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Learning under stress: how does it work?

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The effects of stress on learning and memory are not always clear: both facilitating and impairing influences are described in the literature. Here we propose a unifying theory, which states that stress will only facilitate learning and memory processes: (i) when stress is experienced in the context and around the time of the event that needs to be remembered, and (ii) when the hormones and transmitters released in response to stress exert their actions on the same circuits as those activated by the situation, that is, when convergence in time and space takes place. The mechanism of action of stress hormones, particularly corticosteroids, can explain how stress within the context of a learning experience induces focused attention and improves memory of relevant information.

Introduction

Our daily lives are full of emotionally arousing experiences, ranging from small annoyances to major life events like the loss of a spouse. Collectively, these potential threats of our bodily homeostasis are referred to as 'stress' [1]. Stressful events ('stressors') can be tangible or mentally evoked, and of a physical or psychological nature.

Many studies have examined how stress affects learning and memory abilities [2–4]. The literature, though, is extremely confusing. On the one hand it is generally accepted that stressful events are very well remembered: the more salient, the better remembered, up to the point that people would like to forget what they experienced but can't do so, as in post-traumatic stress disorder (PTSD; [5]). Studies with animals, using pharmacological and genetic tools, have indeed shown that stress facilitates, and might even be indispensable for, good learning and memory performance [6–10]. Likewise, facilitating effects of stress and arousal have been demonstrated in humans [11,12]. Yet, stress has also been associated with impaired cognitive performance. For instance, people who experience a very stressful event often show unreliable memory for details [13]. Furthermore, cognitive decline has been observed in conditions that – in predisposed individuals – are linked to persistent hyperactivity of stress systems, such as major depression or aging [3,4].

How can these paradoxical findings be explained? In the first part of this article we will describe which variables play a major role in determining whether stress improves or impairs learning and memory performance. In the second part we propose a new, unifying theory of *how* stress can lead to these seemingly opposite effects, based on the mechanisms by which stress hormones affect cell and network function. We will argue that the activity of networks can be shifted into opposite directions by stress-released transmitters and hormones, depending on the timing and localization of their respective actions.

Factors determining the effect of stress on learning

Stress leads to the activation of two biological systems that are highly conserved among vertebrates: the autonomic nervous system (ANS) and the hypothalamo–pituitary–adrenal (HPA) axis (see Box 1; [14]). The main actors of these systems are (nor)adrenaline, corticotropin releasing hormone and cortisol (corticosterone in most rodents). As the transmitters and hormones that are released in response to stress are highly conserved among vertebrates, animal models have often been used to try to understand more about the effects of stress on learning in humans.

The degree to which the ANS and HPA-axis are activated depends on the severity of the stressor but can also show considerable individual variation due to genetic background and life history [14]. When studying the effect of stress on learning, these individual differences and the severity of the stressor are important but so too other variables, such as the context and memory phase during which stress is experienced, gender [3,15,16], age [2,3] and so on. Below we highlight some of these variables.

Glossary

ACTH: adrenocorticotropin hormone
AMY: amygdala nuclei
ANS: autonomic nervous system
CORT: corticosterone
CRH: corticotropin releasing hormone
HIPP: hippocampus
HPA axis: hypothalamo–pituitary–adrenal axis
HYP: hypothalamus
LC: locus coeruleus
NA: noradrenaline
PFC: prefrontal cortex

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Importance of context

Several studies have shown that stress induced by and in close association with a learning task (i.e. stress that forms an intrinsic part of the situation to be remembered) facilitates consolidation of the event [17]. For instance, rats trained to find a hidden platform in a Morris water maze using spatial cues [18] show elevated circulating corticosteroid levels [10]. The elevation is more pronounced when the temperature of the water is lowered [8]. This rise in corticosteroid level correlates positively with the memory of the platform location one day, and even one week, after training [8]. However, the corticosteroid-dependent improvement is only true down to a certain water temperature; lower temperatures do not give further improvement but impair performance. This is often used as an argument in support of a U-shaped dose-dependency, meaning that only moderate stressors improve memory whereas severe stressors do not [19]. Although such a dose-dependency for corticosteroid hormone actions in the brain undeniably exists [14,19], the seemingly delayed learning with lower water temperatures can also be interpreted in a different way: that at these temperatures animals switch to another strategy (conserving energy), which starts to interfere with the learning task.

Importantly, preventing corticosterone from being active during water-maze learning, either by blocking the glucocorticoid receptor (GR) pharmacologically [6] or

Box 1. Systems activated by stress

If an organism is subjected to physical or psychological challenges, information-gathering behavior is enhanced to assess the destabilizing potential of the stressor. Comparison of the ongoing event with a cognitive representation based on previous experience will stimulate arousal, alertness, vigilance and focused attention, and requires mnemonic processing. The interface between the incoming sensory information and the appraisal process is formed by limbic brain structures including the hippocampus, amygdala and prefrontal cortex. These brain regions are connected to the hypothalamus, which is a key regulator of the rapidly acting autonomic sympathetic system (ANS) and the slower hypothalamo-pituitary-adrenal (HPA) axis (see Figure I).

HPA axis activation will through intermediate steps release corticosterone (in most rodents) or cortisol (humans) from the adrenal gland. Corticosteroid hormones enter the brain and bind to discretely localized intracellular receptors. These comprise high-affinity mineralocorticoid receptors, which are extensively occupied when hormone levels are low, are enriched in limbic areas, and involved in the ongoing transfer of information and stability of circuits; and the lower affinity glucocorticoid receptors (GRs), which become substantially activated when hormone levels rise after stress, are ubiquitous and play a role in normalizing the activity. Via GRs in the hypothalamus and pituitary, corticosteroids exert a negative feedback action, thereby reducing the enhanced HPA-activity. Autonomic activation can indirectly (via the vagal nerve, solitary tract nucleus and locus coeruleus) lead to release of noradrenaline in the brain. Corticosteroids and noradrenaline – as well as transmitters and peptides not mentioned in this review, such as acetylcholine, glutamate, GABA, CRH, ACTH, vasopressin and opioids [4] – act together, not only helping to face imminent threats but also to prepare the organism for similar challenging situations in the future.

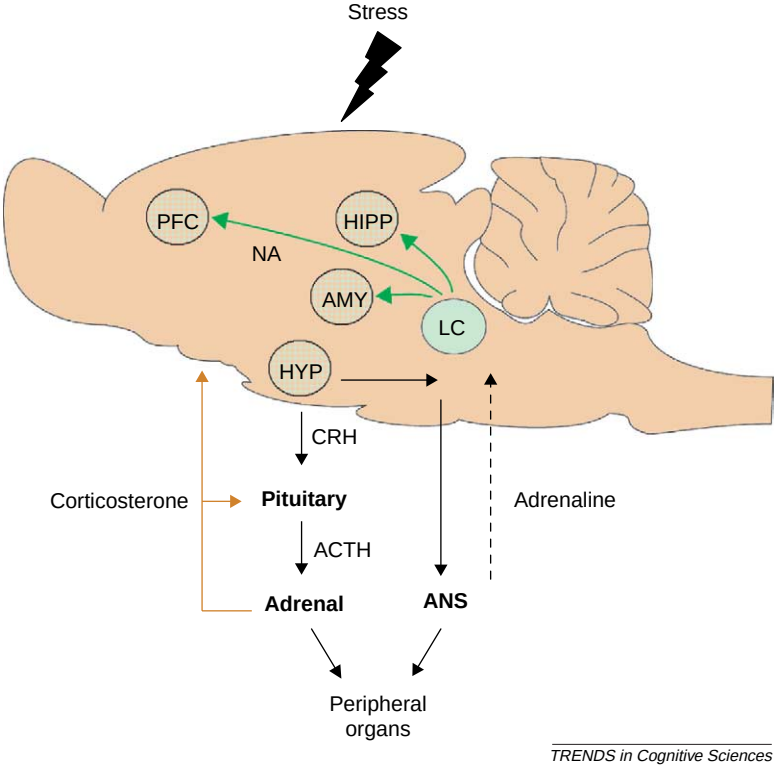

Figure I. The brain areas and hormone systems involved in repsonse to stress (see text and Glossary for details).

by using mice with genetically modified GRs [10], impairs the performance one day after training. This points to an important role for glucocorticoids in the consolidation of spatial memory. Facilitatory effects of corticosteroids have also been observed with conditioned taste aversion in one-day-old chicks [7], and during extinction of passive avoidance behavior in rats [20].

Both corticosterone and noradrenaline are important for optimal memory performance in rats subjected to an inhibitory avoidance task [9]. In humans too, changes in the level of these hormones at the time of learning play a major role in memory performance. For instance, interfering with the effect of corticosteroids by a steroid-synthesis inhibitor during learning of a verbal task impairs the delayed, but not immediate, recall of learned information [11]. Likewise, raising stress hormone levels at the time of learning, for example, by exposing the subjects to a cold stressor or infusing adrenaline, facilitates delayed recall in declarative memory tasks [12].

Collectively, these studies underline an important principle regarding stress and memory: increases in stress hormone levels, particularly of corticosteroid hormones, within the context (and around the time) of the learning situation help to remember that particular event.

Convergence in time

In addition to the learning context, convergence in time seems to be crucial for the nature of the effects. Thus, although stress hormones generally act in a facilitatory way when they are present around the time of learning, they have opposite effects when present in high amounts either *before* or a considerable time *after* a learning task. For instance, declarative memory is impaired if humans are exposed to stress or high cortisol levels before (15 min or 1 h respectively) the acquisition of a learning task [21]. In rats, a foot shock or injection of corticosterone one day after training in a Morris maze and 30 min before a free swim trial was found to impair the discrimination between the former platform quadrant and the opposite quadrant of the pool [22]. Along the same lines, humans who experience stress or receive a high dose of hydrocortisone 24 h after training in a verbal task, show poorer recall than control subjects shortly afterwards [23,24].

Clearly, stress has differential effects on distinct phases of the learning and memory processes: consolidation can be facilitated when stress is experienced at the time and within the context of the event to be remembered, whereas retention seems to be impaired by exposure to stress shortly before a retrieval test. The latter results are sometimes interpreted as a specific, negative effect of corticosteroid hormones on retrieval of information [22,23], but they could also signify a facilitated new process of learning, in competition with or overwriting earlier learned information [25]. For instance, during a stressful examination people often have problems recalling earlier learned information (impaired retrieval), but at the same time this 'embarrassing' situation is burnt deeply into their memory (enhanced consolidation). Such competition between earlier learned information and current challenges is certainly not always maladaptive, because consolidating information about new (physical or psychological) threats can improve chances of survival in the future.

Convergence in space

The nature of the stressor and the learning task itself also determine how stress affects memory. This relates to the brain circuits that are activated by the stressful situation. Physical stressors will activate lower brain regions that are implicated, for example, in pain responses, whereas psychological stressors are more likely to activate limbic regions [26]. This is exemplified by studies using stressful information or situations that entail a strong emotional component: under such circumstances the (baso)lateral amygdala is prominently activated and this process is facilitated by a local rise in noradrenaline [4]. The coinciding activation of the circuit involving the basolateral amygdala *and* the local presence of stress hormones promotes the memory of salient but not neutral information [12]. We propose that facilitation will only occur when stress hormones (corticosteroids, noradrenaline, CRH) exert their actions in the same areas as those activated by the particular stressful situation; that is, when convergence in space takes place. This hypothesis can explain why a predator stress (strongly activating the amygdala–hippocampus loop), but not arousal in general, interferes with recently acquired spatial memory [27]. Obviously, such influences of stress can only be perceived when the test probes the functionality of the area in which convergence took place. For instance, the facilitating effect of stress on fear memory will be seen when the trial involves reactivation of the amygdala, but not necessarily when the function of other circuits is examined.

Single versus repetitive stress

Finally, much of the confusion about stress effects on learning and memory stems from conflating short-lived physiological stressors with chronic or repetitive stressors. Most of the examples discussed above concern brief stress, around the time of learning. We propose that if convergence in time and space takes place, stress hormones help to store the information attached to the event for future use. This beneficial, adaptive process is fundamentally different from the situation in which the brain has been exposed for a long period of time to uncontrollable stressors and then is tested for its ability to learn and remember. Chronic overactivity of the HPA axis, as in predisposed individuals, can occur in association with many diseases and with aging, is known to result in dendritic atrophy, reduce neurogenesis, alter responsivity to neurotransmitters and impair synaptic plasticity [28–30]. It is therefore not surprising that the learning abilities of a brain in such a condition are impaired. This cognitive decline, however, refers to somewhat extreme situations that are risk factors for pathology.

The importance of neurotransmitter networks

The emerging picture from the studies discussed above is that stress facilitates learning and memory if convergence in space and time occurs. We argue that the transmitters and/or hormones released by the stressful situation have to reach the very neuronal circuits that are involved in

processing the information, at approximately the time that these circuits are activated by the event. If increases in corticosteroid hormone levels are separated in time from the event to be remembered, suppression of learning content is observed. How can this be understood at the cellular and network level?

Catecholamines, peptides and steroids: action in different but overlapping domains

It is important to consider first the mechanism of action by which catecholamines, peptides and corticosteroid hormones change cell and network function. Peptides and catecholamines like noradrenaline are released at specific sites from nerve terminals. After binding to G-protein-coupled receptors in the membrane they induce rapid but short-lasting changes in neuronal excitability. In some cases secondary gene-mediated effects occur, which are slow in onset and long-lasting.

Corticosteroid hormones, by contrast, reach all parts of the brain but are only active at those sites where receptors are expressed (Box 1). These receptors are transcriptional regulators, so that elevations in corticosterone level after stress will primarily evoke gene-mediated changes in cellular excitability. These become apparent after approximately an hour, that is, when hormone levels have largely been normalized again [14]. Recently, though, rapid non-genomic effects of these hormones have been observed [31,32]. Thus, although catecholamines will predominantly alter neuronal activity quickly and transiently after stress, and corticosteroids will do so with a considerable delay but with a longer-lasting effect, some overlap in the time domains seems to exist.

Action of stress hormones at the sites of information processing

What happens when an organism is exposed to a psychological stressor? Information is perceived through sensory organs and relayed to various brain areas [33] (see Figure 1). This will eventually lead to activation of the autonomic nervous system and HPA-axis [4]. Via some intermediate steps this will result in the rapid release of catecholamines (noradrenaline) and peptides (e.g. CRH) in those areas where strengthening of contacts is taking place. Similarly, with a short delay corticosteroid hormones will reach areas where their receptors are highly expressed, including the amygdala nuclei, hippocampus and parts of the prefrontal cortex. Exchange of information between the amygdala and hippocampus will further strengthen the link between emotional and contextual aspects of the event, and reciprocal connections from the prefrontal cortex to the amygdala and brainstem nuclei are also strengthened, which is necessary for control of the system [33].

A crucial question is what stress hormones like noradrenaline, CRH and corticosteroids do to synaptic contacts that at the same time are in the process of being strengthened to preserve information. It has been found that both noradrenaline [34,35] and CRH [36] strengthen synaptic contacts in the hippocampus. Their effects are similar to long-term potentiation (LTP) of synapses, observed after stimulating hippocampal afferents with patterned input. LTP, which is selective and associative, is generally considered to be the best available neurobiological substrate for processes taking place during memory formation [37]. Noradrenaline and CRH not only enhance

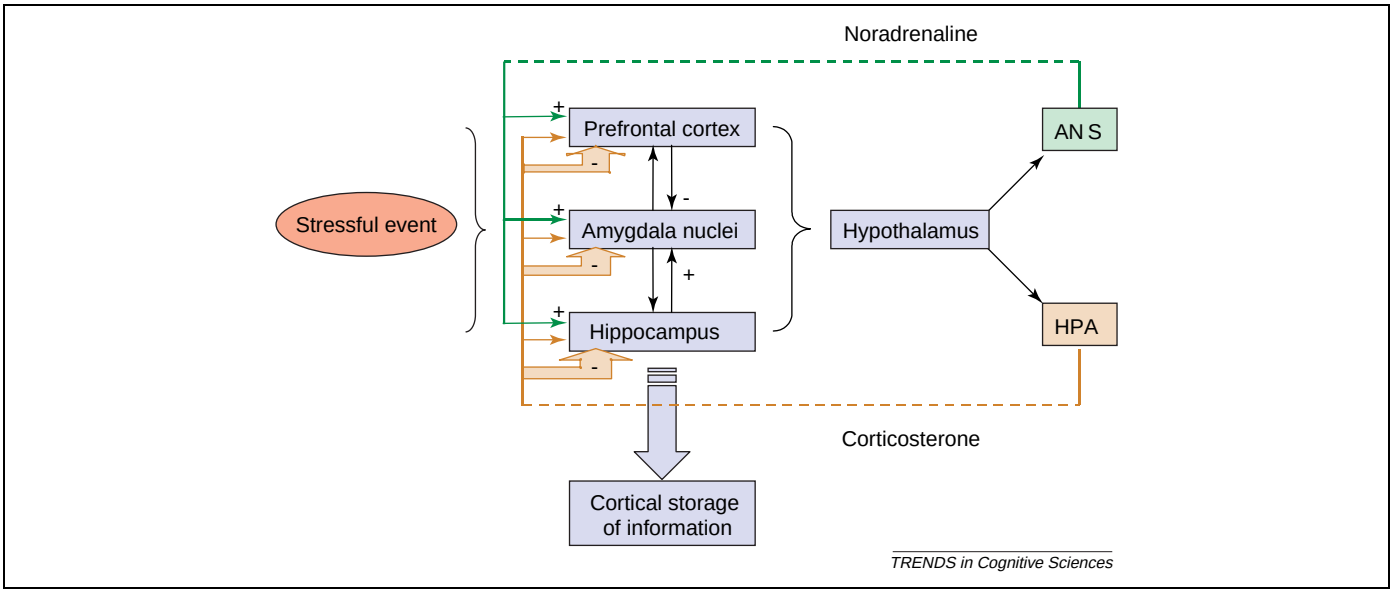

Figure 1. Hormonal and neurotransmitter pathways involved in processing of stressful information in a learning situation. Stressful events are perceived through sensory systems and relayed, via several brain regions (e.g. the thalamus) to limbic and cortical areas, including the hippocampus, amygdala nuclei and prefrontal cortex. By means of recurrent loops, information in these areas becomes more closely linked. From there, output (negative or positive) funnels through the hypothalamus, an area important for activation of the autonomic nervous system (ANS) and the hypothalamo-pituitary-adrenal (HPA) axis. Through several steps (here indicated by the dotted lines) effectors of these two systems, in particular noradrenaline, CRH and corticosterone, reach various brain areas. Rapid effects of these three compounds can facilitate (+) the encoding of information when (i) they act in the same areas that are involved in processing of the information to be remembered and (ii) do so around the time that synaptic strengthening in these areas takes place. Corticosterone also initiates a much slower genomic signal that will suppress (−) unrelated information reaching these circuits some time after the stressful event. This dual effect of corticosterone serves to enhance the signal-to-noise ratio of important information. Consolidated information will eventually be stored in higher cortical regions.

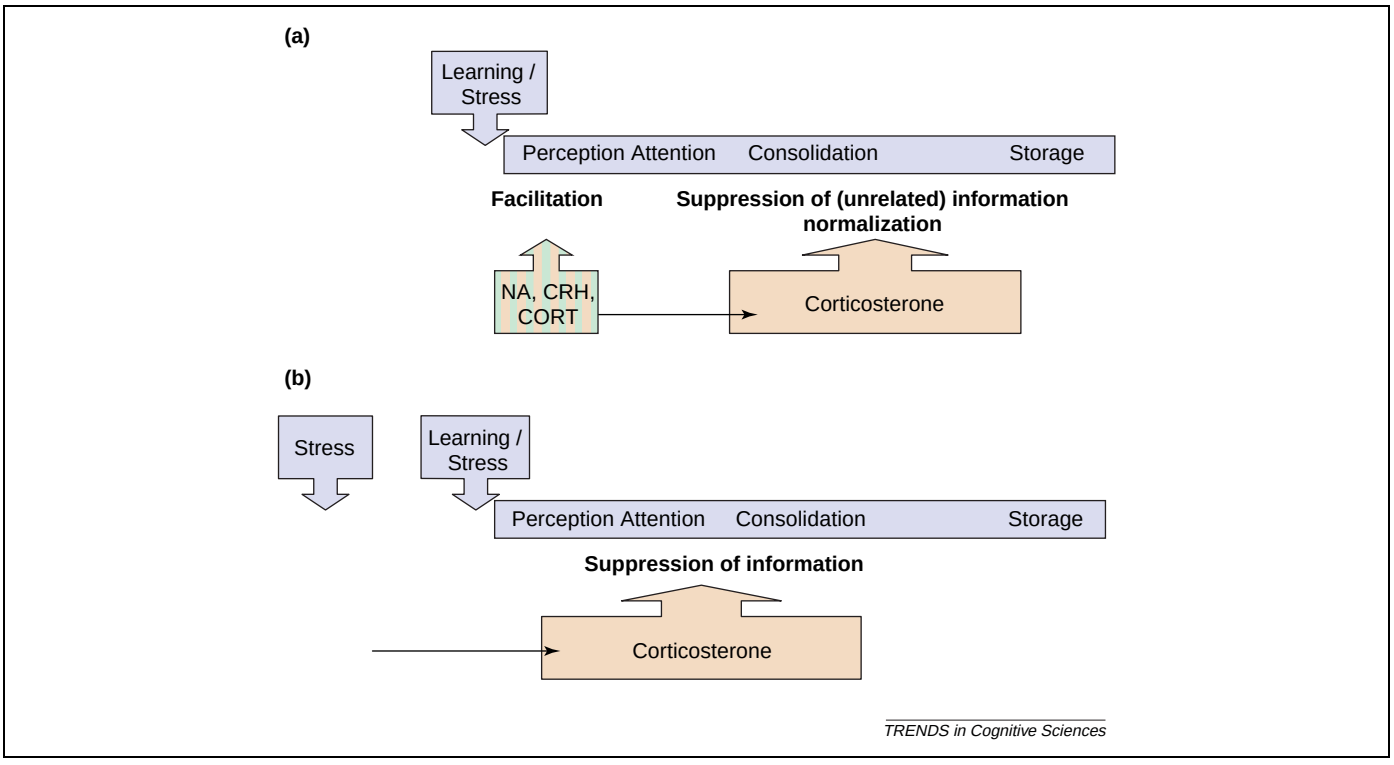

Figure 2. Opposing effects of stress on learning depend on the timing of the events. **(a)** Stress within the context of a learning situation leads to the release of NA, CRH and CORT, all of which are active in the brain at the time that the initial phases of learning take place. At this stage the neurotransmitters and hormones facilitate the ongoing process. Corticosterone, however, also initiates a gene-mediated pathway, which will elevate the threshold for input unrelated to the initial event and restore neuronal activity (normalization), with a delay of more than an hour. **(b)** If an organism has been exposed to a stressor some time before the learning process takes place, the gene-mediated suppression of activity will have developed by the time that acquisition occurs. Under these conditions corticosterone will impair learning processes.

synaptic responses by themselves, they also facilitate electrically evoked LTP.

Corticosterone as a two-stage rocket

Facilitation of LTP is also observed for corticosterone, but only when corticosterone is present around the time that LTP is induced [38,39]. Given the immediate effect of corticosterone this particular action of the hormone is clearly accomplished via a non-genomic pathway. However, the main action of corticosterone is slow and gene-mediated. Through this gene-mediated action high amounts of corticosterone and severe stress were consistently found to suppress LTP and to promote long-term depression, with a delay of at least an hour [19]. This might be accomplished by insertion of glutamate receptors into the membrane [40,41], which would promote ongoing activity but elevate the threshold for synaptic strengthening of input from other sources, in a fashion known as 'meta-plasticity' [42]. This action will enhance the signal-to-noise ratio of information attached to the stressful event, because information reaching the same circuit hours after the initial learning process must be salient enough to overcome this threshold and gain access to memory resources.

In summary, we propose that in the short term, stress-induced hormones will facilitate the strengthening of contacts involved in the formation of memories of the event by which they are released. But at the same time, corticosterone initiates a gene-mediated signal that will suppress any information unrelated to the event reaching the same areas hours later. This is a very efficient strategy to preserve an appropriate priority in the reaction to challenges. The proposed mechanism also explains why the timing of stress application and learning is so important. If corticosterone is released by a stressor one hour before training of a learning task starts, the genomic action will have developed already by the time input related to the learning event reaches the circuit, so this input will encounter an elevated threshold for synaptic strengthening (Figure 2).

The dichotomy in stress hormone actions caused by timing is not only supported by the effects of corticosterone on LTP. For instance, amygdala stimulation facilitates LTP induction in the dentate gyrus when given shortly before tetanic stimulation of dentate afferents; this facilitation of LTP depends on noradrenaline and corticosterone [43]. Yet when amygdala and dentate stimulation are separated in time by, for example, one hour, amygdala stimulation suppresses LTP in the dentate [44]. Another example pertains to the effect of noradrenaline and corticosterone on passive avoidance behavior. Both hormones seem to be necessary to accomplish a facilitatory effect on avoidance memory, but they only do so when acting more or less at the same time [45]. If, however, corticosteroid levels rise some time (e.g. one hour) before noradrenaline is active, the memory-facilitating action by noradrenaline is suppressed and dose-dependently desensitized [46]. In this respect it is revealing that, at the cellular level, corticosterone given several hours before noradrenaline indeed suppresses the effectiveness of the latter, via a gene-mediated pathway [47].

Box 2. Questions for future research

- **Mechanism:** is the mechanism by which stress interferes with retrieval similar to or different from the mechanism by which it promotes consolidation?
- **Convergence in time:** do stressful events experienced some hours before a learning task increase the threshold for acquisition and consolidation of the information to be learned, as opposed to stress around the time of learning?
- **Convergence in space:** will stressors applied around the time of learning and activating the same areas involved in the learning process facilitate consolidation, as opposed to stressors that are not expected to activate areas involved in the learning task?
- **Clinical relevance:** can cognitive impairments associated with over- or under-exposure to stress hormones be corrected by normalization of the hormone levels or modification of their effectiveness?

Conclusion

From the many examples above it is clear that stress affects learning and memory processes. We propose that the direction of changes in memory performance – improvement or impairment – depends on whether the stress is experienced closely linked in time to and within the context of the information to be learned. Future studies will need to supply more experimental evidence for this view (see Box 2). The relevance of stress within a learning context is also something to take into consideration when designing experiments. Particular attention has to be paid to 'hidden' stressors, for example, measurements involving an fMRI apparatus, which can be quite arousing, especially in children.

We predict that stress experienced within the context of a learning experience will induce focused attention and improve memory of relevant over irrelevant (later) information. Importantly, stress-induced release of corticosteroid hormones is necessary to restore (normalize) the activity of circuits involved in the processing of information linked to the event. Both the initial stress-induced facilitation of these circuits and the normalization seem to be required for adequate learning and memory. If the normalization phase is insufficient, for example, when the release of corticosteroid hormones is curtailed, inappropriate recall of salient information might ensue. This could in part explain the burden of traumatic memories in PTSD patients, in whom a strong autonomic response is combined with a strong negative feedback function of the HPA-axis, causing relatively small and transient increases in cortisol level [48]. According to the prevailing view [48], circuits of fear and other negative emotions are underexposed to the hormone, preventing (i) the hormone's role in normalization of activity and (ii) its facilitating effects in extinguishing fixed, maladaptive patterns. In line with this, treatment of PTSD patients with a low dose of cortisol appears to be beneficial [49]. This emphasizes the importance of stress hormones in maintaining optimal memory processing, both in health and in disease.

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