Stress and cognitive function

[Review article]
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Abstract
Stress affects cognition in a number of ways, acting rapidly via catecholamines and more slowly via glucocorticoids. Catecholamine actions involve beta adrenergic receptors and also availability of glucose, whereas glucocorticoids biphasically modulate synaptic plasticity over hours and also produce longer-term changes in dendritic structure that last for weeks. Prolonged exposure to stress leads to loss of neurons, particularly in the hippocampus. Recent evidence suggests that the glucocorticoid- and stress-related cognitive impairments involving declarative memory are probably related to the changes they effect in the hippocampus, whereas the stress-induced catecholamine effects on emotionally laden memories are postulated to involve structures such as the amygdala.

Abbreviations
ACTH—adrenocorticotropic hormone;
AMPA—-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid;
5-HT—5-hydroxytryptamine (serotonin);
LTP—long-term potentiation;
MR—magnetic resonance;
MRI—MR imaging;
NMDA—N-methyl-d-aspartate;
PBP—primed burst potentiation.
**Introduction**

Memory is not a passive process in which we indiscriminately retain information from our environment. Instead, variables such as the context in which the information is delivered, our prior experiences, or even our glycemic state, filter which information is retained and the accuracy with which that retention occurs. An important such filter is our emotional state. As the archetypal example, most of us alive at the time can recall where we were when hearing that John F Kennedy had been shot, whereas few can recall any preceding events from that day.

In this review, we consider how stress, via the physiological responses that accompany it, can alter memory. As will be shown, brief periods of stress can potentiate memory formation, and recent work has uncovered some of the likely underlying mechanisms. In contrast, more severe or prolonged stressors can have deleterious effects upon broad aspects of cognition. Recent evidence suggests that some of these effects can probably be attributed to reversible changes in the morphology of neurons within the hippocampus, a region of the brain that is central to learning and memory. Finally, taken to the extreme, truly prolonged exposure to stress can cause irreversible loss of hippocampal neurons, and may be relevant to the cognitive deficits seen in many aged individuals.

**Catecholamines and glucocorticoids**

One must first briefly review the endocrine mediators of the stress response in order to appreciate their effects upon memory and hippocampal function. Physical and psychological stressors provoke the secretion of the catecholamines epinephrine and norepinephrine by the sympathetic nervous system, and of the glucocorticoids by the adrenal gland. Although the precise ratios of the secretions of these neuromodulators vary to some extent depending on the extent and level of stress exposure, there is nonetheless a consistent pattern to the activation of catecholamines and glucocorticoids in response to stress.

The catecholamine component of the stress response can be thought as representing the first wave, and the glucocorticoid component as being the second wave: in response to a stressor, catecholamines are secreted and trigger second-messenger cascades in postsynaptic target tissues within seconds; whereas, glucocorticoids are secreted following a latency of minutes and the hormone's effects can take hours to emerge, as they typically involve transcriptional events. This issue of time-course will become important in understanding the mechanisms underlying the very different consequences of short- versus long-term stressors.

**Acute arousal and enhancement of memory**

**Memory for emotional events**

It has long been known in both experimental animals and humans that acute instances of emotional arousal enhance memory formation. A recent study by Cahill et al. [1••] presents a rigorous experimental demonstration of this phenomenon. In this study, subjects were read one of two stories: the first story described the trip of a boy and his mother through town in order to visit the boy's father at the hospital, where the hospital staff (including his father) demonstrates various medical procedures to the boy; the second story described the trip of a boy and his mother through town during which the boy is seriously injured by a car, and he is rushed to the hospital where various medical procedures are carried out on him. Although the two stories are of identical length and complexity, and are identical in their beginning and end, there is nevertheless a marked enhancement of the memory for the emotionally laden details of the accident and subsequent procedures carried out on the boy.

Studies with laboratory animals suggest that the enhanced memory for emotional events is mediated by the sympathetic arousal that occurs at such times [2], and the study just discussed [1••] demonstrated that the same is true in humans. Specifically, -adrenergic receptor blockade with propranolol, which blocks sympathetic arousal, eliminated the enhanced memory for the emotionally laden part of the story [1••]. This pharmacological intervention did not disrupt all types of memory formation, however, as it had no effect on the memory of the 'unemotional' story, or memory of the unemotional parts of the story involving the accident.
Glucose and memory

This catecholamine-mediated effect on memory may well arise from enhanced delivery of oxygen and, more importantly, glucose to the brain. Severe hypoglycemia has long been known to impair memory, but recent literature suggests that physiologic fluctuations in glucose availability also affects cognition. Elevation of glucose concentrations into the typical post-prandial range (approximately 160–180 mg dl-1) potentiates both anterograde and retrograde memory formation in laboratory animals and humans [3]. In an extension of this study, Manning et al. [4•] showed that glucose enhances performance of memory tasks in Alzheimer's patients. As will be detailed below, different memory processes have different neuroanatomical substrates, and the enhancing effects of glucose are restricted to facets of memory thought to be dependent on the hippocampus.

Ventricular infusion of glucose is capable of enhancing memory [5], suggesting a central effect, and theories about the underlying mechanisms are of two flavors. Some ideas focus on the direct effects of glucose upon specific neurotransmitter systems. For example, the suggestion that glucose enhances acetylcholine synthesis by enhancing the availability of the acetyl-CoA precursor, and considerable evidence suggests a contribution of acetylcholine to hippocampal-dependent cognition (see [2]). Other ideas posit more general glucose actions, reflecting the likely metabolic costs of some of the rather dramatic changes that occur in neurons in response to plastic events: for example, the synthesis of more glutamate and/or more glutamate receptors, or the cytoskeletal remodelling that occurs in some cases of synaptic plasticity (see [2]). Of relevance to this is the recently characterized hippocampal ATP-dependent potassium channels, in which ample amounts of ATP, derived from energy metabolism of glucose, inhibit current flow, indirectly enhancing neuronal excitability [6][7].

The connection of this literature to that of sympathetically enhanced memory is, of course, the capacity of catecholamines to increase glucose utilization in the brain [1••][2]. This is due to both peripheral effects (such as stimulation of glycogenolysis) and increased cerebral perfusion rate. In tightening this link, the catecholamine concentrations that have optimal effects on memory are those that produce the concentration of circulating glucose that has the optimal effect on memory. Other possible mechanisms for the sympathetic effect on memory exist as well (see [2]).

Disruptive effects of stress and glucocorticoids on long-term potentiation

Biphasic effects of adrenal steroids

The deleterious effects of more disruptive stressors are probably mediated in part by the sympathetic nervous system: excessive exposure to catecholamines disrupts memory, as does exposure to supraphysiological concentrations of glucose (see [2]). The reasons for this inverted U-shaped effect (i.e. certain levels of catecholamine and glucose are beneficial to memory, whereas higher levels are deleterious) are not known (see [2]). Most of the current literature, however, focuses on the adverse effects of glucocorticoids, rather than catecholamines, during longer exposure to and higher levels of stress. In this section, we will review the impairment to memory, over the course of a few hours up to days, that occurs in response to exposure to stress or glucocorticoids.

One of the best characterized effects is the capacity of psychological stress and stress-induced levels of glucocorticoids to disrupt long-term potentiation (LTP) and/or the closely related, primed burst potentiation (PBP) in the hippocampus [8••]. Glucocorticoids have a biphasic effect on LTP and PBP [9]. Whereas stress-induced levels of the adrenal steroids inhibit LTP [9][10•][11], lower concentrations of the hormone, such as those that occur naturally during the diurnal rise, enhance such plasticity [9][12•].

This dissociation between the effects of basal and stress levels of this hormone is not surprising as there are two types of receptors for glucocorticoids (Type I, also known as the mineralocorticoid receptors, and Type II, also called the glucocorticoid receptors), and the hippocampus is one of the few sites in the body in which there are substantial concentrations of both types of receptors [13]. The high-affinity Type I receptors are heavily occupied by basal levels of adrenal steroids during the diurnal cycle, whereas elevation of glucocorticoid concentrations into the stress range increases the occupation of the lower-affinity Type II receptors. Thus, this provides an ideal mechanism.
by which circulating adrenal steroids can have different, or even opposing, effects upon the hippocampus during basal versus stress conditions. In support of this view, selective activation of Type I receptors in the hippocampus increases LTP [12••][14], just as low levels of endogenous corticosterone enhance PBP [9], whereas occupation of Type II receptors by high levels of endogenous glucocorticoids suppresses LTP [10••][14] (see Fig. 1) and PBP [9]. It has also been reported that Type II receptor stimulation induces a long-term synaptic depression or depotentiation [15].

Fig. 1. Schematic summary of actions of adrenal steroids that affect hippocampal function and alter cognitive performance. (a) Adrenal steroids biphasically modulate LTP, facilitating it via Type I receptors and inhibiting it via Type II receptors; Type I and Type II receptors co-exist in hippocampal neurons. (b) The biphasic modulation of excitability is also seen for PBP as a function of increasing levels of circulating corticosterone, and this may be relevant to diurnal changes in hippocampal function, to the phenomenon of jet-lag and to the effects of acute stress elevation of glucocorticoids that impair PBP. (c) Hippocampal circuitry is diagrammed showing some of the main connections between entorhinal cortex (ENT), Ammon's horn (H) and dentate gyrus (DG). f, fornix; pp, perforant pathway. (d) Moderate duration stress, acting through both glucocorticoids and excitatory amino acids (especially glutamate), causes reversible atrophy of apical dendrites of CA3 pyramidal neurons; severe and prolonged stress causes pyramidal cell loss that is especially apparent in CA3, but spreads to CA1 as well. The mechanistic relationship between reversible atrophy and permanent neuron loss is not presently known, although both glucocorticoids and excitatory amino acids are involved.

No doubt related to their effects upon LTP, glucocorticoids also have well-characterized effects on hippocampal electrophysiology [16][17][18][19][20][21]. Stress levels of the hormone have long been known to decrease hippocampal excitability [16][17][18]. One explanation for this is that glucocorticoids enhance after-hyperpolarizations, which prolong the unresponsive refractory period of hippocampal neurons. One way they do this is by enhancing calcium currents, which, in turn, activate a calcium-dependent potassium channel [16]. Like its effect on LTP, glucocorticoid effects on hippocampal excitability are biphasic: stress levels of the hormone are inhibitory, whereas basal levels are stimulatory [20][21]. Once again, this biphasic response appears to be mediated by the varying effects of Type I and II receptor occupancy in response to different amounts of stress [16][19][20][21]. The various components that play a role in mediating these contrasting responses are being characterized, for example, it is known that Type I receptor activation leads to a reduction of the serotonin 5-HT1A receptor activated, calcium-independent potassium channel hyperpolarization [16].

**Excitatory amino acids**

Excitatory amino acid receptors have been implicated in the effects of stress on the hippocampus, but the possible mediating role of adrenal steroids is unclear. In rats, a single social stress experience (e.g. confrontation with a dominant rat) was shown to increase NMDA antagonist binding in the CA3 region of the hippocampus 24 hours later [22•], whereas one hour of tail-shock stress was reported to acutely increase AMPA agonist binding in several fields of the hippocampus [23]. Repeated restraint stress over 14 days failed to change either NMDA antagonist binding or AMPA antagonist binding in any region of the hippocampus [24]. It is impossible to interpret what these various results mean without further studies that would examine the time course for a single stressor and the relationship between agonist and antagonist binding for both NMDA and AMPA receptors. Moreover, adrenal steroid involvement is not clearly demonstrated. Although adrenalectomy decreased AMPA antagonist binding in dentate gyrus and Type I adrenal steroid receptor stimulation reversed the effect, repeated high dose corticosterone treatment over several weeks failed to change hippocampal AMPA antagonist binding, nor did it have any effect on NMDA antagonist binding in any hippocampal region [24].

**Endogenous opiate peptides**

An additional route by which stress can disrupt LTP appears to involve endogenous opiates. The first hint of this role for opiates came from a study by Thompson and colleagues [25], who found that removing only the adrenal medulla,
rather than the entire adrenal, blunted stress-induced disruption of LTP. Although this finding might suggest the release of catecholamines mediated by the adrenal medulla as a candidate mechanism for such disruption, epinephrine does not normally pass the blood-brain barrier, nor has it been shown previously to have strong effects on LTP. Instead, it appears that it's the adrenomedullary secretion of enkephalins that is critical, because an opiate antagonist is able to block the stress-induced impairment of LTP [26]. That enkephalins play such a role in stress-induced effects shouldn't come as a surprise given that it is known that enkephalins are released in response to painful stressors such as shock and help mediate stress-induced analgesia; nevertheless, their impairment of LTP is probably a secondary effect resulting from their interaction with other neurotransmitter systems.

In a subtle but important finding, Thompson and colleagues [27] showed, however, that the enkephalin effect upon LTP did not so much correlate with the level of physical pain induced by the stressor as with its psychological context. They designed a paradigm in which one group of rats had to repeatedly press a lever to decrease the likelihood of receiving a shock (i.e. they were exposed to a 'controllable' stressor), whereas a second group of rats were physically restrained and received the identical shock pattern, but had no means of controlling it. In these studies, LTP was disrupted only in the rats exposed to the uncontrollable stressor.

**Glucose uptake**

A third mechanism by which stress might impact the cellular underpinnings of memory formation is via glucocorticoid inhibition of glucose transport in the hippocampus, as assessed by 2-deoxyglucose mapping in vivo [28][29][30][31]. Furthermore, glucocorticoids inhibit glucose uptake into both cultured hippocampal neurons and glia [32][33]. Paralleling a theme that has cropped up throughout this section, these disruptive glucocorticoid actions are mediated by the Type II receptor [32], and appear to involve both translocation of pre-existing glucose transporter molecules from the cell surface to intracellular storage sites [34], as well as decreases in levels of mRNA for the glucose transporter [35].

Two points should be emphasized in considering this literature. First, a pair of studies have failed to observe a suppressive effect of glucocorticoids upon 2-deoxyglucose uptake into the hippocampus [36][37]; however, in the two studies, the glucocorticoids were administered 15 and 75 minutes, respectively, before killing, times that were probably too short for the transcriptionally dependent phenomenon to have occurred. Second, in vitro studies indicate that glucocorticoids inhibit glucose transport in hippocampal cultures, but not in neural cultures from other brain regions [33]; however, in vivo studies indicate that the inhibition of glucose transport by glucocorticoids occurs throughout the brain [28][29][30]. A possible explanation of this phenomenon is that glucocorticoids probably inhibit glucose transport at vascular endothelium throughout the brain [28], but only further inhibit target neurons in the hippocampus. The selective vulnerability of the hippocampus suggests that the extent of glucocorticoid inhibition of glucose transport should be significantly greater in the hippocampus than in other regions. This was found to be the case in a careful analysis of genetically obese (fa/fa) Zucker strain rats, in which glucocorticoid concentrations are approximately doubled [30].

So, how might this decrease in glucose transport affect LTP? Glucocorticoid inhibition of glucose transport (typically on the order of 25%, both in vitro and in vivo) is insufficient to decrease the basal levels of ATP in hippocampal neurons or glia [38][39]. However, during periods of increased energy demand, glucocorticoids accelerate the loss of ATP [38][39]. A highly plastic event such as LTP is energetically demanding for a neuron, and the glucocorticoid-induced rapid depletion of ATP stores might impair the efficacy of LTP. As noted above, ATP depletion leads to a hyperpolarizing outward current in the ATP-dependent potassium channel, damping neuronal excitability [6][7].

**Effects of stress and glucocorticoid on learning and memory**

**Animal studies**

The effects of stress-induced levels of glucocorticoids upon LTP, hippocampal excitability in general, and hippocampal energetics collectively suggest that similar concentrations of these steroids should disrupt learning and memory. In parallel with the work on LTP and PBP, there is some evidence for the biphasic effects of adrenal steroids on memory in experimental animals. Adrenalectomy impairs spatial memory performance in adult rats under
conditions in which there is no continuing adrenalectomy-induced dentate gyrus neuron loss [40•]: Type I receptor activation restores performance, whereas Type II receptor activation impairs performance ([40•]; P Vaher et al., unpublished data). Adrenalectomy also impairs spatial learning in a Morris water maze: Type I receptor blockade of adenally intact rats altered search–escape strategies and impaired reactivity to spatial novelty, whereas Type II receptor blockade increased latencies to find the platform [41][42•]. In chicks, both Type I and Type II receptor antagonists impair passive avoidance learning, with each type of antagonist appearing to have different effects on the animal's behavior [43•]. Looking at passive avoidance learning in adrenalectomized rats, Borrell et al. [44] found that a low-dose corticosterone treatment, presumed to work via Type I receptors because dexamethasone did not mimic it, caused a very large rightward shift in the dose response curve for adrenaline administration, which restores passive avoidance learning.

Surprisingly, however, with the exception of a chronic stress study and a chronic corticosterone treatment study (discussed below), there is no published investigation of the effects of high doses of glucocorticoids on hippocampally related learning, and so we must turn to studies on human subjects.

**Human studies**

Recent human studies have provided direct evidence for an inhibitory effect of high levels of glucocorticoids on human learning and memory. The clinical literature (discussed below) links memory impairments with syndromes of sustained hypercortisolism, such as seen in hypercortisolemic depressives, patients with Cushing's syndrome, hypercortisolemic patients with Alzheimer's disease, and patients on long-term therapeutic glucocorticoid treatment.

Experimental work in recent years has linked the memory loss and glucocorticoid exposure more tightly in three ways.

First, an obvious problem in studying the types of patients listed above is that there is an underlying coincident disease. Furthermore, some of these disorders are associated with elevated adrenocorticotropic hormone (ACTH) concentrations, whereas others may have suppressed concentrations. As ACTH itself may play a role in cognitive function, this needs to be taken into account when interpreting results from studies on these patients (see e.g. [45]).

Circumventing these problems, a number of recent studies have reported deleterious effects of glucocorticoids upon cognition after a few days of a high-dose steroid regime in healthy volunteers [46][47••].

Second, several studies have more closely linked learning and memory deficits with the hippocampus. A broad dichotomy has been made between 'declarative' and 'procedural' knowledge, the latter concerning implicit knowledge of how to do something, the former involving explicit knowledge that you know something. Declarative knowledge has come to be viewed as the province of the hippocampus, whereas the more motoric procedural knowledge appears centered in extrapyramidal systems and the cerebellum. In human volunteers, glucocorticoids increase the frequency of declarative errors (i.e. mistakes on both immediate and delayed recall of information from a paragraph read to them) [47••]. In contrast, glucocorticoids had no effect on tasks that had a less declarative and, in some cases, more procedural or arousal component, such as serial addition, vigilance tasks, or line orientations tasks.

Finally, recent studies have generated some confusion as to which features of hippocampal-dependent cognition are disrupted. In one study, subjects were asked to remember a list of objects read to them earlier, after having listened to a list of related 'distractor' objects in-between [46]. Glucocorticoids did not impair the memory for objects on the original list (i.e. did not cause omission errors), but instead, increased the rate of intrusion by distractor items (i.e. commission errors). In effect, glucocorticoids disrupted the filtering out of irrelevant stimuli. However, a more recent study [47••] failed to replicate this finding for reasons that could not be explained by the authors.

One exception to the findings that glucocorticoids impair cognition is the report that daily, low doses of prednisone (0.5 mg day-1 over three weeks) produced some improvement of global indices of cognition in patients with systemic lupus erythematosus [48]. The reported cognitive changes were not broken down in such a way as to determine if there was any specificity, for example, for semantic or episodic memory. As low doses of prednisone may behave like dexamethasone (which does not enter the brain at doses sufficient to suppress ACTH secretion [49]), it is conceivable that the effect of prednisone on cognition in lupus patients is due to suppression of endogenous glucocorticoid secretion, which has an effect on brain, rather than to a direct effect of prednisone on the brain. The results of the study by Newcomer et al. [47••], using dexamethasone, are subject to the same uncertainty. As mentioned above, in animal models, glucocorticoids have biphasic effects on LTP and PBP, both of which are putative neural indices of cognitive function, therefore, it is plausible that suppressing elevated glucocorticoid
secretion may have a beneficial effect on cognition.

The consequences of prolonged exposure to stress or glucocorticoids

Animal studies

One of the more striking findings in the field in recent years was the observation that exposure to glucocorticoids or stress over the course of 21 days could cause atrophy of dendritic branches in pyramidal neurons of the CA3 region of rat hippocampus [50][51]. The atrophy is specific to apical dendrites of CA3 neurons [50][51] and is reversible (A-M Magarinos, BS McEwen, unpublished data). The apical dendrites are the site of the mossy fiber input from the dentate gyrus and associative connections from other CA3 cells, which release excitatory amino acids. Administration of either Dilantin, an antiepileptic drug that blocks glutamate release and certain types of calcium channels, or an NMDA receptor blocker prevent glucocorticoid- or stress-induced atrophy ([51]; A-M Magarinos, BS McEwen, unpublished data). Dilantin was able to block the dendritic atrophy caused by 21 days of repeated restraint stress, as well as the atrophy produced by 21 days of daily injections of corticosterone, thus implicating glutamate release as a mediator of the actions of glucocorticoids [52] (see Fig. 1). Several recent reports indicate that glucocorticoids potentiate the actions of kainic acid to cause damage [53]; they also potentiate the release of excitatory amino acids in the hippocampus [54][55][56], and they are also able to affect a variety of postsynaptic processes, including the expression of neurotrophins [57•].

The dendritic atrophy of CA3 pyramidal neurons caused by 21 days of repeated stress is accompanied by a reversible impairment of the initial learning of a spatial memory task on an eight-arm radial maze [58••]. As with the dendritic atrophy, the learning impairment is prevented by treatment with Dilantin during the 21-day stress regimen [58••].

Thus, exposure to certain levels of glucocorticoids can cause reversible changes in the morphology of hippocampal neurons. However, with even longer periods of exposure to glucocorticoids, overt loss of such neurons occurs, causing irreversible hippocampal dysfunction (see Fig. 1). The evidence for such glucocorticoid neurotoxicity first emerged in the 1960s, while more recent work has emphasized the physiologic relevance of this phenomenon. A series of studies has shown that exposure to glucocorticoid concentrations in the stress range for a period of months, or similar exposure to stressors themselves, will cause hippocampal neuron loss in the rat [59][60][61]. More specifically, this pattern of loss and associated glial hypertrophy in the hippocampus resembles the pattern seen in aging animals, however, at an accelerated rate. Furthermore, the more aged the animal, the more vulnerable it is to such damage [60]. Conversely, a series of studies has shown that surgical or behavioral manipulations that reduce cumulative glucocorticoid exposure over the lifetime of an animal delay or eliminate such senescent loss of hippocampal neurons [62][63][64].

A related literature has been cited to explain this phenomenon. Shorter periods of glucocorticoid exposure 'endanger' hippocampal neurons, impairing their capacity to survive neurological insults, such as hypoxia/ischemia, seizure or hypoglycemia (reviewed in [64][65•]). All such insults involve a degenerative cascade of events (Fig. 2), including accumulation of glutamate in the synapse and subsequent mobilization of cytosolic calcium to pathologically elevated levels, resulting in cytoskeletal damage and the generation of oxygen radicals (reviewed in [64][65•]). Glucocorticoids have been shown to exacerbate each of those steps. Moreover, this endangerment is energy-dependent, as supplementing rats (or hippocampal cultures) with an external source of energy reverses the exacerbating effects of glucocorticoids [65•].

Fig. 2. Schematic diagram of neuronal endangerment. The synaptic accumulation of glutamate that typically accompanies a necrotic insult, such as ischemia or seizure, is worsened by glucocorticoids (GCs). (a) This is likely to arise from GCs inhibiting the removal of glutamate from the synaptic cleft. Such inhibition has been demonstrated to occur at glia, and are speculated to occur at neurons as well; however, (b)GCs do not appear to enhance the initial release of glutamate. (c) As a result of these GC actions, there is enhanced mobilization of free cytosolic calcium in the postsynaptic neuron. (d) In addition, this accumulation of calcium is augmented by GCs inhibiting the efflux of calcium (via both the Ca2+/ATPase and the Ca2+/Na+ exchanger). (e) At present, however, there is no evidence that GCs directly enhance the influx of calcium, either by opening voltage-gated calcium channels or by acting at NMDA receptor-gated channels.
As a result of the excessive cytosolic calcium, GCs exacerbate calcium-dependent degenerative events. To date, these have been shown to include worsening the proteolysis of the cytoskeletal protein spectrin, the accumulation of the abnormally phosphorylated tau protein, and the production of oxygen radicals during necrotic insults (see [65*]).

Thus, a model has been proposed in which the inhibition of glucose transport by stress levels of glucocorticoids and the resulting energetic vulnerability makes it more difficult for the hippocampus to carry out the costly and vital tasks of glutamate re-uptake, calcium sequestering and efflux, and oxidative damage repair (reviewed in [64][65*]). This model accounts for how glucocorticoids might exacerbate the effects of a coincident neurological insult over the course of hours to days. (It has often been tacitly assumed that the results of testing this model will be relevant to understanding how glucocorticoids can be directly toxic, on their own, over the course of months.) This thinking focuses on the possibility that neurons experience frequent 'mini'-neurological crises in the normal process of wear and tear — for example, a transient and mild hypoglycemia if an animal is fed late, causing a vasospasm of a capillary bed resulting in a brief hypoxia. In this framework, glucocorticoids might appear to be directly toxic over long periods of time by subtly exacerbating the minute effects of these insults. This idea remains to be tested.

Studies with primates also report neuron loss induced by long-term stress or glucocorticoid exposure. One study concerned a population of vervet monkeys in which 'subordinate' animals were essentially subordinated to death via a syndrome that involves multiple gastric ulcers, colitis, splenic lymphoid depletion and adrenocortical hyperplasia [66]. At post-mortem, these animals were shown to have extensive damage in the CA3 region of the hippocampus. No other parts of the brain were damaged, except some mild damage in layers 3–5 of the cortex, and no damage was observed in the brains of unstressed control monkeys matched for post-mortem time. Subsequent work suggested that hypercortisolism was responsible for the damage observed in the hippocampus [67]. In the latter study, vervet monkeys were implanted with a cortisol-secreting pellet into the hippocampus unilaterally, and a cholesterol-secreting pellet as a contralateral control; one year later, mild but selective damage had occurred on the glucocorticoid-treated side.

A pattern of stress-induced atrophy of apical dendrites of CA3 pyramidal neurons in the hippocampus has now been reported in the tree shrew as well (A-M Magarinos, BS McEwen, EFuchs, G Flugge, unpublished data), which suggests that these effects are not species specific, and that chronic social stress causes dendritic atrophy first and subsequently leads to neuronal death.

**Studies on the human hippocampus**

A handful of studies hint that sustained glucocorticoid exposure can cause selective hippocampal atrophy in human brain as well. An older literature reported diffuse limbic atrophy in the brains of patients with Cushing's syndrome. More recently, a magnetic resonance imaging (MRI) study reported selective atrophy of the hippocampus in individuals who were estimated to have suffered from Cushing's syndrome for one to four years [68]. A weakness of the study is that there was no control population, and the authors instead compared the cortisol values for the Cushingoid patients with those of normal values reported in the literature. However, a strength of the study was the finding of a significant correlation within the Cushingoid patients between the severity of the hypercortisolemia and the extent of hippocampal atrophy (as well as with the severity of the accompanying cognitive deficits).

An even more tentative literature suggests a link between the hypercortisolism of some depressives and hippocampal atrophy. A number of older studies reported that depression was associated with ventricular enlargement, as assessed by computerized tomography (CT) or magnetic resonance (MR) scanning (reviewed in [69]). Such enlargement was most common in hypercortisolemic or dexamethasone-resistant patients, older patients, or those with the psychotic subtype of depression — it should be noted that hypercortisolism in depression is a particular marker of both older depressives and psychotic depressives.

In more explicit support of a link to the hippocampus was the MRI finding of Axelson et al. [70] that decreased
hippocampal volume was correlated with more pronounced hypercortisolism at one time-point in the dexamethasone suppression test, a test that measures the hyperactivity of the hypothalamic–pituitary–adrenal axis and its ability to be negatively regulated by a synthetic adrenal steroid. However, most of their indices of hypercortisolism did not correlate with changes in hippocampal volume. As a complication, the authors noted the lack of resolution of their particular imaging system in which, for example, they were unable to distinguish between the hippocampus and amygdala.

Even more difficult to interpret is an earlier finding by the same group [71], in an MRI study that measured regional brain T1 spin-lattice relaxation times. The authors observed that depressives had significantly shorter T1 relaxation times in the hippocampus, but not in any other brain region examined, as compared with healthy controls. Moreover, this effect was most pronounced in aged depressives. However, the difficulty in interpreting these results arises from the lack of certainty as to the physiological meaning of this measure, which, in a rather undefined manner, is thought to reflect the content or macromolecular environment of the water in different brain tissues. Another drawback of this analysis is that the authors did not analyze the data in their depressives as a function of glucocorticoid levels.

**Prolonged stress and cognitive impairments**

**Animal studies**

Collectively, these rodent, primate and human findings suggest that instances of prolonged glucocorticoid exposure should be associated with cognitive impairments. This has been borne out in rodent studies where surgical or behavioral strategies that reduced lifelong exposure to glucocorticoid and senescent hippocampal neuron loss either delayed or eliminated the spatial learning deficits typical of the aged rodent [62][63][64]. This link was strengthened further in an important study by Issa and colleagues [72]. The authors initially tested spatial memory in aged rats. As would be expected, average performance was worse compared to that of young controls but, as is typical in virtually all gerontological studies, a subset of rats showed no age-related decrements in performance. Such 'unimpaired' individuals were then shown to have been spared the hippocampal neuron loss and glucocorticoid hypersecretion typical of their aged cohort. The interpretation given was that this subset of animals, which, for whatever reasons of physiology and/or experience, had been spared the typical cumulative effect of glucocorticoid exposure over their lifetime, had been spared the consequent hippocampal degeneration and dysfunction.

Studies of the aging rodent hippocampus have provided additional insights into processes underlying the vulnerability of this structure to neuronal loss, particularly as it ages [73]. The glucocorticoid (Type II) receptor is a key mediator of the glucocorticoid effects causing neuronal loss [65•], and aging rats fail to down-regulate hippocampal Type II receptors in response to repeated stress [73]. This loss of plasticity makes the aging rat more vulnerable to stress-induced loss of hippocampal pyramidal neurons [60]. That is, in the aging rat, the stress-induced glucocorticoid secretion operates on a larger 'target' caused by a failure to down-regulate glucocorticoid receptors [73]. Another factor that may play a role in the increased neuronal vulnerability and neuronal loss found in older brains is an increase in cytosolic calcium, which has been observed in aged hippocampal neurons and probably results from the glucocorticoid-dependent increase of calcium action potentials and voltage-activated calcium currents [19].

Consistent with the results of studies looking at the effects of stress on the aging rat hippocampus are those from a study by Bodnoff et al.[74••], who found that mid-aged but not young rats had impaired spatial learning after being treated for three months with a high (stress level, but not supraphysiologic) dose of corticosterone. Mid-aged rats also exhibited impaired spatial learning after being exposed to six months of social stress [74••]. Electrophysiological analysis revealed decreased PBP in the corticosterone-treated mid-aged rats, but no evidence of pyramidal neuron loss, indicating that cognitive impairment is possible without overt neuronal loss [74••]. Unfortunately, morphology of the CA1 and CA3 pyramidal neurons was not investigated for possible dendritic and synaptic remodelling.

**Human studies: individual differences**
Studies on human populations have also demonstrated individual differences in glucocorticoid levels and in cognitive impairment. As mentioned above, cognitive impairments have long been noted to accompany the elevated glucocorticoid concentrations seen in Cushing's syndrome [45], in some depressives [46] and Alzheimer's patients and in individuals maintained on high-dose glucocorticoid regimes [75][76]. Recent results have strengthened this relationship further by showing that the severity of the cognitive deficits co-varies with the level of hypercortisolism (in response to exogenous steroids [46]; in Alzheimer's patients [76][77•]; in depressives [78][79]). Moreover, the cognitive deficits are declarative in nature, again implicating the hippocampus. For example, in Cushingoid patients, the cognitive deficits are demonstrable in verbal paired association tasks and a visual episodic memory task, though not for copying visual design [69].

As noted above, the interpretation of some of these studies is clouded by the coincident disease in these individuals. A recent study by Lupien and colleagues [80••] on healthy individuals presents an important advance towards characterizing the specific cognitive impairments caused by the chronic exposure to glucocorticoids. They measured the basal level of glucocorticoids in a group of moderately aged subjects (median age 70 years) over a period of four years. The subjects were divided into three groups: group 1 (38%) contained individuals whose basal level of glucocorticoids had risen over the four year period, resulting in their being at least mildly hypercortisolemic; group 2 (46%) contained individuals whose levels of glucocorticoids had risen, but whose resting values were still in the normal range; and group 3 (16%) contained individuals whose level of glucocorticoids had either remained stable or declined. A variety of neuropsychological measures of hippocampal-dependent memory (i.e. explicit or declarative) showed a marked deficit in group 1 subjects, unchanged values in group 3 individuals (versus young controls), and intermediate values in group 2 individuals. In contrast, there were no deficits in any of the groups in nonhippocampal-dependent, implicit memory processes.

In a related study (T Seeman for the MacArthur Study of Successful Aging, personal communication), preliminary data from a community-based longitudinal study of 200 males and females (age 70–79) indicate that increases in 12 hour overnight urinary cortisol levels, as measured over a 2.5 year period, correlate with declines in memory performance, as measured by detailed recall of a story.

**Possible mechanisms of glucocorticoid/stress-induced cognitive deficits: individual differences**

Thus, studies of animals and humans show that prolonged glucocorticoid exposure, whether in response to disease or as part of normal aging, are associated with deficits in hippocampal-dependent cognition, and that individual differences in cognitive vulnerability can be understood in the context of differences in the extent of such glucocorticoid exposure. What are the neurobiological underpinnings of these deficits? In some of the rodent studies, the link between glucocorticoids and cognition was further associated with overt neuron loss [59][62][63]. However, in some cases, cognitive or electrophysiological deficits were induced by chronic glucocorticoid exposure or stress without explicit neuron loss [60][74••].

Similarly, most of the studies linking prolonged hypercortisolism with cognitive impairments in humans have reported that cognition improves significantly following normalization of glucocorticoid exposure (for Cushing's syndrome, see [46][81]; for exogenous steroid regimes, see [75]). To most investigators, this would imply that the underlying neurobiological defect does not involve the irreversible state of neuron loss. This raises a number of issues for future investigation.

First, the effects of glucocorticoids upon hippocampal electrophysiology and dendritic branching patterns (independent of neuron loss) are plausible candidates to explain the reversible effects of the hormone on cognition. Should these apply to the human hippocampus, it will be important to know if the loss of dendritic branching can account for the hippocampal atrophy detected in some MRI studies.

Second, the reversibility of the hippocampal atrophy and of the cognitive deficits in these various human conditions following diminution of glucocorticoid exposure is not really surprising. Most such studies involve individuals exposed to high glucocorticoid concentrations for relatively few years, and in the sole relevant primate study [67], even a year of extremely high glucocorticoid exposure caused only qualitative, rather than quantitative damage to the
hippocampus. To our knowledge, there are no studies of individuals exposed to glucocorticoids over the course of many years that have determined whether the length and/or cumulative extent of exposure predict the severity of cognitive impairments or of any morphometric hippocampal changes. Such studies, although extremely difficult to carry out, seem vital.

Third, another group of individuals worth studying are those who show mild cognitive impairment as a result of chronic exposure to glucocorticoids, such as in the studies by Starkman et al. [45][68] and Lupien et al. [80••]. This is because another line of inquiry, related to Alzheimer's disease, has demonstrated hippocampal atrophy associated with moderate cognitive impairment [77•]. In those individuals, there is an 80% or better probability that they will develop a senile dementia of the Alzheimer's type [77•]. It is important to find out if there is any relationship between the two types of cognitive impairment. If so, would pharmacological interventions such as Dilantin, which blocks the 'reversible' atrophy of dendrites in the CA3 region of rat hippocampus, be able to reverse the hippocampal atrophy seen in these patients and possibly slow down or arrest the progression of permanent damage?

Conclusions

The actions of stress on cognition involve multiple mechanisms and different time courses. Whereas painful experiences activate opioid pathways and emotionally laden events activate the adrenergic system, the information that the brain records with or without these additional influences appears to involve the hippocampus and temporal lobe, which are highly vulnerable and plastic regions of the brain. Adrenal steroids, acting via two types of receptors, modulate biphasically the ability of the hippocampal region to store and retrieve information. Under conditions of prolonged stress, these same adrenal steroids, acting in concert with excitatory amino acid neurotransmitters, can, depending on the extent and level of exposure, cause either reversible dendritic alterations or permanent neuronal loss, particularly in the aging brain. One of the great challenges is to determine the basis of the individual differences in vulnerability to stress-induced effects in both animal and human populations, and to devise strategies that may help to protect the brain against long-term damage.
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