Stress, glucocorticoids and memory: implications for treating fear-related disorders

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Abstract | Glucocorticoid stress hormones are crucially involved in modulating mnemonic processing of emotionally arousing experiences. They enhance the consolidation of new memories, including those that extinguish older memories, but impair the retrieval of information stored in long-term memory. As strong aversive memories lie at the core of several fear-related disorders, including post-traumatic stress disorder and phobias, the memory-modulating properties of glucocorticoids have recently become of considerable translational interest. Clinical trials have provided the first evidence that glucocorticoid-based pharmacotherapies aimed at attenuating aversive memories might be helpful in the treatment of fear-related disorders. Here, we review important advances in the understanding of how glucocorticoids mediate stress effects on memory processes, and discuss the translational potential of these new conceptual insights.

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Stressful encounters lead to orchestrated signalling by various hormones, peptides and neurotransmitters in both the periphery and the brain[1]. These stress mediators not only prepare an individual for the acute consequences of a dangerous or threatening situation but also induce long-term adaptive responses, including influences on learning and memory[2]. Notably, stressful and emotionally arousing events are typically remembered better and more vividly than mundane events[3]. By contrast, memory retrieval can be hampered by stress[4].

Animal research into the neurobiological mechanisms underlying these phenomena has revealed that glucocorticoid hormones that are released in response to stressful experiences play a central part in mediating the modulatory effects of stress on both the consolidation and the retrieval of memory[5–7]. Furthermore, precisely timed interactions of glucocorticoids with arousal-associated noradrenergic signalling in the brain render emotionally arousing information particularly sensitive to the modulatory effects of glucocorticoids[4]. Studies in healthy humans have confirmed the importance of glucocorticoids in emotional memory processes[4,8,9].

The tight regulation of emotional memories is usually considered to be highly adaptive and pivotal for survival[3,4]. However, the compelling evidence that aberrant processing of emotionally aversive memories lies at the core of several fear-related disorders, including post-traumatic stress disorder (PTSD) and phobias (BOX 1), has recently stimulated a wealth of clinical investigations specifically aimed at understanding the role of glucocorticoid signalling mechanisms in the pathogenesis, symptomatology and treatment of these disorders.

The current treatment options for fear-related disorders mainly consist of psychotherapy and/or anxiety-reducing and antidepressant medications. Psychotherapeutic interventions have had some success, especially in phobias, but not all patients respond adequately to the treatment, and the return of fear in treated patients is a well-known problem[10]. Pharmacological first-line treatments for phobias usually include drugs with anxiolytic actions (such as benzodiazepines), whereas drugs with antidepressant actions (such as serotonin- or other monoamine-reuptake inhibitors) tend to be used for phobias and PTSD[11]. However, many patients who are treated with such anxiolytic or antidepressant drugs continue to have symptoms[12]. Of note, such pharmacotherapies are primarily aimed at alleviating chronic stress and anxiety symptoms[13] and fail to tackle the underlying aversive-memory trace[14]. Therefore, new approaches are urgently needed.

In recent years, the idea to target memory processes relevant to fear-related disorders has received lots of attention (BOX 2). This idea is further bolstered by evidence from neuroimaging studies that indicate a large overlap between the neural substrates of fear-related disorders and those of emotional memory processes[15]. One proposed strategy to target memory processes in order to prevent PTSD is to pharmacologically reduce the initial memory consolidation of aversive events, for example, by using opioids[16] or β-adrenergic receptor blockers[17]. In established

Box 1 | **The role of memory in fear-related disorders**

Memory functions have important roles in the pathogenesis, symptomatology and treatment of fear-related disorders such as post-traumatic stress disorder (PTSD) and phobias.

Pathogenesis

After experiencing an aversive event, the formation of an excessively strong aversive-memory trace is an important pathogenic mechanism in the development of fear-related disorders[159–163]. A central mechanism in the pathogenesis of anxiety disorders is associative learning or conditioning, which can lead to both conscious and unconscious aversive memories[164]. Animal models and human studies have shown that the amygdala has a central role in the modulation of memory by emotion[5,165]. More specifically, neuroimaging studies have shown that, compared with controls, patients with PTSD or phobias show enhanced amygdala activity in response to aversive stimuli and that this increase in amygdala activity correlates with subsequent recall of aversive memory and symptom severity[166–171].

Symptomatology

Activation of an aversive-memory trace — often induced by a reminder cue — leads to the expression of fear in animal models and in patients[172,173]. The symptoms of PTSD include aversive-memory retrieval in which components of the event are relived in the form of intrusive daytime recollections, traumatic nightmares and flashbacks[122]. The symptoms of phobic disorders include fear that is excessive or unreasonable.

Treatment

Behavioural therapy of fear-related disorders is based on the extinction of fear responses, which in turn depends on the formation of a non-fearful extinction memory[174–177]. However, patients suffering from chronic fear often show a reduced capacity for proper fear extinction[15,18]. A different approach to treat fear-related disorders aims at disrupting the aversive-memory trace by interfering (for example, using β-adrenergic receptor blockers) with reconsolidation after memory reactivation[15,178].

fear-related disorders, a different approach could be to reduce the excessive retrieval of aversive memories, thereby reducing the severity and/or frequency of symptoms such as intrusions and nightmares. A third approach would be to aid the extinction of the traumatic-memory trace (a process that is often impaired in patients with fear-related disorders)[18]. A promising novel strategy to achieve this is combining drug treatment (for example, the partial glutamate agonist D-cycloserine[19]) with exposure therapy in a timed manner to enhance extinction and improve the long-term outcome of exposure therapy. A fourth strategy is the use of pharmacological agents such as β-adrenergic receptor blockers[20] at the time of reactivation of the aversive-memory trace to interfere with reconsolidation of the traumatic memory.

In this Review, we argue that glucocorticoid-related interventions are of special interest in the clinical context because, unlike most other memory-modifying drugs, they can affect distinct memory processes that can synergistically contribute to a reduction of fear-related symptoms; for example, by both reducing aversive-memory retrieval and enhancing fear extinction (BOX 2). The current Review includes an integrative discussion of important recent advances in the understanding of stress and glucocorticoid effects on memory, including the involvement of endocannabinoid signalling, the role of multiple memory systems, and epigenetic and genetic findings, and discusses the translational implications of these new conceptual insights, in particular for the treatment of fear-related disorders.

Post-traumatic stress disorder
(PTSD). A disorder that can occur after the exposure to a traumatic event; it includes symptoms of intrusion, avoidance, negative alterations in cognition and mood, and alterations in arousal and reactivity.

Phobias
Anxiety disorders that are characterized by intense fear or anxiety that is circumscribed to the presence or anticipation of a particular object or situation.

Stress, glucocorticoids and memory

Stress activates the hypothalamus–pituitary–adrenal (HPA) axis, which leads to the release of glucocorticoid hormones (mainly cortisol in humans and corticosterone in rodents) from the adrenal cortex. These hormones can access the brain easily and, once there, bind to mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs)[5,21,22] to exert both rapid, non-genomic and slow, genomic actions on physiology and behaviour[23]. GRs are highly ubiquitous and expressed in most brain regions, whereas MRs are predominantly expressed in limbic regions such as the hippocampus and central amygdala[24]. GR activation has been linked to adaptive processes such as memory consolidation, whereas MR-mediated effects have been associated with the appraisal and responsiveness to stressful experiences and with the negative feedback control of the HPA axis[24].

Early reports that acute stress or glucocorticoids can have both deleterious and enhancing effects on memory have indicated that these hormones have complex effects on cognitive functions. Two decades of research have identified that these stress hormones can have opposite effects on different memory processes, including consolidation, retrieval, extinction and reconsolidation[4,8] (BOX 2). Most of these specific stress-hormone effects have been investigated in conditions with acute elevations of glucocorticoid levels. Although chronic stress differs in many aspects from acute stress (for example, unlike acute stress, chronic stress induces dendritic remodelling at the cellular level[21]), acute administration of glucocorticoids can have similar effects on memory processes in both acute and chronic stress conditions. For example, comparable to the memory effects in acute conditions, glucocorticoid administration reduces recall of trauma-related memory in PTSD and enhances fear extinction in people with PTSD and phobias (which are chronic stress conditions)[4]. Furthermore, the effects of acute glucocorticoid administration on memory retrieval are also observed in patients who have chronically elevated glucocorticoid levels as a result of medication[25]. In this section, we discuss acute glucocorticoid effects on different memory processes, the importance of timing of glucocorticoid administration, and the impact of stress and glucocorticoids on multiple, often competing, memory systems.

Consolidation. Memory consolidation refers to a molecular process by which a short-term memory trace is transferred into stable long-term memory[26]. From looking back into one's own past, it quickly becomes clear that not all information is equally well transferred into long-term memory. In particular, emotionally arousing (pleasant or unpleasant) life events are remembered better than neutral events, even after a long period of time[3].

Animal model and human studies provide compelling evidence that glucocorticoids are important in regulating the consolidation of memory processes[27] (FIG. 1). Administration of the glucocorticoid-synthesis inhibitor metyrapone to rats or humans prevents the enhancing effects of stress and emotional arousal on memory consolidation[28,29]. By contrast, glucocorticoids or synthetic GR ligands such as dexamethasone[30,31] administered

Box 2 | **Glucocorticoid effects on memory processes**

Memory involves several distinct processes that can be differentially affected by a specific intervention. Here, we elaborate on the memory processes that are most relevant for fear-related disorders — consolidation, retrieval, extinction and reconsolidation — and explain how these processes are affected by glucocorticoids.

Consolidation

Consolidation is a protein synthesis-dependent molecular process by which a short-term memory trace is transferred into stable long-term memory[26,179]. Depending on the form of memory (for example, episodic memory or habitual memory), memory consolidation takes place in partly different brain regions[180]. Consolidation plays an important part in the pathogenesis of fear-related disorders by stabilizing aversive memories after an aversive event[159–163]. Glucocorticoids enhance memory consolidation for emotionally arousing information in a dose-dependent manner[27,33], and this effect depends on the concomitant activation of the noradrenergic system[2]. High doses of glucocorticoids without noradrenergic activation can impair memory[32].

Retrieval

Retrieval is the process of recollecting previously stored information. Depending on the form of memory (for example, episodic memory or habitual memory), different brain regions can be involved in this process[180]. Retrieval of aversive memories can lead to experiencing fear, which is the core symptom of fear-related disorders. Elevated glucocorticoid levels impair memory retrieval[4,7] and can thereby contribute, for example, to the well-known phenomenon of impaired memory recall in stressful situations[4]. In addition, the effect of glucocorticoids on retrieval depends on the concomitant activation of the noradrenergic system[4,9].

Extinction

Extinction is the process during which conditioned responses to a stimulus that was previously paired with an aversive event diminish if the stimulus is presented repeatedly without the aversive event[63,181]. After successful extinction, the newly formed extinction memory competes against, but does not erase, the original memory of the aversive event. Spontaneous recovery (that is, the reappearance of a previously extinguished conditioned response after a delay) is often observed after extinction. Extinction is the process underlying exposure-based psychotherapy of fear-related disorders[174–177]. Newly formed extinction memories undergo consolidation, which is facilitated by glucocorticoids[65–68].

Reconsolidation

Reconsolidation is the process during which memories that have been rendered labile after memory reactivation are stabilized anew[71]. The molecular mechanisms of reconsolidation and initial consolidation seem to be at least partly distinct[74]. A blockade of reconsolidation leads to an erasure of the original memory; spontaneous recovery is not observed[71]. Reconsolidation may be a process vulnerable to interference in order to alter aversive memories in fear-related disorders[73]. Reconsolidation depends on intact glucocorticoid signalling; the administration of glucocorticoid receptor antagonists after reactivation disrupts reconsolidation[78,79].

either shortly before or immediately after training in emotionally arousing learning tasks enhance long-term memory consolidation in rats and humans (reviewed in REFS 4,9). Importantly, the memory-enhancing effects of pharmacologically administered glucocorticoids or GR agonists follow an inverted U-shaped dose–response relationship. Moderate doses enhance memory, whereas lower or higher doses are typically less effective or impair memory consolidation[32,33].

Furthermore, several studies have found that stress effects on memory consolidation are more pronounced in men than in women[33–35]. Some studies have proposed that there might be an interaction between stress effects and sex hormones; in particular, oral contraceptives can lead to a blunted HPA-axis response to stress and thereby reduce stress effects on memory[34,35]. In line with this idea, no sex differences in memory effects were reported among people acutely dosed with exogenous cortisol[36].

The enhancing effects of glucocorticoids on memory consolidation are dependent on the arousal-induced activation of noradrenergic transmission in the amygdala, particularly the basolateral amygdala, as well as on interactions of the amygdala with other regions, including the hippocampus and cortex[2]. For example, animal model studies have shown that a β-adrenergic receptor antagonist administered systemically or directly into the basolateral amygdala blocks glucocorticoid effects on memory consolidation for an emotionally arousing training experience[6,37]. Further, post-training glucocorticoid administration does not enhance retention of training experiences (for example, object recognition) that induce relatively low emotional arousal. However, with such low-arousing conditions, administration of yohimbine, a drug that stimulates noradrenaline release, enables glucocorticoid-induced memory enhancement[37]. In line with this, studies in humans showed that administered glucocorticoids require emotional arousal and noradrenergic activation (measured via salivary α-amylase) at encoding to enhance long-term memory for emotional material[38,39]. By contrast, glucocorticoids impair or have little effect on memory consolidation of emotionally neutral information in humans[36,38,39].

Glucocorticoids enhance memory consolidation and synaptic plasticity by influencing various cellular functions, including intra- and inter-cell signalling, ion channel properties and cell structure[40–42]. It has long been recognized that glucocorticoids primarily exert their effects on neuronal function through their ability to affect gene transcription; glucocorticoid-bound GR homodimers can bind directly to glucocorticoid response-elements on DNA[43]. However, recent evidence indicates that glucocorticoids also have various non-genomic actions on neuroplasticity and memory, through their interactions with a membrane-associated variant (or variants) of the steroid receptor[44–48]. Activation of these membrane steroid receptors results in effects such as rapid increases in glutamate-release probability from presynaptic sites[49] and rapid insertion of AMPA-receptor subunits into postsynaptic membranes[50,51]. Glucocorticoids and noradrenaline signalling mechanisms might act synergistically to rapidly enhance AMPA-receptor function[52] and to influence several other molecular events — for example, such interactions may induce rapid activation of the transcription factor cyclic AMP-responsive element-binding protein (CREB) and promote associated epigenetic mechanisms such as histone acetylation[47,53]. Recent findings indicate that the actions of glucocorticoids on memory also involve intriguing rapid signalling interactions with the endocannabinoid system[54] that can enhance noradrenergic transmission in the amygdala and other brain regions (BOX 3).

Retrieval. Memory retrieval is the process of recollecting previously stored information. In contrast to the enhancing effects of glucocorticoids on memory consolidation, several studies have indicated that stress exposure or glucocorticoid administration to rats or mice shortly before retention testing impairs the retrieval of inhibitory

avoidance memory, contextual fear-conditioned memory or spatial memory acquired 24 hours earlier[7] (FIG. 1). Such rapid glucocorticoid effects on memory retrieval selectively depend on the membrane GR[55] and are mediated via non-genomic actions[56].

These findings from animal models have now been translated to healthy humans: a single administration of cortisone (at a dose resulting in high physiological cortisol levels) 1 hour before retention testing impaired the recall of words learned 24 hours earlier[57]. Further studies demonstrated that glucocorticoids impair the retrieval of hippocampus-dependent spatial or contextual memory in rodents and of declarative memory in humans (reviewed in REFS 4,9). Importantly, another study has shown that cortisone impairs the retrieval of emotionally arousing words but leaves the retrieval of neutral words unaffected[58]. Thus, similar to memory consolidation, the retrieval of emotionally arousing information is also particularly sensitive to impairment by glucocorticoids[58,59].

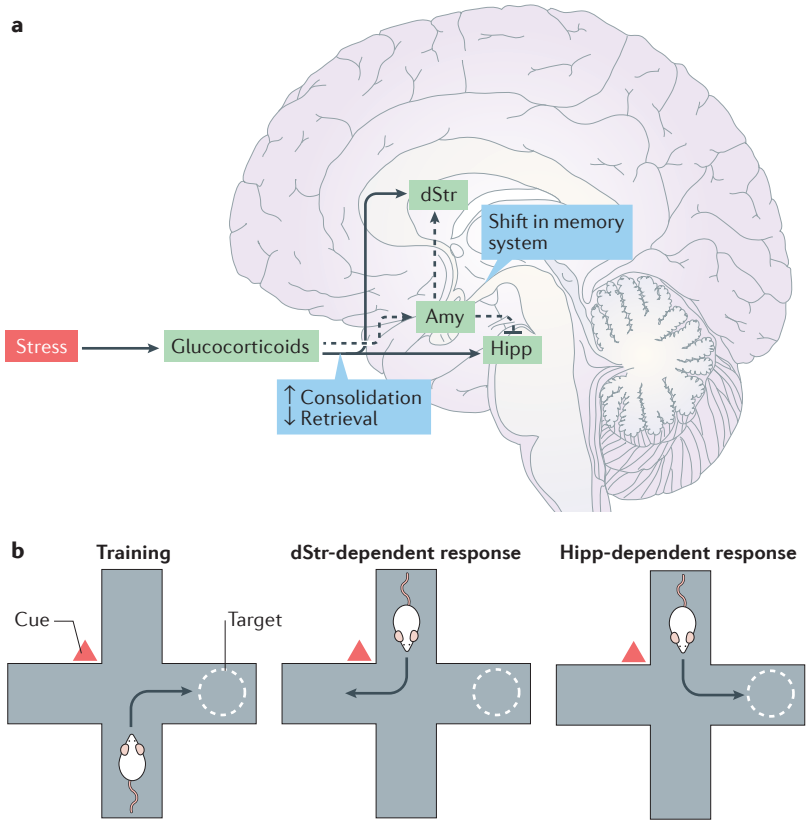


Figure 1 | **Glucocorticoid effects on different memory systems under stress.** **a** | Stress acts through the hypothalamus–pituitary–adrenal axis to stimulate the release of glucocorticoids. These in turn enhance memory consolidation and impair memory retrieval. In addition, stress promotes a shift from a hippocampus (Hipp)-dependent, 'cognitive' memory system to a dorsal striatum (dStr)-dependent, 'habitual' memory system. Such a shift, which is thought to be orchestrated by the amygdala (Amy), is often observed in stress- and fear-related disorders. **b** | The schematics show an example of a test of dStr- and Hipp-dependent memory retrieval. The animal is trained in a plus maze that contains spatial cues to turn right to the target (left panel). When tested from another part of the maze (middle and right panels), the animal can either use a dStr-dependent, habitual strategy ('turn right'), or a Hipp-dependent, cognitive strategy (using the cues to navigate to the target).

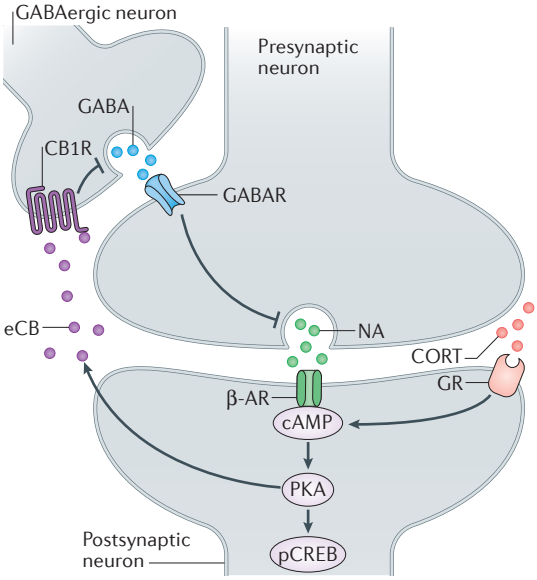
Moreover, as with the effects on memory consolidation, the effects of glucocorticoids on memory retrieval are also abolished by a β-adrenergic receptor antagonist[58,60]. The influence of glucocorticoid–noradrenergic interactions on memory retrieval was further shown to also depend on the endocannabinoid system[61] (BOX 3). Also comparable to memory consolidation, glucocorticoid effects on memory retrieval seem to be more prominent in men than in women who use oral contraceptives[62], suggesting possible interactions with sex hormones.

Extinction and reconsolidation. Extinction is a process in which conditioned responses to a stimulus that was previously paired with an aversive event diminish if the stimulus is presented repeatedly without the aversive event[63]. Like other forms of learning, extinction learning is followed by a consolidation phase. Whereas the consolidation of extinction memory and that of new memory show partially distinct molecular and neuroanatomical profiles[64] (for example, the prefrontal cortex has a different role in these two types of memory), glucocorticoids seem to have a similar role in both. Specifically, animal models have shown that consolidation of extinction memory is facilitated by the administration of exogenous glucocorticoids[65–68] but impaired by suppression of glucocorticoid signalling[65,67–70]. More specifically, glucocorticoids are involved in the extinction of several types of fear memory, including auditory fear conditioning[65], contextual fear conditioning[66,68] and fear-potentiated startle[67], and in the predator stress paradigm[70].

Memories that are already consolidated may be targeted in two distinct ways: by enhancing extinction, which depends on the formation of a new memory trace that competes with the original fear memory, or by inhibiting reconsolidation of the original fear memory when it is rendered labile during reactivation in order to diminish or erase the memory[71]. During reconsolidation, reactivated memories are again susceptible to various amnesic agents[72]. Thus, reconsolidation may provide a window of opportunity to alter established, unwanted memories retrospectively, with notable implications for fear-related disorders[73].

Although the mechanisms of initial memory consolidation and post-reactivation reconsolidation seem to be at least partly distinct[74], in particular with respect to the recruited brain circuits and the temporal profiles, several studies showed that stress hormones are also important in memory reconsolidation. How acute stress affects reconsolidation is debated; some studies show that stressful events after memory reactivation enhance reconsolidation, whereas other reports show the opposite effect[75–77]. However, animal model studies of the effects of glucocorticoids have shown that systemic or intrahippocampal administration of a GR antagonist after reactivation interferes with the reconsolidation process[78,79]. Administration of a GR agonist after reactivation also impairs 24-hour recall, but this effect is more likely to be due to increased memory extinction than to reduced reconsolidation[66,80]. Evidence for this comes from a study in rats that examined the persistence of the deleterious effect of post-retrieval glucocorticoids

Box 3 | **Glucocorticoid interactions with the endocannabinoid system**



Growing evidence indicates that the effects of glucocorticoids on both the consolidation and the retrieval of memory depend on interactions with the endocannabinoid (eCB) system[54]: a fast-acting retrograde messenger system in the brain. eCBs (mainly anandamide and 2-arachidonoyl glycerol) are released from postsynaptic membranes and feed back in a retrograde manner onto either glutamatergic or GABAergic presynaptic terminals, thus suppressing both excitatory and inhibitory signalling within specific neuronal circuits[182]. Recently, the eCB system has emerged as a key modulator of the stress response[183,184], emotional regulation[185] and memory functions[54,186].

Emotionally arousing training conditions or systemic glucocorticoid (specifically, corticosterone; CORT in the figure) administration to rats induce rapid release of eCBs in limbic regions including the amygdala and hippocampus[187,188]. Blockade of cannabinoid type 1 receptors (CB1Rs) in these brain regions prevents the enhancement of memory consolidation that is triggered by administration of exogenous glucocorticoids[54,188,189], indicating that this stimulated eCB signalling is involved in mediating glucocorticoid effects on memory consolidation. Consistent with the view that glucocorticoid-induced release of eCBs is rapid, other recent findings indicate that glucocorticoid–eCB interactions depend on a membrane glucocorticoid receptor (GR)[188]. Glucocorticoid-induced recruitment of eCB signalling might then enhance memory consolidation by modulating GABAergic or glutamatergic signalling. In the amygdala, GABAergic interneurons are particularly enriched for CB1Rs[190], and activation of these receptors inhibits GABA release[190,191]. These findings suggest that glucocorticoids might bind to a membrane GR and rapidly induce the release of eCBs, which then bind to CB1Rs on GABAergic interneurons to inhibit GABA release[192], in turn possibly resulting in a disinhibited release of noradrenaline (NA) in the amygdala (see the figure). Other recent findings indicate that glucocorticoid–eCB interactions also play a part in other memory processes. For example, blockade of CB1Rs in the hippocampus prevented glucocorticoid-induced impairment of the retrieval of contextual fear memory[61].

Interestingly, two studies have suggested that a polymorphism (rs1049353) of the gene encoding CB1R (*CNR1*) is associated with post-traumatic stress disorder (PTSD) risk[193,194]. Furthermore, stimulation of CB1Rs promotes memory extinction (reviewed in REF. 195), and initial clinical evidence suggests that cannabinoids might be useful in the treatment of PTSD[196,197]. Thus, there is independent evidence implicating the glucocorticoid and eCB systems in extinction and suggesting that targeting these systems may potentially be useful in the treatment of PTSD.

Notably, the evidence discussed above indicates that considering both these interacting systems together might bear substantial clinical potential. Indeed, changes in both systems have been described in PTSD[122,198]. Most importantly, the combined analysis of eCB and glucocorticoid markers has a higher predictive value for classifying PTSD than does individual analysis[198]. Therefore, combined targeting of glucocorticoid and cannabinoid signalling might be promising and should be explored in animal and human models of fear learning and extinction to inform future clinical studies[195].

β-AR, β-adrenergic receptor; cAMP, cyclic AMP; GABAR, GABA receptor; pCREB, phosphorylated cAMP-responsive element-binding protein; PKA, protein kinase A.

on recall, to determine whether there was a deficit in the underlying stability of the memory trace[66]. Whereas post-reactivation administration of either glucocorticoids or anisomycin impaired memory recall tested 24 hours later, only rats treated with anisomycin still showed an impairment when tested 72 hours later. Because memory impairment after successful blockage of reconsolidation is permanent, but spontaneous recovery is typically observed after extinction[4], the relative transience of the effect of glucocorticoids suggests that they affect extinction rather than reconsolidation. It has been shown in humans that administration of cortisol immediately after reactivation enhances reconsolidation in men[81] but not in women[82]. Because of potentially important clinical implications, further studies are needed to corroborate possible sex differences with regard to glucocorticoid effects on reconsolidation.

Timing matters. The evidence indicating that the enhancement of memory consolidation of emotionally arousing information depends on the interaction between glucocorticoids and noradrenergic activation suggests that these events must occur in a precisely timed manner[22,83]. Within seconds of the onset of a stressful encounter, acute increases in catecholamines in the brain recruit a so-called salience network that facilitates vigilance and attention[84]. In humans, this network includes the amygdala, the anterior insula and the dorsal anterior cingulate cortex[84]. Noradrenaline is further known to facilitate synaptic plasticity in the hippocampus[85] and thus contributes to enhanced memory for the stressful episode both in rodents and in humans[86,87]. With time after stressor onset, glucocorticoid levels increase and exert rapid, non-genomic actions. These fast glucocorticoid actions, in combination with catecholamines, help to

Retrograde messenger
A chemical substance that is released from postsynaptic neurons and acts on presynaptic neurons to regulate neurotransmitter release.

Anisomycin
An antibiotic that prevents the synthesis of proteins.

Spontaneous recovery
The reappearance of a previously extinguished conditioned response after a delay.

increase glutamate transmission[50] and strengthen memories of the stressful experience[26]. As soon as glucocorticoid levels are elevated (typically within 15–30 minutes of stressor onset), retrieval processes are impaired[7,88], possibly to avoid interference and protect the consolidation of the stressful event. At longer delays (longer than ~1 hour) after the onset of a stressful event, genomic glucocorticoid actions manifest that are thought to hamper the encoding of new experiences and memory retrieval processes[89,90].

In line with the view that glucocorticoids have biphasic timing-dependent effects on memory formation, glucocorticoids facilitate synaptic potentiation in the rodent hippocampus when administered immediately before tetanic stimulation[91] but not when administered about 1 hour before stimulation[92]. Acute stress or glucocorticoids enhance memory consolidation only when synchronized with an increase of noradrenaline[37,83]; mistiming of glucocorticoid elevations with respect to noradrenaline release suppresses the effects of noradrenaline, preventing glucocorticoid–noradrenaline synergy[83]. For instance, cortisol administered alone more than 1 hour before imaging human brain responses to neutral or negative stimuli reduced amygdala and hippocampal activity[93,94], possibly pointing to an increased threshold for information processing.

In sum, acute stress or glucocorticoid exposure around the time of learning seems to facilitate memory consolidation processes, whereas such exposure out of the learning context impairs memory consolidation and the retrieval of previously encoded memories[8,22]. This information is crucial to consider when designing clinical drug trials: after defining which memory phase (or phases) should be targeted by glucocorticoid-based interventions, drug administration has to be well timed to get the desired effect and not the opposite.

Multiple memory systems: beyond the hippocampus. For decades, research on the impact of stress and stress hormones on memory focused mainly on the hippocampus, presumably because it expresses MRs and GRs at a high density and is thus thought to be highly stress sensitive. However, more recent research has demonstrated that stress and glucocorticoids may also affect memory processes in other brain regions — for example, in the insula (to affect object recognition[47], taste aversion[95] and inhibitory avoidance memory[96]) or in the dorsal striatum, which acquires habits or stimulus–response (S–R) associations[97]. Importantly, glucocorticoid actions in these brain regions were shown to depend on concurrent noradrenergic activity within the amygdala[2], supporting the view that stress effects on learning and memory involve the recruitment of large-scale neural networks[98].

Learning and memory can be supported by anatomically and functionally distinct systems that operate in parallel[99] and may be in competition with one another[100]. Stress seems to induce a shift in the memory system that dominates learning and behaviour (reviewed in REFS 101–103). Specifically, converging lines of evidence from human and animal model studies using dual-solution navigation tasks that could be solved by either a hippocampus-dependent spatial system or a dorsal striatum-dependent S–R system showed that stress promotes a switch from hippocampal 'cognitive' to dorsal striatal 'habitual' (or S–R) learning[104,105] (FIG. 1). Importantly, this stress-induced shift was blocked by the administration of an MR antagonist in mice and humans[106,107], thus demonstrating a crucial role of glucocorticoids[108].

Moreover, acute stress decreases functional connectivity between the amygdala and the hippocampus but increases functional connectivity between the amygdala and the dorsal striatum, suggesting that the amygdala orchestrates the shift from cognitive to habitual memory systems[107,108]. In line with the stress-induced bias towards S–R learning, stress promotes habitual responding at the expense of prefrontal cortex-dependent goal-directed instrumental actions both in humans and in rodents[109,110]. Interestingly, in humans, the impact of stress on the control of instrumental learning, like stress effects on consolidation and retrieval, depends on an interaction between glucocorticoids and noradrenergic activation[111–113].

The stress-induced shift from cognitive to habitual learning also has important implications for our understanding of fear-related disorders. Whereas the cognitive memory system has been shown to be involved in fear-related disorders, for example by reactivating contextual fear memories[114], there is accumulating evidence that the habitual memory system also has an important role. In PTSD, experiences are encoded under extreme stress, and the basic findings referred to above suggest that this might lead to a preferential engagement of habitual systems[101]. Furthermore, dorsal striatal activity is often observed when patients with PTSD are asked to re-imagine their trauma[115]. The strong response of patients with PTSD to single, trauma-related cues (such as odours or tones), and their difficulties to integrate the traumatic experience into their autobiographic memory (as reflected, for example, in a lack of episodic details), might be taken as indications of an aberrant recruitment of habitual S–R memory processes.

Thus, an important question is whether glucocorticoids influence habitual memory systems as well. Indeed, similar to the effects on hippocampus-dependent memory, stress or glucocorticoids administered systemically in humans or directly into the rodent dorsal striatum shortly before or after training on an S–R or inhibitory avoidance task enhance subsequent memory[116–118]. Further, stress or glucocorticoids before retention testing impair S–R memory retrieval both in humans and rodents[118,119]. In rodents, the stress-induced deficit in S–R memory retrieval, reflected in more errors, was blocked by the glucocorticoid-synthesis inhibitor metyrapone and could be mimicked by corticosterone injection[119]. Thus, glucocorticoids are implicated in the consolidation and retrieval of S-R memory. Although individuals tend to switch from cognitive to habit memory processes when stressed[108], these habitual memories can also be affected by stress and glucocorticoids. These findings have important clinical implications, as glucocorticoid-based interventions might also be effective in regulating habitual memory in stress- and fear-related disorders including obsessive–compulsive disorder, which comprises a strong S-R component[120] (FIG. 1).

Stimulus–response (S–R) associations
A type of learning that links single stimuli to responses. This type of learning is considered to be cognitively less demanding than, for example, spatial memory and relies on the dorsal striatum.

Inhibitory avoidance task
A learning and memory task in which animals learn to avoid the place in an apparatus where they received a single footshock during the training.

Clinical implications

There are several theoretical time points at which glucocorticoid-based interventions might be useful for reducing aversive memory. First, GR blockade could attenuate the initial consolidation of an aversive experience. This intervention would be referred to as a secondary prevention of a fear-related disorder. Second, glucocorticoids could be administered to reduce the retrieval of aversive memories and thus to curtail the expression of fear, such as of flashbacks in PTSD (see also BOX 1). Third, glucocorticoids could be used to enhance memory extinction in patients who undergo extinction-based psychotherapy. Last, GR blockade could help to reduce reconsolidation after memory reactivation. These glucocorticoid signalling-based intervention strategies are illustrated in FIG. 2. Below, we review the clinical studies that used glucocorticoid signalling-based interventions to prevent or treat fear-related disorders (TABLE 1).

PTSD. Interestingly, and perhaps unexpectedly, PTSD is not characterized by elevated glucocorticoid levels[121] but rather by enhanced HPA-axis feedback[122,123], which can sometimes result in lower circulating cortisol levels in individuals with PTSD than in healthy people[121]. Furthermore, altered HPA-axis regulation and a high number of GRs in peripheral blood mononuclear cells can represent a pre-trauma risk factor for the disorder[124–126]. Approximately 30% of the variance in PTSD risk can be attributed to genetic factors, and a number of risk-related polymorphisms in glucocorticoid signalling-related genes have been identified[127]. Genetic and epigenetic risk and resistance factors for PTSD are discussed in BOX 4.

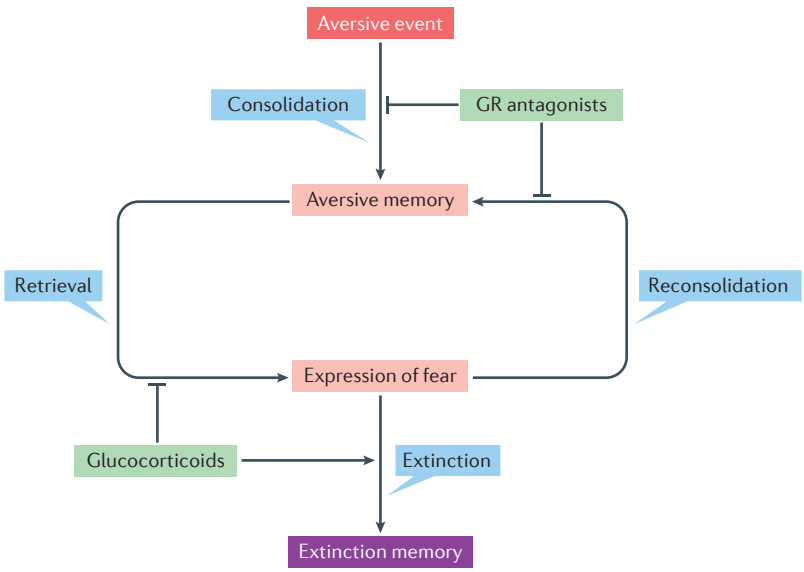


Figure 2 | **Glucocorticoid signalling-based intervention strategies.** Glucocorticoids have been tested for their potential to reduce the retrieval of aversive memory or to enhance memory-extinction processes (for clinical trials, see TABLE 1). Glucocorticoid receptor (GR) antagonists or very high doses of glucocorticoids resulting in a response beyond the peak of the inverted U of the glucocorticoid dose–response curve could be used to block initial consolidation of aversive memory or to block memory reconsolidation. For these approaches targeting consolidation or reconsolidation processes, there are only a few studies available, with mixed results (see the main text).

There are currently no clinical data available on the effects of inhibiting the initial consolidation of a traumatic memory by blocking glucocorticoid signalling (FIG. 2). However, a preliminary study showed that a single high dose (100–140 mg) of cortisol within 6 hours of the traumatic event (mostly motor vehicle accidents) reduced the risk of developing PTSD[128]. This treatment may have resulted in cortisol levels corresponding to a response beyond the peak of the inverted-U-shaped dose–response curve and therefore impaired consolidation[32]. Another study in which a high dose of dexamethasone was intraoperatively administered to cardiac patients did not find a preventive effect on PTSD risk 18 months later in the entire sample, but a sex-specific analysis revealed a significant reduction in PTSD risk in females[129].

Two other studies aimed to reduce retrieval of aversive memories to curtail symptoms of PTSD. The first — a double-blind, placebo-controlled, cross-over study in three patients — found that low-dose cortisol treatment (10 mg per day for 1 month) reduced re-experiencing symptoms and nightmares[130]. The second study, which used a similar design but in a larger group of patients who were receiving various psychotropic medications (including serotonin- or noradrenaline-reuptake inhibitors), failed to show beneficial effects of cortisol (10 mg or 30 mg per day for 1 week) treatment on PTSD symptoms[131].

Clinical studies testing the effects of glucocorticoids on extinction memory have consistently shown that such treatment enhances extinction[130,132–134]. In particular, a recent randomized, double-blind, placebo-controlled trial in 24 veterans with PTSD showed that cortisol (30 mg) combined with exposure treatment improved treatment retention and outcome[134]. Only one clinical trial has examined the ability of the GR antagonist mifepristone to reduce reconsolidation after reactivation, but it did not find evidence for such an effect[135].

There have been several studies using high-dose glucocorticoid administration for a longer time period (for example, several days) after a traumatic event, potentially affecting several memory processes (FIG. 2; TABLE 1). These studies indicate that prolonged treatment with high doses of cortisol starting within 12 hours of the trauma reduces the risk of later PTSD[136–139]. This may be attributable to an initial shift in the glucocorticoid response to the right of the peak of the inverted U-shaped dose–response curve and, consequently, in an impairment of consolidation[32], and/or to a later reduction in the retrieval of traumatic memories, thereby interrupting the vicious cycle of retrieving, re-experiencing and reconsolidating aversive memories[4]. The preventive effect of exogenous glucocorticoid administration is consistent with studies that suggest that PTSD risk after a traumatic event is decreased by higher excretion of endogenous cortisol in the first hours after the event[140–142].

Two systematic reviews indicate that prolonged administration of glucocorticoids after a traumatic event is the most effective pharmacological intervention that is currently available for preventing PTSD[143,144]. One review included seven randomized controlled trials

Table 1 | **Clinical trials with glucocorticoid-based interventions in fear-related disorders**

Drug	Design	Timing and duration	Memory phase exposed	Outcome	Refs
Treatment of PTSD					
Cort	DB, PC, CO	Daily for 30 days	Retrieval	↓ Intrusions while under treatment	130
		Daily for 7 days	Retrieval	No change in intrusions while under treatment	131
	RCT	Single dose after exposure	Extinction	↓ PTSD symptoms at 1 week	132
		20 min before exposure therapy, which was administered on 8 days	Retrieval and extinction	↓ PTSD symptoms at 6 weeks	134
Prevention of PTSD					
Cort	RCT	Starting <12 h after trauma, for 10 days	Consolidation and retrieval	↓ PTSD symptoms at 3 months	139
		Starting <6 h after trauma, for 6 days	Consolidation and retrieval	↓ PTSD incidence at 31 months	137
		Starting <6 h after trauma, for 4 days	Consolidation and retrieval	↓ Stress scores at 6 months	136, 138
		Single dose <6 h after trauma	Consolidation	↓ PTSD incidence at 3 months	128
Dex	RCT	Single intraoperative dose	Consolidation	No difference in PTSD incidence at 18 months	129
Treatment of social phobia					
Cort	RCT	Single dose 1 h before phobic stimulus	Retrieval	↓ Fear while under treatment	149
Treatment of spider phobia					
Cort	RCT	1 h before phobic stimulus, which was administered on 4 days	Retrieval and extinction	↓ Fear while under treatment	149
		1 h before exposure therapy, which was administered on 2 days	Retrieval and extinction	↓ Fear at 1 month	151
Treatment of phobia of heights					
Cort	RCT	1 h before exposure therapy, which was administered on 3 days	Retrieval and extinction	↓ Fear at 1 month	150

Only randomized controlled trials (RCT) or double-blind (DB), placebo-controlled (PC), cross-over (CO) trials are included. Cort, cortisol; Dex, dexamethasone; PTSD, post-traumatic stress disorder.

of different pharmacological treatments (four with cortisol, three with the β-adrenergic receptor antagonist propranolol, one with the selective serotonin-reuptake inhibitor escitalopram and one with the benzodiazepine temazepam) and reported that cortisol, but not the other drugs, showed efficacy in preventing PTSD development in adults[144]. The other review included five placebo-controlled studies with cortisol and showed a large effect of cortisol in reducing the risk of PTSD[143]. Currently, there are several ongoing studies investigating the effects of cortisol administration on the prevention of PTSD[145,146] and on fear extinction in veterans with PTSD[147].

Phobias. There have been several clinical studies investigating the beneficial effects of glucocorticoids for the treatment of phobias. However, not all memory phases (FIG. 2) are well accessible to pharmacological interventions in phobias, as the pathogenic events in phobias are generally not known, and preventive strategies are therefore not feasible. There are also no studies available that have tested the effects of glucocorticoid blockade during reconsolidation of fear memory (after reactivation), although this approach would be feasible. In addition, unlike in PTSD, there is not much evidence for alterations of the glucocorticoid system in phobias; specifically, there are no clear alterations in the HPA axis[148], and no genetic or epigenetic studies on glucocorticoid-related genes in phobias have been performed.

Nevertheless, because the administration of glucocorticoids might exert beneficial effects in phobias by reducing retrieval of fear memories and by enhancing extinction processes, there are several studies investigating these effects in phobic patients. In a randomized, double-blind, placebo-controlled study in 40 patients with social phobia, a single oral dose of cortisone (25 mg) was administered 1 hour before a socio-evaluative stressor (the Trier Social Stress Test). This treatment significantly reduced subjectively reported fear during the anticipation, exposure and recovery phases of the test[149]. Moreover, the stress-induced release of cortisol in the placebo-treated participants correlated negatively with the change in fear ratings, suggesting that endogenously released cortisol in the context of a phobic situation may counteract fear symptoms in patients with social phobia[149]. In another randomized, double-blind, placebo-controlled study with 20 patients with spider phobia, 10 mg oral cortisol administered 1 hour before the presentation of a spider photograph resulted in a gradual reduction of stimulus-induced fear[149]. The cortisol-induced reduction of fear was still observed 2 days after the last dose, suggesting that cortisol might have facilitated the extinction of phobic fear and have impaired retrieval.

Trier Social Stress Test
A test that is designed to trigger social stress; participants must prepare and give a presentation and perform an arithmetic task in front of an audience.

Box 4 | **Genetic and epigenetic changes in the glucocorticoid system in PTSD**

Studies in humans have identified several genetic and epigenetic alterations in the glucocorticoid system that are associated with increased or decreased risk of developing post-traumatic stress disorder (PTSD).

***NR3C1* alterations**

A well-known single nucleotide polymorphism of the glucocorticoid receptor (GR) gene nuclear receptor subfamily 3 group C member 1 (*NR3C1*) is the common *BclI* polymorphism, a C-to-G nucleotide change that is associated with receptor hypersensitivity to glucocorticoids[199]. In humans, GG carriers (as compared with GC and CC carriers) of the *BclI* polymorphism show enhanced emotional memory in healthy individuals[200] and lower cortisol levels and an increased incidence of traumatic memories and PTSD symptoms in patients after intensive care therapy[201].

Increased *NR3C1* expression in peripheral blood mononuclear cells has been shown to be associated with higher PTSD risk, in line with the enhanced GR feedback that is reported in individuals with PTSD[125]. Moreover, there is evidence that these changes are in part epigenetically controlled. Two recent studies indicated that methylation of the *NR3C1* promoter is inversely correlated with lifetime PTSD risk[202,203]. A study of survivors of genocide indicated that increased methylation at the nerve growth factor-induced protein A (NGFIA; also known as EGR1)-binding site of the *NR3C1* promoter was associated with reduced PTSD risk and fewer intrusive traumatic memories[204]. In support of the idea that methylation might regulate memory processes, increased methylation at this same site — which was accompanied by lower GR expression — was also associated with reduced picture recognition and recognition-related brain activity in healthy participants. These studies suggest an epigenetic and genetic link between the predisposition to form strong aversive memories and the risk of PTSD.

***FKBP5* alterations**

FK506-binding protein 5 (FKPB5) acts as a co-chaperone that modulates GR activity[205], and risk alleles of *FKPB5* have been associated with differences in GR sensitivity, higher risk of PTSD and increased incidence of intrusive memories of aversive photographs in a laboratory experiment[206,207]. Moreover, allele-specific demethylation of *FKBP5* has been found to mediate gene–childhood-trauma interactions; specifically, this demethylation was associated with increased stress-dependent gene transcription, followed by a long-term dysregulation of the hypothalamus–pituitary–adrenal axis[208]. Furthermore, *FKBP5* alleles may influence the effectiveness of exposure-based psychotherapy for PTSD[209], and *FKBP5* allele-specific changes in methylation are associated with treatment response to psychological treatments for anxiety disorders[210].

Implications

Taken together, the evidence that genetic and epigenetic variations in the glucocorticoid system are related to traumatic memory and to PTSD risk and treatment adds to the understanding of individual risk and resilience factors for PTSD. Although common genetic polymorphisms typically have small effect sizes, more research is needed to evaluate whether rare genetic variants or specific methylation events might be suited for diagnostic and/or personalized treatment purposes.

One randomized, double-blind, placebo-controlled study in patients with phobia for heights tested whether glucocorticoids might enhance extinction processes induced by exposure therapy[150]. One hour before each of three virtual-reality exposure sessions, cortisol (20 mg) or placebo was administered orally. Compared with the placebo group, the cortisol-treated group showed significantly lower fear levels at post-treatment and at the 1-month follow-up. Furthermore, administration of cortisol to people with spider phobia during therapy in which they were exposed (in groups) to live spiders also enhanced treatment outcome[151]. Another study investigated whether differences in endogenous glucocorticoid levels (which fluctuate with time of day) might also affect the outcome of exposure therapy[152]. Women with spider phobia who were treated with a single exposure session at 8:00 (when cortisol levels are high) exhibited significantly less fear of spiders in the behavioural approach test at post-treatment and at the 3-month follow-up than did women who were treated at 18:00 (when cortisol levels are low). In conclusion, cortisol may reduce symptoms of phobic fear — presumably by reducing aversive-memory retrieval and enhancing memory extinction — in particular if combined with exposure therapy. These synergistic actions may be important in the successful treatment of phobias.

Behavioural approach test
A test that is used to measure approach behaviour in the context of a feared stimulus.

Addiction and other psychiatric disorders. Glucocorticoids probably have also beneficial effects in other psychiatric disorders in which memory has an important role. In drug addiction, for example, memory encodes and stores the associations that provide the powerful incentives for drug taking and that produce cravings[153–156]. A recent randomized, double-blind, placebo-controlled trial in patients with heroin addiction found that, 90 minutes after a single administration of cortisol (20 mg), low-dose heroin addicts showed reduced craving before and 15 min after heroin administration[157]. Thus, cortisol might reduce craving by reducing retrieval of addiction memory. Glucocorticoids could also be tested for their potential to enhance the extinction of addiction memory. Furthermore, glucocorticoid-based interventions might have therapeutic value in other psychiatric disorders in which aversive memory plays an important part, such as obsessive–compulsive disorder. In patients with this disorder, impaired fear extinction and neurobiological changes in the fear circuit have been reported[158].

Conclusions

Over the past decades, compelling evidence has accumulated for a crucial role of glucocorticoids in memory consolidation, retrieval, extinction and reconsolidation — all processes that are highly relevant in the

pathogenesis, maintenance and treatment of fear-related disorders. These effects are not limited to hippocampus-dependent memories but can also be found in other memory systems, such as habitual memory, which relies on the dorsal striatum and also plays an important part in fear-related disorders. Novel treatment approaches that are based on basic studies have been developed that use the memory-modulating properties of glucocorticoids to weaken dysfunctional memories and to strengthen treatment-related memories of safety.

Many of the clinical studies reviewed above suggest that the strategy to enhance extinction processes by combining exposure-based psychotherapy with timed glucocorticoid administration is a particularly promising approach to treat fear-related disorders. Furthermore, there is evidence that the use of glucocorticoids in the aftermath of a traumatic event may help to prevent development of PTSD. However, the existing evidence for the usefulness of glucocorticoids in treatment and prevention of fear-related disorders comes from rather small proof-of-concept studies. Therefore, there is an urgent need for large randomized controlled clinical trials.

Moreover, from the most recent advances regarding timing, glucocorticoid–endocannabinoid interactions (BOX 3), multiple memory systems, and genetics and epigenetics (BOX 4), several open questions prompt further basic and clinical studies. For example, the optimal dosage, time point and duration of treatment with glucocorticoids need to be elucidated, and the usefulness and safety of such treatments for fear-related disorders must be tested in large randomized controlled trials. It would also be interesting to test the effects of glucocorticoids in other neuropsychiatric disorders in which memory has an important role, such as obsessive–compulsive disorder, and to search for epigenetic and genetic markers for diagnostic and/or personalized treatment purposes. Further basic research should explore novel approaches to modulating glucocorticoid signalling — for example, combining glucocorticoids with cannabinoids — to further investigate the signalling cascades that are involved and to identify safer more-specific glucocorticoid-related drugs. The field of stress and memory represents one of the very few areas in neuroscience in which insights from basic science studies have translated into direct clinical interventions and will hopefully continue to do so in the future.

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Competing interests statement
The authors declare no competing interests.