Stress and memory retrieval: mechanisms and consequences
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Stress impairs memory retrieval. Recent findings illustrate the temporal dynamics and the underlying mechanisms of this effect. The effect appears to occur in multiple memory systems, ranging from striatal-based stimulus-response memory to prefrontal-based extinction memory. The effects of stress on memory retrieval might have long-term consequences due to their impact on re-encoding and re-consolidation. These properties could be of interest for future intervention studies.

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http://dx.doi.org/10.1016/j.cobeha.2016.12.001
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Introduction
Our memories are influenced by stress and its associated neuroendocrine responses. A frightening encounter with a robber or an especially poor performance during a job interview may be vividly remembered for a life time. These are examples of the enhancing effects stress can have on memory encoding and consolidation. At the same time, we might forget our wedding anniversary because we are stressed at work, or we might be unable to retrieve the name of a specific brain region during a stressful neurobiology exam. The latter two are examples for the impairing effects stress can have on memory retrieval. This phenomenon in particular is the focus of the present brief and selective review, which will address the following main points: the temporal development and underlying mechanisms of retrieval impairment, its occurrence outside of the domain of hippocampus-based memories, long-term consequences of this retrieval impairment, and its relevance for mental disorders (see Box 1).

When faced with a real or anticipated threat, the organism responds with a complex and well-orchestrated neuroendocrine stress response [1*]. The rapid activation of the sympathetic nervous system (SNS) leads to the release of (nor)adrenalin (NA) from the adrenal medulla. This initial response causes hypervigilance at the expense of selective attention and other top-down control processes [2,3*], and, with respect to memory, leads to enhanced encoding of salient and relevant features of the environment [4,5]. In parallel, the hypothalamic–pituitary–adrenal (HPA) axis is activated. Corticotrophin-releasing hormone (CRH), secreted from the paraventricular nucleus of the hypothalamus, stimulates the anterior pituitary to release adrenocorticotropic hormone (ACTH). This messenger, in turn, causes the adrenal cortex to release glucocorticoids (GCs; mostly cortisol in humans, and corticosterone in most laboratory rodents). These stress hormones first increase 5–10 min after stress onset and typically reach their peak 20–30 min post-onset [6]. Glucocorticoids exert their action via mineralocorticoid (MRs) and glucocorticoid receptors (GRs). These two receptor types differ in their localization (MRs are more restricted to limbic regions, GRs are expressed more widespread in the brain) and affinity. It was initially assumed that these receptors exist exclusively within the cell and exert slow but potentially long-lasting action by directly influencing the genome (genomic GC effects) [7**]. More recently, however, convincing evidence has shown rapid, non-genomic GC effects mediated via membrane-bound (as opposed to intracellular) versions of these receptors [7**,8]. Three interacting and partially overlapping stress response signals must thus be considered: (1) The initial arousal response mediated by NA and CRH, (2) the slightly delayed non-genomic GC signal with mostly excitatory properties, which occurs in interaction with the initial NA signal, and (3) the further delayed genomic GC signal, which, mostly mediated by intracellular GRs, reduces neuronal excitability and promotes normalization of the system [1,9,10,11**]. These three response waves are illustrated in Figure 1. The time frames mentioned represent rough estimates, as they are likely to differ depending on the intensity of the stressor and/or the investigated brain region.

Stress and episodic memory retrieval: temporal development and underlying mechanisms
Initial findings on the enhancing effects of stress and GC treatment on memory consolidation were already described in the 1960s (e.g., [12]). Since then research
Stress and memory retrieval

Box 1 Summary of key points

The effects of stress on memory retrieval last longer than initially expected. They reflect non-genomic and genomic GC effects.

The effects of stress on memory retrieval are not restricted to hippocampus-based episodic memory retrieval. Striatum-based SR memory retrieval as well as PFC-based (fear) extinction memory retrieval are two examples for this.

The impairing effect of stress on retrieval can have long-lasting consequences through the modification of re-encoding and re-consolidation. This feature could make cortisol a useful add-on to therapeutic interventions (e.g., exposure psychotherapy).

Patients with mental disorders (e.g., MDD and PTSD) show different responsivities to GC, which are in line with an altered central GC sensitivity in these disorders.

Neuroendocrine stress responses to a brief stressor (e.g., the Trier Social Stress Test) and their transcriptional and cognitive consequences. Stress influences the brain via a rapid increase in noradrenalin (NA). With a slight delay, glucocorticoids (GCs) are released. These hormones can exert rapid non-genomic and delayed genomic effects. Both effects are likely to co-occur around one hour after stress exposure. Genomic and non-genomic GC effects typically cause impaired memory retrieval. In contrast, initial encoding as well as consolidation of material perceived around the time of the stressor is enhanced. Note: The depicted temporal development is based on a broad estimate derived from the literature. For further explanations, see the associated text.
blocker preventing this arousal [21]. Regarding the neural correlates of GC-induced memory retrieval impairments, pharmacological neuroimaging studies were able to show GC-mediated reduced activity in the hippocampus and adjacent cortical structures during memory retrieval [22,23].

Stimulated by the mounting evidence for rapid non-genomic GC effects, studies have started to compare rapid and delayed effects of stress or GC treatment in several cognitive domains, including memory [17,24]. While substantial progress has been made, time-dependent variations in the effect of stress on memory retrieval have received relatively little attention. One relevant pharmacological study was recently able to show that a cortisol injection affected memory retrieval within eight minutes, which is strongly suggestive of a non-genomic effect [25]. Another recent study in humans reported that memory retrieval was impaired 25 min (at the time of peak cortisol) but also 90 min stress exposure, illustrating that the impairing effect of stress on memory might last longer than initially expected [26*]. Interestingly, cortisol concentrations were already back to baseline levels in the group tested 90 min after stress exposure, demonstrating that impairing effects of stress on memory retrieval can occur even when GC levels are no longer elevated. Together with the initial findings observed in rodents [16**], this study suggests that the impairing effects of stress on memory retrieval occur rapidly once cortisol concentrations are sufficiently elevated, but that these effects also persist for at least 90 min. This implies that both initial non-genomic effects and later genomic effects lead to impaired memory retrieval (for an in-depth review, see [11*]). This interpretation is also in line with recent studies in rodents [27]. Roozendaal postulates that membrane-bound GRs in the BLA interact with central NA signaling in rapidly boosting memory consolidation and impairing memory retrieval [8]. In contrast, work by Dorey and colleagues has provided evidence that hippocampal membrane-bound MRs, but not GRs, play a role in mediating the rapid stress effects on memory retrieval [28]. With respect to genomic effects, Rimmer and colleagues could demonstrate that blocking the MR impaired memory retrieval, while blocking the GR enhanced retrieval [29]. In this study, the drugs were administered several hours before memory retrieval was tested, which suggests that it was indeed the consequences of genomic GC actions that were being measured. In summary, it seems that both non-genomic and genomic GC effects induce memory retrieval deficits (see Figure 1).

While an inverted-U-shaped dose–response curve between GCs and memory consolidation is well-established [14], the investigation of dose–response relationships has received little attention with respect to memory retrieval. Stress studies in humans illustrate that even a moderate increase in cortisol in the late afternoon (when endogenous cortisol concentrations are low) can impair memory retrieval [30]. In contrast, a recent pharmacological study using cortisol injections provided initial evidence for an inverted-U-shaped function instead [25]. The dose–response curve might differ depending on the presence (stress) or absence (pharmacological cortisol administration) of strong prior noradrenergic activation [1*]. Moreover, there may be differences in dose–response relationships between non-genomic and genomic effects. If an inverted-U-shaped dose–response curve indeed exists, its peak may lie in the range of basal (stress-free) physiological cortisol concentrations.

Conceptually, it has been proposed that the retrieval impairment is restricted to the ‘memory formation mode’ but is no longer present during the ‘memory storage mode’ (during consolidation) [31]. However, the findings discussed above indicate that the effects occur later and last longer, thus primarily occurring during the consolidation phase.

**Stress and memory retrieval outside the domain of hippocampus-based memories**

Initially, it appeared that the effects of stress on memory retrieval are restricted to hippocampus-based episodic/spatial memory tasks [16**,19]. This was in line with the notion that the hippocampus is especially sensitive to stress due to its high number of MRs and GRs [32]. Indeed, recognition and cued recall were not influenced by stress in initial studies in humans, further supporting the notion of a specific effect on hippocampus-based episodic recollection [18,19]. More recently, however, several studies have demonstrated stress-induced recognition impairments, evidencing that not only free recall is affected by stress [33]. Accumulating evidence reviewed below has quite convincingly shown that the effects of stress on memory retrieval are far broader than initially conceived.

Stimulus-response (SR) memory describes the learned association between a specific cue and a specific response. It has been linked to the basal ganglia [34] and can be tested in humans and rodents by using maze tasks with a single, clearly visible cue [35]. In the first human study on this topic, participants exposed to stress prior to SR retrieval showed impaired retrieval performance [36]. Similar findings were obtained recently in rodents [37*]. In this study, the authors could additionally demonstrate that the SR retrieval deficit is indeed mediated by GCs. These findings thus highlight that stress and the associated release of GCs can also impair the retrieval of striatal-based SR memories.

Another area of research in which the impairing effects of stress on memory retrieval have received considerable attention is the field of (fear) extinction. When a neutral
stimulus (e.g., a tone; the conditioned stimulus or CS) is coupled with an aversive event (e.g., a shock; the unconditioned stimulus, or UCS), the organism quickly learns to respond to the CS alone (e.g., by showing freezing behavior; the conditioned response, or CR). During extinction, the CS is no longer coupled with the UCS, and the CR disappears. The majority of current learning models postulate that this decreased responding is not caused by an erasure of the original acquisition memory trace, but rather reflects new inhibitory learning [38,39]. This is demonstrated by the occurrence of several recovery phenomena such as contextual renewal, reinstatement or spontaneous recovery [40]. When it comes to the impact of stress, the fascinating question arises whether stress prior to extinction retrieval will impair the original acquisition memory trace or the inhibitory extinction memory trace formed later on. Evidence is accumulating that stress exposure prior to retrieval typically impairs extinction retrieval, leading to a return of fear in human participants [41] as well as in patients with anxiety disorders [42]. We have demonstrated similar findings using a predictive learning task. Stress induction in the laboratory caused impaired extinction retrieval, manifested as enhanced conditioned responding in the acquisition context (i.e., an enhanced renewal effect) [43]. In a pharmacological fMRI study with the same predictive learning task, cortisol administration prior to extinction retrieval led to impaired extinction retrieval, as evidenced by an enhanced renewal effect. This was associated with reduced neural activity in the ventromedial prefrontal cortex (vmPFC) [44], a key region in the extinction network (e.g., [45]). The available data supports the notion that GCs impair the extinction memory trace. The reason for this selective impairment might be the younger age of this memory trace, its context dependency, or its reliance on the vmPFC for retrieval. By impairing the extinction memory trace, GCs thus cause a return of the initially acquired response (see Figure 2). However, enhanced retrieval of the original memory trace could still be occurring — an explanation in need of empirical assessment. A mechanistic understanding of the impact of stress on extinction retrieval will pave the way toward better, targeted relapse prevention.

**Long-term consequences of retrieval impairment**

Another important issue concerns the long-term consequences of the stress-induced retrieval failure. Is this a temporal blockage which completely disappears once stress has ceased, or does the impaired retrieval have consequences beyond the stressful episode, for example, due to an effect on (re)consolidation? A pharmacological study using cortisol administration before memory retrieval observed that the cortisol group showed a memory...
impairment as long as one week after the retrieval under the influence of cortisol had taken place [46]. In addition, another recent study found impaired memory retrieval at very low cortisol levels, induced by the cortisol-synthesis-inhibitor metyrapone [47*]. Again, this impairment was still detectable a week later. Conceptually, the poor retrieval at times of high (or very low) GC concentrations could lead to impaired re-encoding and/or impaired re-consolidation [48]. Taken together, these findings illustrate that impaired retrieval under stress can have long-lasting consequences for the specific memory.

Beneficial effects of the long-term consequences of cortisol administration on human memory have been observed in the context of extinction-based (i.e., exposure) psychotherapy. Cortisol administered before exposure treatment enhanced the long-term success of therapy in patients with fear of heights and in patients with spider phobia [49**,50]. The combination of impaired retrieval of the initial fear memory with enhanced consolidation of the newly acquired extinction (safety) memory could be the underlying mechanism of this therapeutic effect of the stress hormone [51].

**Alterations in patients with mental disorders**

There is increasing evidence that the effects of stress on memory retrieval are altered in patients with mental disorders. Dysfunctions in the hypothalamic–pituitary–adrenal (HPA) axis have been reported for several mental disorders. While major depressive disorder (MDD) seems to be characterized by enhanced cortisol release in concert with a reduced feedback sensitivity of the HPA axis [52], the opposite pattern has been reported in post-traumatic stress disorder (PTSD) [53]. In a series of studies, we investigated the effects of cortisol on memory retrieval in MDD and PTSD. While cortisol administration failed to affect memory retrieval in MDD patients, patients with PTSD showed enhanced, rather than impaired, memory retrieval after cortisol [54]. These results indicate an altered sensitivity to cortisol in these disorders, which not only influences the HPA axis and its negative feedback, but extends to an altered sensitivity of brain functions involved in episodic memory retrieval (presumably the hippocampus [55]). Future studies are required in order to determine whether these alterations are reversed after successful treatment, thereby elucidating whether they reflect pre-morbid risk factors or reversible disease consequences.

**Conclusion**

Taken together, empirical evidence obtained in recent years has changed the way we look at the impact of stress on memory retrieval. The impairing effects of stress last longer, concern a broader range of memory systems, have lasting consequences and are altered in several mental disorders. These novel findings raise new questions for future research. Some of the most central are summarized in the Box 2.

**Conflict of interest statement**

The author declares no conflict of interest.

**Acknowledgements**

The author’s work was supported by grants from the German Research Foundation (DFG). I thank Shira Meir Drexler for most helpful comments on an earlier version of this manuscript. In addition I thank Eve Hessas for language editing and Melinda Baranyai for support regarding the creation of Figure 1.

**References and recommended reading**

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- of outstanding interest


**Box 2 Open questions**

- How does activation of membrane-bound MRs and GRs influence memory retrieval?
- How do non-genomic and genomic GC effects interact in influencing memory retrieval?
- What is the dose–response relationship between GCs and memory retrieval?
- Are there memory systems which are resistant to the impairing effect of stress on retrieval?
- Are the effects of stress modulated by genetic and epigenetic factors?
- Do the GC alterations observed in several mental disorders (e.g., MDD, PTSD) reflect predispositions or consequences of the disorders?
- Can the beneficial effects of GCs observed in clinical intervention studies be translated into the clinical praxis?


In depth review on the impact of stress on episodic memory retrieval.


First study demonstrating the impairing effect of stress on long-term memory retrieval.


Human study demonstrating an impairing effect of stress even 90 min after stress exposure.


First study characterizing the impact of GCs on stimulus response memory retrieval.


In depth review on possible mechanisms underlying the impact of stress on fear extinction.


