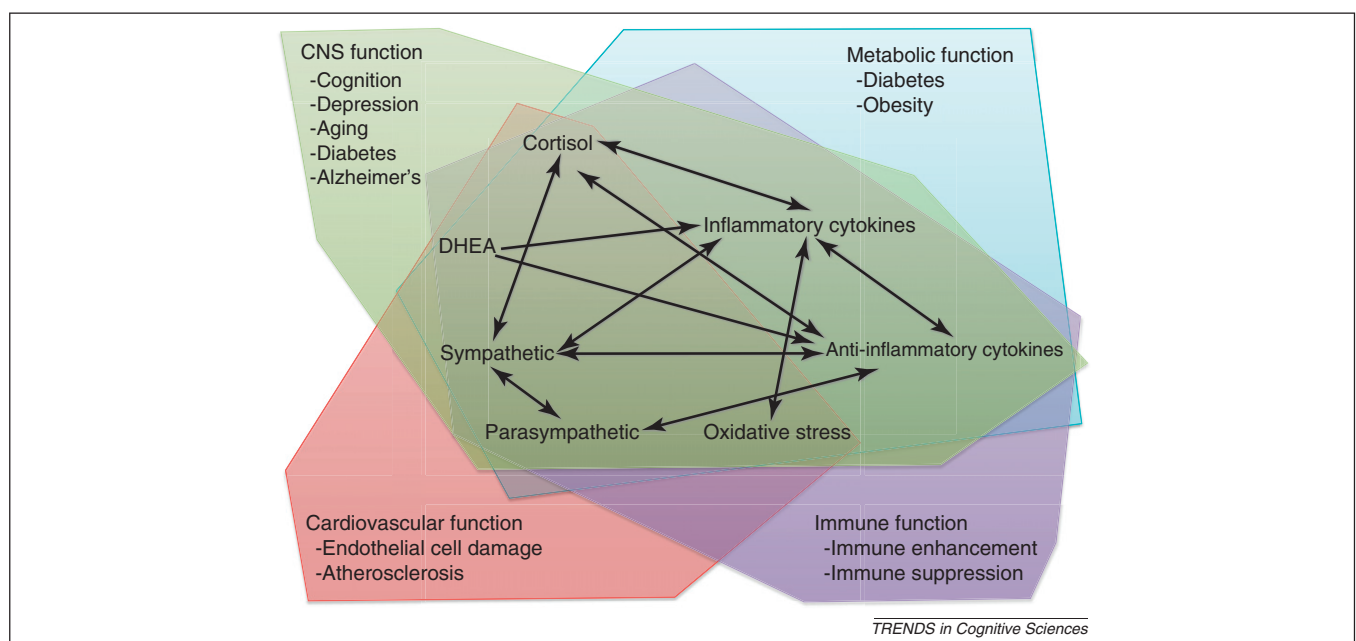


Figure 1. Nonlinear network of mediators of allostasis involved in the stress response. Arrows indicate the general point that each system regulates the others, often in a reciprocal manner and sometimes indirectly, creating a nonlinear network. Moreover, there are multiple pathways for regulation, as elaborated more in depth elsewhere [12]: for example, inflammatory cytokine production is negatively regulated via anti-inflammatory cytokines as well as via parasympathetic and glucocorticoid pathways, whereas sympathetic activity is one way to increase inflammatory cytokine production. Parasympathetic activity, in turn, restrains sympathetic activity. Note that there are many more interacting mediators, both central and peripheral, than can be captured in a single figure and those presented here are aimed to illustrate the concept. Adapted from [12].

Box 1. Interactions between glucocorticoids, plasticity and BDNF

The actions of CORT at the cellular level involve activation of the glucocorticoid (GR) and mineralocorticoid receptors (MR). Importantly, MRs show higher affinity for CORT than GR, and as such, MRs are largely constitutively occupied, while GRs become occupied only at higher CORT levels [19]. This differential sensitivity helps explain the biphasic, U-shaped effects of glucocorticoids [20]. For instance, biphasic effects of CORT in the CA1 region of the hippocampus involve increased excitability mediated by MRs, while opposite effects of high doses of CORT are mediated by GRs [21], leading to inverted U-shaped dose-response curves. Indeed, a moderate level of glucocorticoid signaling or stress enhances cognitive processing [22,23]. Yet, too much, or too little signaling results in sub-optimal responses and can even lead to marked deficits: for instance, whereas acute stress can improve working memory in some cases [24], chronic stress results in memory impairments [25,26]. At the cellular level, for mitochondria and neural protection [27,28], low levels of GR translocation to mitochondria enhances mitochondrial Ca^{++} sequestration, while high CORT causes this protection to fail. Work with BAG-1, a GR co-chaperone involved in regulation of mitochondrial Bcl-2, and related to FKBP51 and HSP70, has demonstrated that this factor can modulate the recovery of animals following manic and depressive-like episodes [29]. Glucocorticoids acting through GRs are also able to block the effects of BDNF on synaptic maturation [30] and acute hippocampal BDNF treatment can ameliorate motivation and forced swim deficits observed due to prior chronic corticosteroid treatment [31]. Yet, glucocorticoids acutely activate *trkB* signaling in a ligand-independent manner [32], a finding that has implications for resilience. However, this effect is transient and accommodates to chronic glucocorticoid exposure, leading to a suppression of BDNF-mediated neurotransmitter release via a glutamate transporter [33]. These findings demonstrate the multiple, sometimes interacting, systems affected by glucocorticoids that can shape plasticity and behavior.

[34]. Chronic stress can decrease BDNF expression in the brain [35,36], but the relationship is complex [37,38] and, in fact, there is reciprocal cross-talk between glucocorticoids and BDNF signaling (see Box 1). In humans, a common polymorphism in the BDNF gene has been identified, resulting in a methionine (Met) substitution for valine (Val) at codon 66 (val66met). Carriers show impaired performance in hippocampal-dependent memory tasks and increased anxiety. Studies in the val66met transgenic mouse demonstrate a decrease in BDNF secretion, a reduction in hippocampal volume, and changes in cognition [39,40], in addition to increased anxiety [41,42]. Thus, alterations in BDNF signaling can be considered 'risk factors' in the development of neuropsychiatric disease [43,44], although some evidence suggests that compromised BDNF signaling negates at least some stress effects (Box 1). On the other hand, compromised BDNF signaling may result in a lack of a stress effect, that is, while BDNF haploinsufficient mice show shrunken dendrites in the CA3 region of the hippocampus when compared to WT mice, these mice do not show further shrinkage of hippocampal dendrites when chronically stressed in contrast to WT mice, which do show stress induced shrinkage [45]. While such results may be explained by a 'floor effect', another possibility is that BDNF is a limiting factor in the ability of the brain to show plasticity, whether consisting of neurite outgrowth or spine remodeling, including destabilization of existing spines [46,47]. Thus trophic factors such as BDNF are

facilitators of plasticity, and the outcome may be negative (e.g. epilepsy [48]) or positive (e.g. recovery from depression [49]) depending on other factors operating at the time.

Overcoming compromised resilience

It is widely held that depression, and associated cognitive impairment, as it manifests in humans, may be the result of an inability to return to normal functioning following a stressful or distressing psychological or physical situation, and as such may be an example of a reduction in the capacity for plasticity and/or lack of resilience. In a sense, brain circuits become 'locked' and only exogenous interventions may succeed in promoting recovery and ameliorating the behavioral effects. Prolonged depression is associated with hippocampal [50,51] and prefrontal cortical [52] atrophy. These changes appear to be due to shrinkage of neuronal cell nuclei and potentially loss of glial cells but not wholesale neuronal cell death [53,54]. In non-human animal models, chronic stress results in dendritic remodeling, particularly shrinkage of the apical dendritic tree [55].

This shrinkage of brain regions and a lack of plasticity could be a failure of resilience, in that the individual was able to accommodate to the stress initially but then failing to 'bounce back'. As such, factors modulating plasticity provide a way to ameliorate the neural and behavioral components of depression. For instance, it has been shown that lithium treatment can increase gray matter volume [56], while treatment with selective serotonin reuptake inhibitors (SSRIs) can increase the volume of the hippocampus [57–59].

A feature of depressive states may be reduced BDNF, and treatments as diverse as antidepressant drugs (e.g. fluoxetine) and regular physical activity [60] can increase BDNF activity and improve symptoms. This forms part of the notion that depression may be a deficit in plasticity, while antidepressants can increase plasticity. A key aspect of this view [61] is that such drugs open a 'window of opportunity' that may be capitalized upon by positive behavioral interventions, such as behavioral therapy in the case of depression or intensive therapy to promote neuroplasticity and counteract the effects of a stroke. In other words, treatments with factors that increase brain plasticity can effectively mobilize a brain that has become 'stuck', improving the behavioral symptoms by treating an underlying problem of plasticity. For example, it has been reported that fluoxetine can enhance recovery from stroke [62]. However, enhancing brain plasticity for someone who is depressed and in a negative environment may lead to adverse outcomes, such as suicide [61]. Moreover, BDNF may be a facilitator of 'negative plasticity', such as epilepsy [48,63,64].

In parallel with work on BDNF and antidepressants in regulating plasticity, perhaps opening or re-opening windows of plasticity, novel work on other methods to reopen critical periods is also under way. Maffei and colleagues have explored how food restriction can restore plasticity in the visual cortex of adult rats long after ocular dominance columns are established [65], demonstrating that this effect is largely independent of BDNF. Further, similar effects can be induced by chronic low-dose alternate day

treatment with CORT in the drinking water. Maffei and colleagues proposed that both these effects may converge on chromatin remodeling, a potential final common step in the induction of plasticity. Interestingly, a recent finding showed that acute CORT can increase spine turnover, while chronic exposure results in loss of stable spines [66]. Such studies further support a positive role for CORT in intermittent or small doses on plasticity, with chronic exposure resulting in a loss of plasticity.

Circadian disruption and allostatic load and overload

When exploring how systems are affected by stress, it is sometimes overlooked that they may be regulated by time-of-day. Almost all modulators of allostasis (Figure 1) show rhythms of activity over the sleep-wake cycle [67–69]. For instance, CORT shows clear diurnality, with peak plasma CORT occurring just before waking in both nocturnal animals (such as rats and mice) and diurnal animals (such as humans). Importantly, many of these factors are also impacted by sleep deprivation, which is demonstrated to decrease parasympathetic tone, increase CORT and metabolic hormones when they should be low (i.e. ‘flattening’ of

rhythms), and increase proinflammatory cytokines [70–73]. As such, we propose that underlying allostasis and the capacity for resilience in response to stressors is a well functioning circadian timing system. The circadian system in mammals is centered in the suprachiasmatic nucleus (SCN; Figure 2), with both neural and hormonal projections throughout the brain and body, impacting many of the systems involved in mediating allostasis. We hypothesize that disruption of the circadian system places the organism in a state of high allostatic load and eventually overload (see Box 2). Some good evidence already exists showing that disrupted circadian patterns of CORT result in a ‘sluggish’ HPA axis response, with poor shut-off of adrenocorticotrophic hormone (ACTH) following withdrawal of a stressor [74]. CORT is also able to reset peripheral oscillators in many body tissues (see Box 2), lending credence to an important relationship between disrupted rhythms and allostatic load. If current and future research supports such a hypothesis, it will be of great significance, as circadian disruption (e.g., shift work and jet lag) and sleep deprivation are common in the modern world and constitute an increasing health concern [75,76].

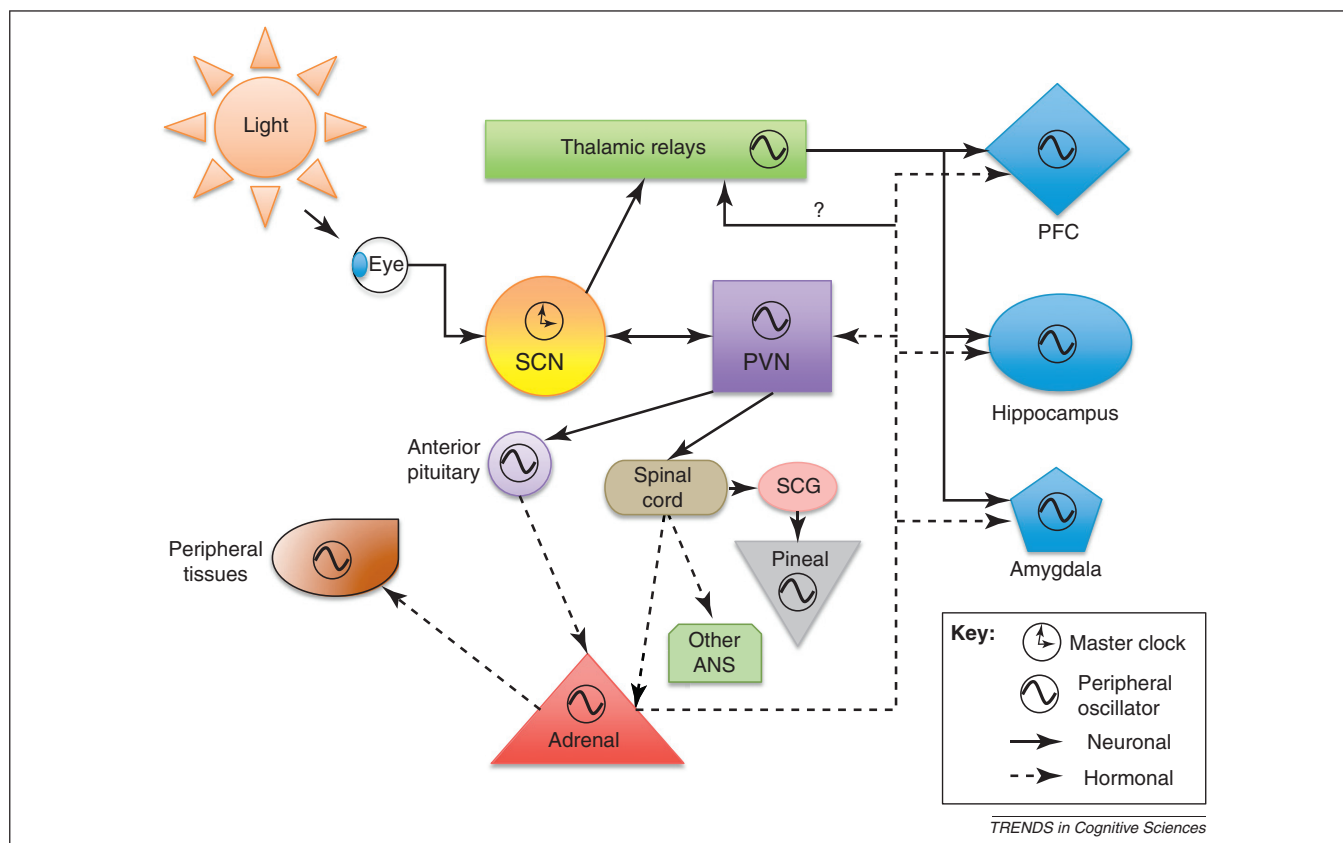


Figure 2. Illustration of neural and humoral connections between the brain clock and other body tissues. The brain clock in the SCN sends monosynaptic neural projections to various brain regions, including the paraventricular nucleus (PVN) of the hypothalamus, and to numerous thalamic nuclei. The SCN exercises some neural regulation of the adrenal via a multisynaptic projection through the PVN and sympathetic nervous system. The thalamic relays of the SCN project to the PFC, hippocampus and amygdala. Importantly, although the role that these neural projections play is still unclear, they are hypothesized to provide a means of regulating local time in these tissues. Circadian patterns of corticosteroid secretion are regulated through the classic hypothalamic-pituitary-adrenal (HPA) axis, with the PVN communicating with neurosecretory cells via corticotrophin releasing hormone (CRH) to the anterior pituitary, which releases adrenocorticotrophic hormone (ACTH) into the general circulation, which then releases cortisol (CORT; corticosterone in rodents). Several studies have shown that putative peripheral clocks in organs and also in brain nuclei, such as the hippocampus and amygdala, can be ‘reset’ by this CORT signal. This organization sets up multiple levels of circadian regulation and mechanisms to keep these brain regions and organ systems ‘in sync’ with each other. Disrupting circadian rhythms or altering CORT secretion can thus clearly impact the system at multiple points, resulting in cascading desynchronizations, and potentially impacting the ability of the organism to respond plastically to other stressors in the environment. Dotted lines denote hormonal regulation. Not all known connections are depicted. ANS=autonomic nervous system; PFC=prefrontal cortex; PVN=paraventricular nucleus; SCG=superior cervical ganglion; SCN=suprachiasmatic nucleus.

Box 2. Circadian clocks

The circadian clock in the suprachiasmatic nucleus (SCN) of the hypothalamus drives all rhythms in physiology and behavior [77–79]. On the tissue level, ‘peripheral’ circadian clocks serve to set local time and are synchronized to the SCN by a multitude of signals, with glucocorticoids being able to ‘reset’ some peripheral clocks in the brain and body (e.g., in the liver) but not others (Figure 2) [79]. Rhythms in glucocorticoids have been shown to affect clock protein expression in the oval nucleus of the bed nucleus of the stria terminalis, as well as the central amygdala (CEA) [80]. It is also known that the basolateral nuclei of the amygdala and the dentate gyrus of the hippocampus express opposite diurnal rhythms of *Period2* (a core clock component) when compared to the CEA, and that the CEA rhythm is influenced by adrenalectomy [81]. This regulation of a subset of rhythms by the adrenals and CORT is particularly interesting when considered alongside findings showing that ‘normal’ regulation of HPA function requires a rhythm in CORT [74], in that flat CORT rhythms prevent efficient initiation or termination of the ACTH response following a stressor. If efficient regulation of the HPA axis is a hallmark of a ‘healthy’ response, then disrupted or flat circadian rhythms can result in an unhealthy regulation of the HPA, and thus could contribute to allostatic load.

Whereas the SCN clock ‘shifts’ rather quickly (on the order of hours) after a change in the light-dark cycle, oscillators in the rest of the body shift more slowly, each with its own rate of resynchronization [82]. Both descriptive and epidemiological studies show that individuals who suffer from chronic circadian misalignment show physiological, neural and behavioral abnormalities. For instance, a study of flight crews found that those who endure more bouts of jet-lag (short-recovery crews) show shrunken medial temporal lobes, increased reaction time and poorer performance in visual-spatial cognitive tasks compared to long-recovery crews [83]. Moreover, the short-recovery crews displayed a significant correlation between salivary cortisol levels and volume of the medial temporal cortex, while long-recovery flight crews did not. One interesting speculation is that shrunken temporal lobes may impart decreased resilience to negative outcomes of stress, as has been observed in PTSD [84,85]. Similarly, sleep deprivation appears to compromise formation of new memories [86] and increases the amygdalar response to negative emotional stimuli due to a amygdalar-prefrontal disconnect [87]. Such effects could also exacerbate cardiovascular reactivity, contributing to pathophysiology [88,89]. While sleep deprivation studies have investigated the effects on cognitive performance, in both animal and human subjects, few studies on circadian disruption *per se* have been conducted.

Recently, a mouse model of chronic circadian disruption (CD) was developed by housing mice in a light-dark cycle of 20 hrs (10 hrs light, 10 hrs dark) compared to standard 24hr cycles. These mice show metabolic signs of allostatic load, with increased weight, adiposity and leptin levels, as well as an imbalance between insulin and plasma glucose, suggesting a pre-diabetic state. The metabolic changes are accompanied by changes in prefrontal cortex (PFC) cellular morphology, mirroring those observed in chronic stress, with CD animals having shrunken and less complex apical dendritic trees of cells in layer II/III of the medial PFC (Figure 3) [90]. The effects are very similar to those observed in 21d of chronic restraint stress in rodents, which

results in morphological simplification of prefrontal cortical neurons and impairment in prefrontal mediated behaviors, such as attentional set-shifting or other working memory tasks [12,91,92]. Importantly, similar effects are observed in humans [93]. Behaviorally, CD animals show cognitive rigidity in a version of the Morris Water maze, being slower to learn a reversed location of a hidden platform, and making more perseverative errors by returning to the original location of the platform [90]. At the same time, CD mice display an ‘impulsive’ like phenotype in the light-dark box, while not showing any outward behavioral anxiety phenotype [90]. It is important to emphasize that, just as whole lesions of the hippocampus provided insight into the role this brain structure played in learning and memory, such circadian models are purposefully extreme (shortened 20hr days are not expected to become a common occurrence in human society), providing important proof-of-principle manipulations setting the stage for development of more refined and ecologically relevant models.

Mechanistically, a hypothesis taking shape suggests disruption of circadian clocks can push central and peripheral oscillators out of phase with each other, creating internal desynchrony within neural circuits (see Box 2). Over many cycles, this desynchrony could lead to changes in neurobehavioral function (as evidenced in [90]). Perhaps more insidiously, shorter durations of circadian disruption could lead to changes in these circuits, making them more vulnerable to further insult, setting the stage for other stressors in the environment to overwhelm already compromised networks. Additionally, not only could circadian disruption lead to neural circuits becoming vulnerable to insult, it could compromise the allostatic responses meant to help organisms adapt to environmental challenge by disrupting the stress axis. Similar to the ‘two-hits’ of diathesis-stress models, such a situation could explain many of the epidemiologic findings of increased risk for development of psychiatric, cardiovascular or other physiological syndromes in shift workers or populations undergoing chronic circadian disruption [76,94–96].

Synthesis

In order to predict and adapt to new experiences, the brain and body have developed coordinated, interacting mechanisms that are engaged when changes in the environment are perceived to potentially threaten survival. More neutral than the word ‘stress’, with its ambiguity and negative connotations, the concept of allostasis is a useful descriptor of the biological mechanisms employed to achieve stability of homeostatic systems through active intervention by biochemical mediators, resulting in adaptive plasticity in both brain and body. This adaptation leads to readjustment of set points and operating ranges of body and brain systems allowing the individual to cope, at least in the short term. This ability to respond to and then bounce back from stressors in the environment is known as resilience, a term that also includes active resistance as well as recovery. Indeed, the ability to adapt – to actively resist, to ‘bend but not break’, or to ‘bounce back’ and recover from an injury – are all components of resilience. This is also true of the ability to protect against damage, including the accumulation of damage that is described by the terms

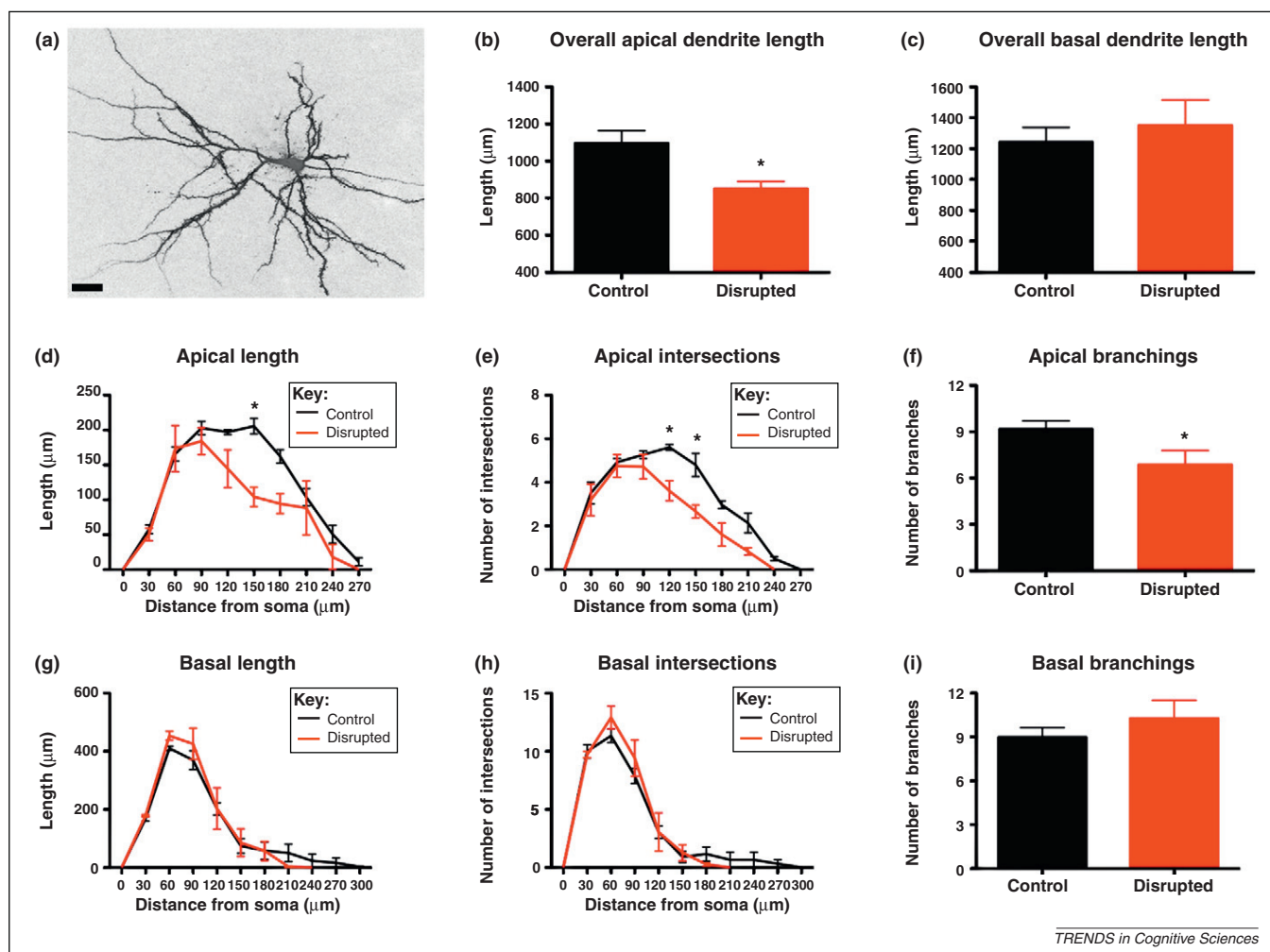


Figure 3. Circadian disruption results in changes to the morphology of medial prefrontal neurons. Cells of layer 2/3 of prelimbic medial prefrontal cortex (PL) were labeled with Lucifer Yellow (a). CD mice show shrunken apical dendrites in the PL (Two-tailed t-test, $p=0.0332$; b), but with no effect on basal dendrites (two-tailed t-test, $p=0.5975$; c). Sholl analysis reveals decreased complexity of the apical dendrites of PL neurons in CD mice (two-way RM ANOVA; interaction $F_{9,36}=2.191$, $p=0.0462$), with decreased length particularly 150 μm from the soma (Bonferroni post-test, $p<0.001$; d), and fewer intersections (two-way RM ANOVA; interaction $F_{9,20}=2.57$, $p=0.0378$), particularly at 120 and 150 μm from the soma (Bonferroni post-test, $p<0.01$; e), as well as fewer overall branchings (two-tailed t-test, $p=0.048$; f). There were no statistically significant differences in the basal dendrite in any of these measures (g-i). Adapted from [81].

allostatic load and overload, whereby sustained allostasis or dysregulation of systems that mediate allostasis causes an accumulation of pathophysiology, such as atherosclerosis, glucose dysregulation or atrophy of brain structures.

The brain is the key organ of resilience because it governs allostatic systems that affect the entire body and also responds to those signals by showing adaptive plasticity. However, dysregulation of those same systems and their overuse can also lead to cumulative damage. We have summarized findings showing that circadian rhythms, governed by the master clock in the SCN and synchronized by light-dark cycles and, in some peripheral cells, by circulating glucocorticoids are an important component of these responses, in that intact rhythms are necessary for efficient regulation of the stress axis, as well as other aspects of systemic physiology. We have reviewed evidence that shows that disrupted rhythms cause changes in neural structure in humans and non-human animals, decrease cognitive flexibility, and dysregulate metabolic systems. Other consequences of circadian disruption need to be explored in view of the widespread occurrence of

circadian disruption in modern society, including urban life, shift work and jet lag.

On a cellular level, growth factors, such as BDNF, are important in facilitating change in neural circuits, thus allowing for resilience through adaptive plasticity. We have also noted evidence that the expression and actions of BDNF are tightly coupled with glucocorticoids in a complex reciprocal network. Glucocorticoids themselves play a key role in adaptive plasticity, including response to antidepressant drugs and metaplasticity [20], in which the timing and activity of other allostatic systems, such as sympathetic arousal, determine the direction and nature of the outcome [21]. Moreover, at the molecular level, glucocorticoids translocate their receptors not only into the nucleus to regulate transcription of the genome but also translocate GRs into mitochondria where they exert biphasic effects on the ability of mitochondria to sequester calcium and protect against free radical damage. Chaperones such as BAG-1 modulate the effects of glucocorticoids on cellular functions, including those by mitochondria, and exert other effects that promote resilience and recovery

from stressors. Finally, we noted that antidepressants, such as fluoxetine, appear to facilitate adaptive plasticity in a broader sense, including depression and recovery from stroke damage, as long as the patient also engages in active behavioral interventions concurrently with drug treatment. In a negative environment, however, the same plasticity may lead to a deleterious outcome.

Concluding remarks

The goal of this review was to overview the factors that can confer resilience or mediate susceptibility not just at the level of an individual but also at the level of cells and neural circuits, since the brain is the master organ of stress and adaptation, and determines whether adaptation will be successful (allostasis) or lead to pathophysiology (allostatic overload).

In the context of the rapid development of modern human society over the past 100 years, these evolutionarily ancient systems have not yet 'caught up'. In a sense, we are asking too much of our physiology, in that allostatic systems that played a key role in survival when resources were scarce or were activated when the individual was threatened by predators are now engaged with worry, social conflict and overwork. In developed societies, this all occurs in an environment of ample metabolic resources in the form of fast food or other high calorie consumables but with less and less physical activity. Coupled with an always-on-the-go society, where the sleep-wake cycle has been almost completely separated from the solar day and electric lighting and electronic gadgets provide us with ample light long into the night, there is no doubt that many of us live in a state of high allostatic load or even overload [97]. The physical and mental health costs of this lifestyle are only now being appreciated, in the form of rampant obesity, increased cardiovascular disease and a rise in

psychiatric disorders [98,99]. By more clearly delineating the different players in this complex web, from the molecular and cellular through to the organismal and even societal levels, we will perhaps be able to tackle more easily some of these issues by finding ways to mitigate their effects, increase the resilience of individuals to such insults or, even better, prevent them from happening in the first place (see also Box 3).

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Box 3. Questions for future research

There are three key concepts discussed in this review, each generating potential goals for future research. The first involves understanding that the stress response is not negative in and of itself. It is a suite of necessary behavioral and physiological responses to promote adaptation in a constantly changing environment. The second is the need to consider the interaction between the brain and the body when one considers how stress affects an organism. The third concept is that both genetic and experiential factors can modulate an individual's resilience or vulnerability to stressors. It is perhaps towards the second and third areas where much future work should be directed. Important areas for future research could include:

- Unraveling the intricate and overlapping relationships of allostatic mediators and exploring their actions both centrally and peripherally.
- Beginning to explore aspects of the environment and lifestyle that can impact mental and physical health in ways that are only beginning to be understood, through modalities not normally associated with 'stress'. Circadian disruption is an excellent example of one such potential silent contributor to allostatic load (see Box 2) and, as noted, it is largely the result of modern society.
- Exploring the long-term effects of previous exposure to high allostatic loads on brain and behavior and their epigenetic and transgenerational impact.
- Investigating interventions after stressful or traumatic experiences, as well as methods to 'inoculate' individuals based upon an individual's genotype and previous experiences, in the spirit of personalized medicine.

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