Effects of stress hormones on the structure and function of the human brain

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In response to stress, the hypothalamus–pituitary–adrenal axis is activated and glucocorticoids are secreted. These hormones exert multiple effects in the periphery as well as the brain. Acutely, they enhance memory consolidation, but at the same time the ability to retrieve previously learned information is reduced. In addition, glucocorticoids appear to interfere with working (short-term) memory. Chronically elevated glucocorticoid levels, as a result of endocrine or psychiatric disorders or as part of age-associated changes in the hypothalamus–pituitary–adrenal system, mostly have a negative influence on memory. In parallel, structural alterations are observed in the hippocampus and the prefrontal cortex. However, it seems that plasticity/reversibility is more common than previously thought. Moreover, several pharmacological interventions in animal models or small-scale human studies have revealed promising results. The advanced understanding of the CNS effects of glucocorticoids will ultimately lead to progress in the treatment of psychiatric and systemic diseases characterized by hypothalamus–pituitary–adrenal hyper- or hypo-activity.

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Interaction with a stressor leads to a cascade of neuroendocrine stress responses, designed to facilitate adaptation [1]. The hypothalamus–pituitary–adrenal (HPA) axis, together with the sympathetic nervous system (SNS), is one of the most important systems in this respect. The hypothalamus activates the HPA axis in response to input from several other brain regions (e.g., the amygdala and the prefrontal cortex [PFC]). Corticotropin-releasing hormone and vasopressin are released in the portal blood system. They reach the pituitary, which in turn releases adrenocorticotrophin (ACTH). In response to ACTH, the adrenal cortex secretes glucocorticoids (GCs), but also other steroid hormones (e.g., dehydroepiandrosterone). In most laboratory rodents, corticosterone is the most important GC, whereas in humans, cortisol is the main adrenal GC. GCs, as lipophilic steroid hormones, can enter the brain, even though access might be restricted by the multidrug-resistant P-glycoprotein [2]. In the brain, GCs exert effects on multiple structures involved in cognition, such as the limbic regions (e.g., amygdala and hippocampus), but also prefrontal regions (e.g., anterior cingulate). These effects are often caused by the binding to the two receptors for the hormone; the mineralocorticoid receptor (MR) and the glucocorticoid receptor (GR). These two receptors differ in their affinity for cortisol (with the MR having a much higher affinity) but also in their localization in the brain. In addition, GCs can exert rapid nongenomic effects by modulating ion channels or neurotransmitter receptors at the cell membrane level [1]. The strength of GC effects on specific brain target structures is determined by multiple factors, in addition to the GC concentration in the blood. Among these are receptor number and sensitivity, but also activity of intracellular enzymes involved in GC metabolism such as 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) [3].

The other hormones of the HPA axis (corticotropin-releasing hormone, vasopressin and ACTH) can influence the brain independently of their effects on GC secretion [4].

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Overview

The goal of this review is the description of acute, as well as chronic, effects of GCs on the human brain, with a special emphasis on memory and the medial temporal lobe memory system. Since a substantial proportion of knowledge about the CNS effects of these hormones has been derived from studies in animals, findings obtained in rodents will be described first. Acute stress effects will be described, followed by chronic effects. The concept of multiple memory systems in the brain will be an additional way that the presentation of the findings is structured.

There is agreement that there is not a single memory system in the brain, but multiple interacting systems [5–7]. This review will focus on declarative, or explicit, long-term memory, since it has been investigated most intensely with respect to stress effects. The episodic (in contrast to the semantic) aspect of declarative memory refers to the explicit and voluntary storage of facts and events, which can later be intentionally retrieved [5–7]. It is a relational and flexible system. This type of memory is tested in humans most often with word lists, short stories or slides. In animals, spatial maze tasks are frequently used.

Long-term memory can be further divided into different memory phases, namely acquisition (or initial learning), consolidation (or storage) and retrieval (or recall). For the successful completion of episodic declarative tasks, an intact medial temporal lobe region (hippocampus and surrounding cortical structures) is essential for the acquisition of the task. The role of the hippocampus for retrieval is debated and it might fulfil a time-limited role only and/or might be crucial for successful retrieval, but not for search efforts associated with retrieval [5,6]. Especially in humans, it is the PFC that is also of importance for (effortful) retrieval.

After the discussion of long-term memory, findings for working (short-term) memory, which is mediated by structures in the PFC, will briefly be mentioned. Nondeclarative, or procedural, forms of learning (e.g., classical conditioning, skill learning or priming) will not be addressed in this review. These memory forms do not rely predominantly on the medial temporal lobe (except for trace conditioning) and stress effects on these memory forms have not been studied well in humans [8].

Stress, memory & the brain: data from animals

Spatial long-term memory: acute effects

The literature regarding the effects of stress on long-term memory has been quite diverse and confusing, with groups reporting enhancing, as well as impairing, effects of GCs on this form of memory. However, thanks to progress made in recent years, it has become apparent that this is largely due to the fact that the different memory phases are modulated by GCs in opposite directions [9].

GCs enhance memory consolidation and this aspect represents the adaptive and beneficial mode of GCs' CNS action. This process has been conceptualized as the beneficial effects of 'stress within the learning context' [10]. Thus, a stressful learning episode is remembered better than a less stressful event [11]. This effect is mediated by the action of stress-released GCs on the hippocampal formation [10]. Studies with mutant mice have demonstrated that DNA binding of the hippocampal GR is crucial in this respect [12]. Roozendaal and McGaugh have shown in their work that adrenergic activation in the basolateral amygdala (BLA) appears to be a prerequisite for the modulating effects of GCs in other brain regions (e.g., hippocampus). Lesions of the BLA, as well as local or systemic injections of β-receptor antagonists, prevent the enhancing effects of post-training GC administration [9].

In contrast to the positive effects on memory consolidation, effects of GCs on memory retrieval are negative. By using a 24-h delay interval, de Quervain and colleagues demonstrated in 1998 that foot-shock stress 30 min before retrieval testing impairs the memory retrieval in rats in the water maze [13]. This impairment was prevented by treating the animals with the corticosterone synthesis inhibitor, metyrapone. Similar deficits occurred after systemic corticosterone administration or intrahippocampal infusion of a GR agonist [13]. The latter finding indicates that GR activation in this brain region is crucial for the induction of this effect [14]. Further studies have revealed that, again, an intact BLA, as well as adrenergic activation, appear to be necessary for the impairing effect of GCs on memory retrieval [15]. Local as well as systemic injection of a β-receptor antagonist abolished the impairing effect on GC treatment on memory retrieval. Roozendaal has summarized his findings as indicative that stress puts the brain into a consolidation mode, which is accompanied by impaired retrieval. Such a retrieval reduction might facilitate consolidation by reducing interference [9].

Spatial long-term memory: chronic effects

For more chronic effects, as a result of prolonged stress or GC treatment, the picture is different. Here, negative effects appear to prevail. Chronic stress in animals has repeatedly been shown to result in impaired spatial memory [16,17]. Again, the hippocampus seems to be an important mediator. Stress-induced dendritic atrophy (or dendritic remodeling) in the hippocampus is one possible mechanism [18]. In contrast, stress- [19,20] or GC- treatment- [21] induced neuronal death appears to occur rarely or only under extreme conditions. However, additional or alternative mediators have to be kept in mind. Among those are reduced neurogenesis in the dentate gyrus and dysregulation of several catecholamine systems. Recent studies demonstrate substantial plasticity in the adult rodent brain. For example, stress-induced dendritic atrophy appears to be reversible [18]. Moreover, and very interesting from a clinical perspective, concurrent treatment of chronically stressed rats, as well as tree shrews, with antidepressants (e.g., tianeptin) or anticonvulsants (e.g., phenytoin) prevented the negative effects of chronic stress on the hippocampus [16,22,23].

Increases in HPA activity also occur in laboratory animals as a result of aging. Some studies have provided evidence that this enhanced HPA activity is associated with poorer spatial

memory. Elderly animals displaying memory deficits were characterized by enhanced HPA activity. In contrast, older animals showing no evidence for memory impairments displayed normal HPA activity [24]. Most interestingly, behavioral (handling) or pharmacological (adrenalectomy with GC replacement) interventions, leading to stable HPA activity throughout the animal's life, prevented age-associated cognitive decline [25,26]. Recently, the importance of local tissue GC concentrations has been illustrated by studies in 11β-HSD1 knockout mice. This enzyme converts inert GC forms into active corticosterone. While aged wild-type mice displayed HPA hyperactivity and cognitive decline, the knockout mice did not show memory impairments and had lower intrahippocampal corticosterone levels [27]. All these studies suggest that GC action in the hippocampus can in fact play a causal role in the occurrence of age-associated memory impairments.

Working (short-term) memory: acute & chronic effects

Working memory refers to the ability to shortly store and manipulate material. This concept has replaced the older notion of short-term memory and emphasizes the active processing capacity of this system. Neuroanatomically, this function has been linked to the PFC [5]. There are a substantial number of GRs in the PFC [28]. In contrast to the effects of GCs on the hippocampus, the effects on the PFC are, however, still less well characterized.

Roozendaal and colleagues also observed that GC treatment impaired short-term memory, as tested using a T-maze. Again, for this effect adrenergic arousal and an intact BLA appear to be prerequisites [9]. Similar impairing effects have been reported by other groups [29]. With respect to more chronic stress, structural alterations (e.g., dendritic atrophy) have been reported, which were reversible after discontinuation of the stress [30]. Reports of impairing effects of acute stress [31] or chronic GC treatment [32] have also been provided by studies with monkeys. For the acute fast-effects of stress on working memory, the dopaminergic system appears to play a key role [31].

Stress & the brain: sex differences in animal studies

Few authors have investigated possible sex differences in the effects of stress on the brain. However, in those still rare studies, quite substantial differences between the two sexes have been reported. Interestingly, the acute impairing effects of stress on spatial memory might only occur in males [29]. In parallel, substantial sex differences are observed at the morphological level. For example, stress suppresses neurogenesis in the hippocampus of male rats, while no such reduction occurs in females [33]. In addition, the negative effect of chronic stress on spatial memory might only occur in male rats [34]. Similarly, chronic stress-induced dendritic atrophy in the hippocampus is also restricted to male animals [35].

Strong sex differences have also been reported after acute stress for classical eyelid conditioning. However, the relationship here is opposite to that for spatial memory. Stressed female rats show impaired conditioning, while stressed males showed an enhancement. This was the case for delay as well as trace conditioning, with the latter depending on the hippocampus [8]. In the studies by Shors and colleagues, the stress-induced corticosterone increase was associated with changes in conditioning in male rats, but not in females [36]. This might suggest that the effects of stress on cognition in females are, at least in part, mediated by other neuroendocrine messengers (e.g., gonadal steroids or peptide hormones such as oxytocin). In summary, animal studies clearly indicate that sex differences exist when it comes to the effects of stress on the brain. These differences are task- and time-specific, so that global conclusions about one sex being more vulnerable than the other sex appear inappropriate.

Stress, memory & the brain: data from humans

Declarative long-term memory: acute effects

In humans, several placebo-controlled, double-blind studies have investigated the acute effects of GCs on declarative memory. Findings have been somewhat inconsistent, but this can be partly explained by the methods used and research designs. The author's group has recently conducted a meta-analysis in order to obtain a quantitative summary of the current state of the field. The results supported the model derived from animal studies (see previously [9]) showing that cortisol impaired memory retrieval [37]. This appears to be a robust effect, which has been replicated by several groups [38–41]. Similar observations have been made in humans (male subjects only in this study), who were exposed to a psychosocial laboratory stressor shortly before retrieval testing took place [42].

Recent work from the author's group has aimed to further characterize the impairing effect of cortisol on memory retrieval. It has been demonstrated that this effect is more pronounced for the retrieval of emotionally arousing material, independent of its valence (positive or negative) [42,43]. Moreover, in line with the animal findings that adrenergic activation is a prerequisite for the effects of cortisol, it was observed that subjects tested under a relaxed, nonarousing test situation were not influenced by cortisol [44]. This observation is supported by other recent studies suggesting that stress-induced cortisol elevations are also only associated with changes in memory when the subjects are still in the stress situation [45] or when they are emotionally aroused [46].

Beneficial effects on consolidation could not be clearly established using meta-analysis as of today, which in part might have reflected a power problem [37]. Some studies using emotionally arousing learning material and a long retention delay, assuring that GCs can influence consolidation and are back to baseline at the retrieval testing, observed enhanced memory consolidation. This beneficial effect was observed after oral cortisol pretreatment [47] or when subjects were stressed immediately after presentation of emotional and neutral slides [48]. In our own work, we observed that oral cortisol shortly before the presentation of arousing and neutral slides led to enhanced emotional memory facilitation. This occurred due to an impaired consolidation of neutral material paralleled by enhanced consolidation

of arousing material [49]. However, it should be acknowledged that some studies failed to find beneficial effects of cortisol on emotional memory consolidation [50,51], thus additional research is warranted.

Interestingly, the beneficial effects on consolidation, as well as the impairing effects on retrieval in humans, are more pronounced for emotionally arousing material (see above). This observation fits nicely with the mentioned animal observation that GCs can only exert effects on memory in the presence of adrenergic activity in the amygdala. This arousal can be the result of specifics of the learning material and/or specifics of the testing conditions [9].

In the above-mentioned meta-analysis, time of day appeared as a second modulatory factor. Studies that administered cortisol before initial acquisition observed impairing effects on memory when they were conducted in the morning, a time of high endogenous cortisol levels in humans. In contrast, studies in the evening were more likely to observe beneficial effects [37]. This supports the idea of an inverted U-shaped function between cortisol levels and memory in humans with too low as well as too high, levels at the time of acquisition being associated with impairments, especially when retrieval is tested at times when cortisol levels are still elevated [28,37].

In summary, studies in animals and humans converge on the idea that GCs acutely enhance memory consolidation of emotionally arousing material while impairing memory retrieval. In addition, within this framework, emotional arousal and a nonlinear dose–response relationship are important modulatory variables.

Cortisol also influences declarative memory consolidation during sleep. Here, the relationships appear to be different to those during daytime. Low cortisol levels during the first half of the night leading to a low GR occupancy appear to be a prerequisite for a sleep-induced enhancement of declarative memory consolidation [52]. Moreover, blocking the rise in cortisol levels, which typically occurs during the second part of the night, leads to enhanced emotional memory facilitation [53].

Declarative long-term memory: chronic effects

Experimental studies

In human experiments, studying the effects of chronic (weeks–months) long-term GC treatment is not possible due to ethical considerations. However, there are some studies that administered GCs (dexamethasone, prednisone or cortisol) for several (3–10) days. These studies observed specific declarative memory impairments or broader effects covering other cognitive domains such as working memory [54–56].

Glucocorticoid therapy

One population of special interest in this context is patients receiving GC therapy for medical reasons (e.g., asthma or rheumatic disease). Surprisingly enough, there are few studies on this topic. Nevertheless, several reports exist pinpointing cognitive deficits in this population, especially in the area of memory. Of course, these findings have to be interpreted with caution, since they are confounded with the underlying disease. In addition, in general the study design did not allow the differentiation between acute GC effects as a result of the last medication intake and chronic GC effects. It is currently unclear whether the negative effects on memory are reversible [57–60]. One recent study reported reduced hippocampal volumes in patients receiving GC therapy when compared with patients with minimal GC lifetime exposure [61]. However, a postmortem study observed no evidence for neuronal loss in a small sample of patients receiving GC therapy [62]. Clearly, this important area calls for additional research efforts. Longitudinal studies, carefully matching different treatment groups to disease type and severity, appear to be especially needed.

Cushing's disease

Cushing's disease patients are another interesting population for the investigation of the effects of chronically and substantially elevated endogenous cortisol levels on memory and the hippocampus. Pioneering work by Starkman and colleagues has documented that these patients have memory impairments [63] and hippocampal volume reductions [64]. The latter was inversely correlated with the cortisol levels of the patients. Recent work from this group and another group suggests that hippocampal atrophy is reversible once successful treatment has occurred [65,66]. This would be in line with the remaining plasticity of this structure observed in animal studies (see above).

Depression

A substantial portion of patients with depression show signs of HPA hyperactivity, which disappears after successful treatment. It has been postulated that this is either due to a central corticotropin-releasing factor hyperactivity and/or to a deficient negative feedback to a reduction of GRs in the hippocampus [67,68]. Some authors have suggested that HPA hyperactivity is characteristic of particular subgroups such as melancholic depression [69] or psychotic depression [70]. However, currently no consensus appears to exist on this issue. Several studies have reported that cortisol elevations are associated with cognitive deficits in these patients, but the results are inconsistent [71]. Hippocampal atrophy has been reported in several structural magnetic resonance imaging (MRI) studies with depressed patients (see [72,73] for recent meta-analyses). Moreover, some studies suggest that this volume reduction is associated with disease length or the recurrence of depressive episodes [74,75]. While these findings would be in line with the idea of a GC- or stress-induced hippocampal atrophy, studies linking these two processes are rare and results have been conflicting [76–78]. In the future, a better characterization and understanding of subtypes of this disorder will hopefully help to resolve the unclear empirical situation [69].

Post-traumatic stress disorder

Patients with post-traumatic stress disorder (PTSD) have been reported to show reduced basal cortisol levels, which is probably due to an enhanced negative feedback of the system [79]. The HPA situation in these patients is, therefore, different from

those occurring during GC therapy, Cushing's disease, aging or depression. Recent small-scale clinical studies have suggested that cortisol treatment shortly after the trauma might help to prevent PTSD [80]. Moreover, even patients with chronic PTSD appear to benefit from low-dose cortisol treatment as suggested by a placebo-controlled pilot study with three patients [81]. The cortisol-induced impaired emotional memory retrieval, in combination with an enhanced and more elaborate (place and time) reconsolidation, might help to reduce the core symptoms of PTSD. Moreover, higher cortisol levels during the second half of the night might reduce the sleep-associated facilitating effect of cortisol on emotional material, which could reduce the amount of nightmares [53]. The PTSD findings illustrate that too much, as well as too little, endogenous cortisol can be associated with distinct memory disturbances. Moreover, the small clinical studies suggest that cortisol might have interesting and so far underused psychopharmacological properties.

Aging

Subtle increases in cortisol levels occur during human aging. In particular, an increase in basal HPA activity during the nadir (first half of the night) has been reported in several studies [82]. In addition, pharmacological challenge studies observed a reduced negative feedback of healthy older subjects when compared with younger subjects [83–85].

Animal studies have suggested that enhanced HPA activity is associated with poorer memory and that behavioral or pharmacological studies, leading to stable HPA activity throughout life, prevent age-associated decline (see above). In older, otherwise healthy humans, several observational studies reported associations between elevated or rising cortisol levels and declarative memory impairments [86–89]. Whether these associations are specific for declarative memory or are, in fact, broader (also including working memory or attention) is debatable. Obviously, all of these human studies do not allow a clear cause–effect interpretation. In addition, the possible structural correlate of these hormone-performance associations remains to be firmly established. Here, the possible association between rising cortisol levels and atrophy of the hippocampus is still not sufficiently understood and the current empirical situation is heterogeneous. While two small studies observed a negative association between hippocampal volumes and basal cortisol levels [85,90], a larger study failed to find such an association [89].

Similar to the animal studies mentioned above, recent evidence provided by Yau and Seckl suggests that local GC metabolism might also be important for memory during human aging. mRNA of the enzyme 11β-HSD, which converts inactive into active GCs, is expressed in the human hippocampus and frontal cortex. A small pilot-study showed that the 11β-HSD inhibitor, carbenoxolone, improved some aspects of memory in older men, as well as in older patients with Type 2 diabetes [91]. In addition, underlining the importance of local GC metabolism is a study reporting that a genetic susceptibility for Alzheimer dementia could be linked to the gene encoding 11β-HSD [92].

Finally, even though the present chapter focuses on GCs and memory, it should be emphasized that other hormonal influences are important. With respect to aging, elevated cortisol levels are often part of the metabolic syndrome or part of several indices of chronic stress summarized within the allostatic load model [93]. Other aspects of these nonfavorable endocrine conditions are impaired glucose tolerance and hypertension. These alterations have also been associated with memory impairment and hippocampal atrophy during aging [94,95]. In fact, chronic stress, depression and Type 2 diabetes might exacerbate in a synergistic fashion the negative impact on the hippocampus. Future studies on the issue of HPA activity in aging should be aware of the fact that these changes most often do not occur in isolation and should obtain a broader endocrine assessment.

Working memory: acute & chronic effects

Similar to the situation in animals, the effects of GCs on PFC-mediated working memory have received less attention. Acute impairing effects on working memory have been reported in some studies in humans [28,96,97] but results have been somewhat inconsistent [42,43].

With respect to chronic effects, elevated basal GC levels have been associated in some studies with smaller volumes of some regions within the PFC (e.g., the anterior cingualte [85]). The PFC is, of course, not only involved in working memory but also in executive functions. These have received even less attention, thus additional research efforts are still needed.

Stress & the brain: sex differences in human studies

The area of sex differences on the effects of stress on the human brain has received little attention to date. For emotional memory and its neuronal correlates, sex differences have been reported. Differences in emotional memory lateralization and differences in the effects of adrenergic manipulations have been found [98]. In addition, some studies observed that psychosocial stress has different effects on memory or fear conditioning in men versus women [99–101]. In all three of these studies, stress-induced cortisol elevations or basal cortisol levels were more closely associated with changes in cognition in men – a finding in line with animal studies [36]. In contrast, exogenous cortisol application appears to influence declarative memory for women and men to a similar degree [38,39,41,102]. However, in one study, we observed a reduced effect in women taking oral contraceptives (OCs) [102]; whether this is caused by the action of the synthetic sex steroids in the brain and/or by the reduced endogenous sex steroids of OC users awaits investigation.

For more chronic GC studies and for studies examining associations between cortisol and cognition in aging or disease, no systematic sex differences have been observed or reported.

So, while there is some evidence for sex differences in the CNS effects of stress hormones in humans, this area does not receive the attention needed.

Expert commentary

Studies conducted within the last 10 years have substantially helped to better characterize the effects of GCs on brain function and structure. The scientific exchange and the close interaction of researchers working with animal models with researchers studying human volunteers or patients has resulted in a more differentiated understanding of the effects of stress on memory. Naturally, things have become more complex since over simplifications such as 'stress impairs memory' are no longer possible. Acutely, the stress-induced GC rise supports memory consolidation but, in parallel, impairs memory retrieval. The positive effect of stress on consolidation ensures that we remember well the most important information, thus enabling us to separate relevant from irrelevant issues. The negative effects of stress on retrieval might hinder us in performing well in a school or university exam or at an important job meeting. In addition, GCs also appear to reduce the amount of items storable in working memory, but this is less well documented than the effects on declarative long-term memory. Interestingly, there is now convincing evidence that for several acute effects of GCs on memory, adrenergic activation in the basolateral nucleus of the amygdale is a prerequisite. This activation can be induced either through the cognitive task itself, through the test situation (e.g., novel unfamiliar environment), or through the test material (e.g., emotional items). This interaction of the two stress systems (SNS and HPA) is important and opens up a new avenue for behavioral as well as pharmacological interventions.

Quite striking sex differences have been observed in several animal studies. The direction of the effect appears to be task specific. For example, in animals, acute stress enhances spatial memory but impairs classical eyelid conditioning in females while, for both tasks, the opposite is observed for male animals. In humans, this area is less well investigated. Since not only sex, but also phase of the menstrual cycle and intake of synthetic hormones as a way of contraception or postmenopausal hormone replacement, could influence the effects of stress hormones on the brain, studies on sex differences in humans require large subject numbers. However, this should not be accepted as a continuous excuse to only study men, thereby ignoring 50% of the population.

Chronic stress or chronic GC treatment by and large has negative effects on the brain as well as on the body. These observations are relevant to psychiatric disorders, as well as to the aging process. It is very difficult and time consuming to study these relationships in the human, so the current empirical situation still relies on mostly small cross-sectional studies. While most of these suggest that chronically elevated GC levels have a negative impact on the brain, it is encouraging that recent research has observed evidence for preserved functional and structural plasticity once the stress has ceased or GCs are back to normal levels. Moreover, several pharmacological interventions have been proven successful in animal models and await clinical trials in human patients.

Five-year view

Neuroimaging

Animal studies have used site-specific lesions as well as site-specific injections in order to demonstrate the brain regions important for the modulatory actions of GCs on memory. While these approaches cannot be applied to human volunteers, advances in the field of functional imaging (positron emission tomography [PET] or functional MRI) allow for a localization of hormone effects on the brain. Currently, only one study has investigated the effects of cortisol administration on memory retrieval with PET [40]. More studies will be published aiming at characterizing *in vivo* the neuronal circuits influenced by the hormone or by stress. Those studies will help to bridge the gap between the detailed neuroanatomical knowledge obtained in studies with rodents and the behavioral findings obtained in humans, which only indirectly allow a speculation about the involved brain structures.

With respect to more chronic effects, longitudinal studies will be conducted. These will, in addition to volumentric measures, also incorporate new imaging techniques such as diffusion tensor imaging. So, in addition to information about the volume of a specific structure, information about the connectivity of this structure will also be available. The combination of different imaging techniques will provide a more elaborate view of the impacts of stress hormones on the human brain.

Individual differences

One of the most striking observations when it comes to stress is the substantial presence of interindividual differences. While some advances have been made to explain interindividual differences in the endocrine stress response, little effort has been made to characterize differences in the response of the brain to stress or stress hormones. Such differences might be able to account for the variance observed within, as well as between, studies. Individual differences could reflect genetic factors [92], but could also be related to pre- or postnatal influences or differences in lifetime cortisol exposure [103]. Attempts to characterize subgroups with high versus low cortisol sensitivity will be one important goal for the next 5 years. Individuals with high CNS GC sensitivity might be at a higher risk for stress-associated psychiatric diseases and might respond with more negative side effects (e.g., steroid dementia) to GC therapy.

One aspect closely related to individual differences is the issue of sex differences. More knowledge will be presented, which, in the long run, will help us to understand sex differences in stress-associated disorders. Future studies will better characterize whether these sex differences are related to differences in the neuroendocrine stress response or differences in the response of the brain to endocrine stress messengers. Moreover, it will become more apparent whether these effects are the result of organizational effects of gonadal steroids (estradiol, progesterone and testosterone) *in utero* or early in life, or whether these effects are mediated by the current

activational action of gonadal steroids. Based on the preliminary data obtained in humans and the impressive results from animal models, it can be predicted that sex differences will be different for different memory types as well as for different memory phases.

Pharmacological & clinical perspectives

Animal studies have demonstrated multiple ways to modulate the effects of stress hormones on the brain. For example, acute β-blocker treatment abolished the effects of GCs on memory consolidation, as well as on retrieval. Similar studies will be conducted in human experimental studies. These observations could be the basis for more hypothesis-driven studies in psychiatric disorders. Beneficial effects of cortisol have been documented in the context of PTSD. Future studies will investigate whether cortisol might also display beneficial effects in the context of anxiety disorders.

Chronically elevated GCs influence brain function and structure in several psychiatric or endocrine diseases, as well as during the aging process. More longitudinal studies will be conducted and published on this important topic in the next few years. Ideally, such studies would combine a careful and broad endocrine evaluation with a neuropsychological test battery and structural and functional imaging data. The knowledge gained from these studies will ultimately lead to pharmacological or behavioral interventions aiming to protect the brain from some of the negative impact of chronically elevated GC levels. The recent report of beneficial effects of the 11β-HSD inhibitor carbenoxolone on the memory of older subjects demonstrates the promise of these kind of interventions [91]. These developments will hopefully also influence the pharmaceutical industry to pay more attention to the brain as a location of negative GC side effects. This could lead to novel medications that preserve the beneficial effects of the currently used GCs, but reduce or abolish the negative effects on mood and memory.

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Key issues

- Acutely, glucocorticoids (GCs) have positive, as well as negative, effects on memory.
- GCs enhance emotional long-term memory consolidation, while in parallel impairing long-term memory retrieval.
- GCs interact with adrenergic activation in the amygdala in order to modulate other brain regions (e.g., the hippocampus and the prefrontal cortex).
- Chronically elevated GC levels are associated with memory impairments, a finding of relevance for GC therapy, Cushing's disease, depressive disorder and normal aging.
- An insufficient stress response might increase the risk for the occurrence of post-traumatic stress disorder (PTSD). Small placebo controlled studies have suggested that GC treatment might help to prevent or treat PTSD.
- In the face of chronic stress or chronic GC treatment, recent findings suggest that functional and structural plasticity of the brain is often preserved.
- Novel treatment options for several diseases characterized by hypothalamic–pituitary–adrenal axis abnormalities are on the horizon.

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