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Review

Stress effects on memory: An update and integration

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ABSTRACT

It is well known that stressful experiences may affect learning and memory processes. Less clear is the exact nature of these stress effects on memory: both enhancing and impairing effects have been reported. These opposite effects may be explained if the different time courses of stress hormone, in particular catecholamine and glucocorticoid, actions are taken into account. Integrating two popular models, we argue here that rapid catecholamine and non-genomic glucocorticoid actions interact in the basolateral amygdala to shift the organism into a 'memory formation mode' that facilitates the consolidation of stressful experiences into long-term memory. The undisturbed consolidation of these experiences is then promoted by genomic glucocorticoid actions that induce a 'memory storage mode', which suppresses competing cognitive processes and thus reduces interference by unrelated material. Highlighting some current trends in the field, we further argue that stress affects learning and memory processes beyond the basolateral amygdala and hippocampus and that stress may pre-program subsequent memory performance when it is experienced during critical periods of brain development.

Contents

1. Introduction

Everyone is familiar with stress. We experience it in varying forms and degrees every day. When we are exposed to potential threats (stressors), our brain initiates a course of action that releases numerous transmitters, peptides, and hormones throughout our body (Joëls and Baram, 2009), all of which is directed at coping with the stressful situation and bringing our organism back into balance (i.e., homeostasis). In particular, two systems are mobilized under stress: (i) the fast acting sympathetic nervous system and (ii) the slow hypothalamus-pituitary-adrenal (HPA) axis. Sympathetic nervous system responses include the release of the catecholamines adrenaline and noradrenaline from the adrenal medulla, which cause, for example, increases in heart rate or enhanced blood flow to skeletal muscles and thus prepare the organism for a 'fight-or-flight' response. Activation of the HPA-axis leads, via intermediate steps, to the release of glucocorticoids (mainly cortisol in humans, corticosterone in rodents) from the adrenal cortex. Glucocorticoids

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can enter the brain, where they bind to high-affinity mineralocorticoid receptors and lower-affinity glucocorticoid receptors (Reul and de Kloet, 1985).

Stress exerts, mediated via catecholamines and glucocorticoids, manifold effects on health, emotion, and cognition (de Kloet et al., 2005). Here we focus on how stress affects learning and memory processes. In the first part of this review, we briefly summarize the effects of (acute) stress on (hippocampus-dependent) memory. In the second part, we portray two popular models of how stress and stress hormones alter memory processes. Because one of these models concentrates mainly on the mechanism that is underlying stress effects on memory (Roozendaal et al., 2006a), whereas the other one focuses primarily on the changes in stress effects on memory over time (Joëls et al., 2006), we refer to these models as the 'vertical' perspective and the 'horizontal' perspective, respectively. Reconciling these two models, in the third part of this review we propose an integrated model of how stress might affect memory processes. Finally, we discuss some recent trends in the research on stress and memory.

2. Stress effects on memory: timing matters

Memories are highly dynamic entities that are built in stages. After initial encoding, the new and fragile memory trace is stabilized during a consolidation process. When reactivated during memory retrieval, the memory trace can re-enter an unstable state so that a reconsolidation process is needed to stabilize it anew (Dudai, 2006). Stress may have an effect on all these processes – encoding, consolidation, retrieval, and reconsolidation (or extinction). How stress influences memory depends on when an individual is stressed.

If an individual is exposed to stress before learning, encoding processes may be changed and subsequent memory can be enhanced (Domes et al., 2002; Schwabe et al., 2008a; Smeets et al., 2007) or impaired (Diamond et al., 2006; Elzinga et al., 2005; Kirschbaum et al., 1996). The direction of the effect of pre-learning stress is influenced by many variables such as the emotional valence of the learned material (Payne et al., 2007) or the interval between the stressful episode and the learning experience (Diamond et al., 2007). Another important factor might be whether the memory is tested immediately after learning when noradrenaline levels peak, slightly later when particularly glucocorticoids levels are high or even later when all hormone levels have returned to baseline although through genomic action, the hormonal effects may still persist. In other words, the effect of stress before learning depends on the extent to which stress affects, in addition to encoding processes, also consolidation and retrieval processes.

Consolidation processes are typically enhanced by stress. Converging evidence from human and rodent studies shows that stress or glucocorticoid administration within a short time window after learning facilitates subsequent memory (Andreano and Cahill, 2006; Beckner et al., 2006; Buchanan and Lovallo, 2001; Cahill et al., 2003; Roozendaal and McGaugh, 1996; Roozendaal et al., 2006b; Smeets et al., 2008). These effects appear to be particularly strong for emotionally arousing material. For example, participants that were stressed after seeing a slide show with neutral and emotional slides remembered more emotional slides than a non-stressed control group, whereas the memory for the neutral slides remained unaffected by stress (Cahill et al., 2003). Similarly, glucocorticoids administered after training in an object recognition task enhanced subsequent recall in naïve rats that experienced novelty-related arousal during training but not in habituated rats which were in a less aroused state during training (Roozendaal et al., 2006b).

In contrast to memory consolidation, memory retrieval seems to be impaired by stress (but see Buchanan and Tranel, 2008 and Schwabe et al., 2009b for contrary findings), although this could also be interpreted as competitive encoding of new information, related to the stress exposure (de Kloet et al., 1999; Diamond et al., 2007). The exposure to stress or the administration of glucocorticoids shortly before a retention test reduces memory performance in both humans and rodents (Buchanan et al., 2006; De Quervain et al., 1998, 2000; Kuhlmann et al., 2005; Lupien et al., 2002; Roozendaal et al., 2003; Schwabe and Wolf, 2009a; Tollenaar et al., 2009). Again, these effects are most pronounced for emotionally arousing material (Kuhlmann et al., 2005; Roozendaal et al., 2003; Smeets et al., 2009).

Although most studies have focused on the effects of stress before learning, after learning or before memory testing, there is recent evidence that stress can influence subsequent memory also if it is presented after retrieval, thus suggesting that stress affects also reconsolidation and/or extinction processes. In rodents, stress and glucocorticoid administration after memory retrieval impair later recall (Cai et al., 2006; Maroun and Akirav, 2008; Wang et al., 2008). In line with these findings, there is first evidence that stress may disrupt memory reconsolidation in humans as well (Schwabe and Wolf, 2010b; Zhao et al., 2009).

To summarize, the nature of stress effects on memory is critically timing dependent. Why does stress enhance memory at some times but seems to impair it at others? How can these opposite effects be explained and what are the underlying mechanisms? In the following sections, we will present two theoretical frameworks that aim to provide answers to these questions.

3. Explaining stress effects on memory

3.1. The 'vertical' perspective

A large body of evidence indicates that stress effects on both memory consolidation and retrieval require concurrent glucocorticoid and noradrenergic activity in the basolateral part of the amygdala (for reviews see Roozendaal et al., 2008, 2009a, 2006a). Glucocorticoids that are released during stressful episodes can readily cross the blood–brain barrier and bind to mineralocorticoid receptors and glucocorticoid receptors in limbic brain areas (Reul and de Kloet, 1985). On the contrary, catecholamines cannot pass the blood–brain barrier; they activate adrenoceptors on vagal afferents terminating in the nucleus tractus solitarius (Williams and Clayton, 2001). Noradrenergic cells in the nucleus tractus solitarius stimulate the basolateral amygdala directly or indirectly via the locus coeruleus. In the basolateral amygdala, the β-adrenoceptor is coupled directly to adenylate cyclase to stimulate cAMP formation. Glucocorticoids affect the noradrenergic system presynaptically in brainstem noradrenergic cell groups projecting to the basolateral amygdala and interact with the β-adrenergic system in the basolateral amygdala postsynaptically via coupling with α-adrenoceptors. Recent evidence suggests that these rapid effects of glucocorticoids on the noradrenergic system may be mediated by membrane-bound receptors which activate a G-protein-coupled, non-genomic signaling cascade that leads to rapidly developing alterations in neuronal excitability (Barsegyan et al., 2010; Karst et al., 2005, 2010; Roozendaal et al., 2010). Finally, glucocorticoid- and noradrenaline-induced activation of the basolateral amygdala may modulate memory processes in other brain areas such as the hippocampus and the prefrontal cortex (see Fig. 1).

This model leads to several testable predictions. Most importantly, stress effects on memory should be reduced after glucocorticoid blockade, after a decrease of noradrenergic arousal, and after basolateral amygdala lesion or inactivation. There is compelling evidence for each of these predictions. Removal of glucocorticoids by adrenalectomy or synthesis inhibition by

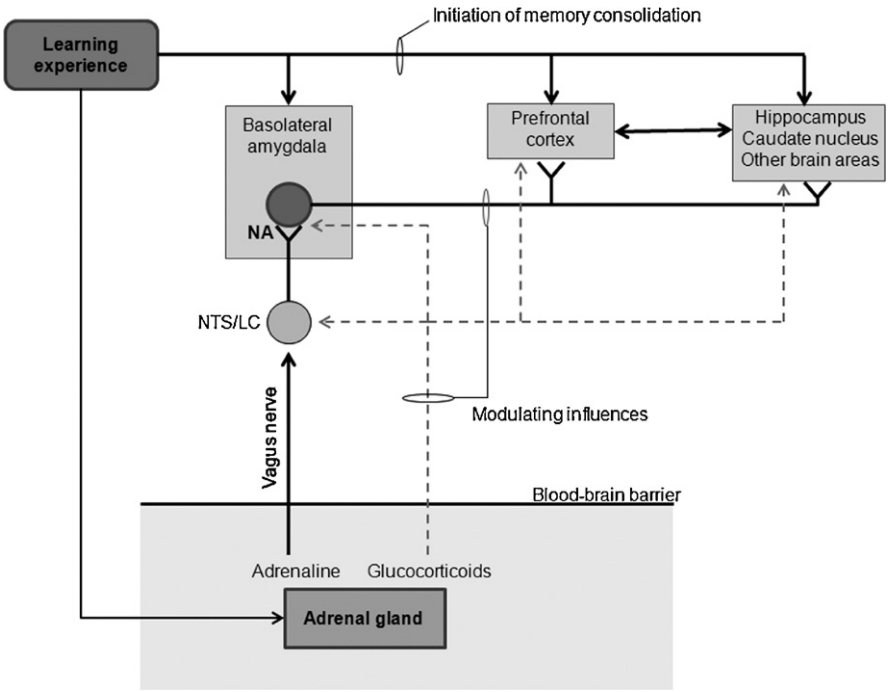

Fig. 1. Glucocorticoids interact with the noradrenergic system at presynaptic and postsynaptic sites to influence memory processes. Learning experiences initiate a consolidation process. In addition, emotional arousal (stress) associated with the learning experience stimulates the release of catecholamines (adrenaline, noradrenaline) and glucocorticoids from the adrenal gland. Catecholamines cannot cross the blood–brain barrier but activate, via vagal afferents, noradrenergic cells in the nucleus tractus solitarius (NTS) and the locus coeruleus (LC), which in turn stimulate the basolateral amygdala. Glucocorticoids can pass the blood–brain barrier and directly influence memory processes in several brain areas. Moreover, they interact with noradrenaline (NA) in the basolateral amygdala, which then modulates memory processes in the prefrontal cortex, hippocampus, caudate nucleus, and other brain areas. Figure is modified, with permission, from (McGaugh, 2000).

metyrapone impairs memory consolidation (Oitzl and de Kloet, 1992; Roozendaal et al., 1996). Furthermore, pharmacological blockade or genetic disruption of the glucocorticoid receptor in the brain or directly in the basolateral amygdala has a detrimental effect on memory consolidation (Oitzl and de Kloet, 1992; Oitzl et al., 2001; Roozendaal and McGaugh, 1997b), thus indicating the critical role of this receptor in mediating glucocorticoid effects on memory consolidation. Infusion of a glucocorticoid receptor antagonist into the brain ventricular system or directly into the hippocampus revealed a dose-dependent facilitating effect on spatial memory (Oitzl et al., 1998a,b), underlining the relevance of a balanced activation of hippocampal glucocorticoid receptors for memory consolidation. Administration of β-adrenoceptor antagonists such as propranolol or atenolol blocks the influence of glucocorticoids on memory processes (Quirarte et al., 1997; Roozendaal et al., 2002). Similarly, glucocorticoids are ineffective in rats that were habituated to the experimental context before training (Okuda et al., 2004). Corroborating the idea that arousal-induced noradrenergic activity is key to glucocorticoid effects on memory, glucocorticoid effects can be reinstated in habituated rats that are administered the α_2-adrenoceptor antagonist yohimbine, which leads to an increased in noradrenergic stimulation (Roozendaal et al., 2006b).

It is well known that glucocorticoid and catecholamine effects on memory are mediated by the amygdala (McGaugh, 2000), in particular by its basolateral part. Infusions of a glucocorticoid receptor agonist into the basolateral amygdala enhance memory consolidation, whereas infusions into the central amygdala have no effect (Roozendaal and McGaugh, 1997b). Furthermore, selective lesions of the basolateral amygdala or injections of a β-adrenoceptor antagonist into the basolateral amygdala block the memory-enhancing effects of post-training glucocorticoids (Quirarte et al., 1997; Roozendaal and McGaugh, 1996). Although the amygdala might be critically involved in storing conditioned fear memories (LeDoux, 1996), it is important to note that the amygdala is not a site of storage for spatial or 'declarative' memories (Packard and Teather, 1998). For these forms of memory, the amygdala acts rather as a modulator which changes memory processes in other brain regions (McGaugh, 2000). For example, post-training infusions of a glucocorticoid receptor agonist into the hippocampus enhance subsequent memory. Selective lesions of the basolateral amygdala or the infusion of a β-adrenoceptor antagonist into the basolateral amygdala abolish this effect (Roozendaal and McGaugh, 1997a; Roozendaal et al., 1999). Others have also shown that the basolateral amygdala strongly affects hippocampal function through glucocorticoid-dependent processes (Akirav and Richter-Levin, 2002; Kim et al., 2001, 2005).

Although this model was primarily based on rodent data, it is also supported by human studies. First, as we have noted above, stress and glucocorticoid effects on memory are most pronounced for emotionally arousing material (Cahill et al., 2003; Kuhlmann et al., 2005) that leads to noradrenergic activation. Second, administration of the β-adrenoceptor antagonist propranolol can prevent the effects of stress or glucocorticoid administration on memory processes (De Quervain et al., 2007; Schwabe et al., 2009b). Third, the effects of glucocorticoids may disappear when participants are tested in a non-arousing testing environment (Kuhlmann and Wolf, 2006). Finally, studies in which participants were classified as 'high-responders' and 'low-responders' in terms of their cortisol elevations and emotional arousal in response to stress suggest that stress affects memory only if participants show a robust increase in both cortisol and arousal (Abercrombie et al., 2006; Schwabe et al., 2008a). Interestingly, a recent functional magnetic resonance imaging (fMRI) study confirmed that also in humans the amygdala is the locus of glucocorticoid–noradrenaline interactions (Van Stegeren et al., 2007). This study showed that participants with a high cortisol response to stress exhibited stronger amygdala activation when watching emotionally arousing pictures compared

to participants with a lower cortisol response. Remarkably, this endogenous cortisol effect on amygdala activity disappeared when participants were administered propranolol before picture presentation.

Another fMRI study showed that the combined administration of hydrocortisone and the α2-adrenoceptor antagonist yohimbine, which leads to an increase in noradrenergic stimulation, shifts the brain from hippocampus–amygdala activation (with either drug alone) to a strong deactivation of the prefrontal cortex (Van Stegeren et al., 2010). The reduced hippocampus–amygdala activation was linked to improved memory performance. Comparable reduced hippocampal activity correlating with good memory performance was also observed after stress exposure (Henckens et al., 2009). Perhaps, hippocampal input during stressful experiences may be characterized by a large proportion of irrelevant information, hampering a clean separation between task-related and -unrelated information. Stress might reduce overall hippocampal activity while leaving activity in synapses related to the encoding of the stressful event intact, thus enhancing the signal-to-noise ratio.

These findings also suggest that simultaneous glucocorticoid and noradrenergic activation changes the patterns of brain activity in a way that may contribute to the differential effects of stress on different memory processes (in particular consolidation and retrieval). Indeed, there are findings from rodent studies indicating that the same glucocorticoid–noradrenaline interactions that facilitate memory consolidation impair memory retrieval and working memory (Roozendaal et al., 2008). All of these effects seem to depend on the activation of membrane-bound glucocorticoid receptors and rapid, non-genomic glucocorticoid actions in the prefrontal cortex (Barsegyan et al., 2010; Roozendaal et al., 2010) as well as functional interactions between the prefrontal cortex and the basolateral amygdala (Roozendaal et al., 2009b). Thus, concurrent glucocorticoid and noradrenergic activity appears to shift brain systems in a manner that favors consolidation, at the expense of other memory processes (Roozendaal, 2002).

In sum, the interactive influence of glucocorticoids and noradrenergic activity has been shown for different memory tasks and systems, including hippocampus-dependent spatial memory and prefrontal cortex-dependent working memory (Roozendaal and McGaugh, 1997b; Roozendaal et al., 2004). Moreover, there is compelling evidence that stress effects on both memory consolidation and memory retrieval require the concerted action of glucocorticoids and noradrenaline in the basolateral amygdala (Roozendaal, 2002; Roozendaal et al., 2006a). Thus, this model sheds light on the mechanism that is underlying stress (hormone) effects on memory and hence provides an answer to the question how stress shapes memories.

3.2. The 'horizontal' perspective

Stress may improve or impair memory. According to the 'vertical' perspective, these opposite effects of stress are owing to a stress-induced shift in the activity of different brain systems. Another recent model assumes that stress enhances memory if it is experienced within the context of the learning episode and if the hormones and neurotransmitters that are released in response to stress act on those brain circuits that are activated by the learning episode. On the other hand, stress impairs memory if it is experienced out of the learning context (Joëls et al., 2006), i.e. without any link to the learning experience or long before or after learning. This view is mainly based on the different time courses of catecholamine and glucocorticoid actions. Catecholamines exert rapid and relatively short-lasting effects. Glucocorticoid actions are mainly genomic, i.e., delayed and long-lasting. In addition to the genomic actions, glucocorticoids have rapid, non-genomic effects that are mediated by membrane-bound receptors (Groeneweg et al., 2011; Karst et al., 2005, 2010). It is proposed that catecholamines and glucocorticoids facilitate learning and memory processes in the short-term. Gene-mediated glucocorticoid actions, however, may suppress the processing of new information and thus impair memory processes unrelated to those linked to glucocorticoid release (see Fig. 2).

This model can explain the seemingly paradoxical, time-dependent effects of stress on memory. If an individual is stressed

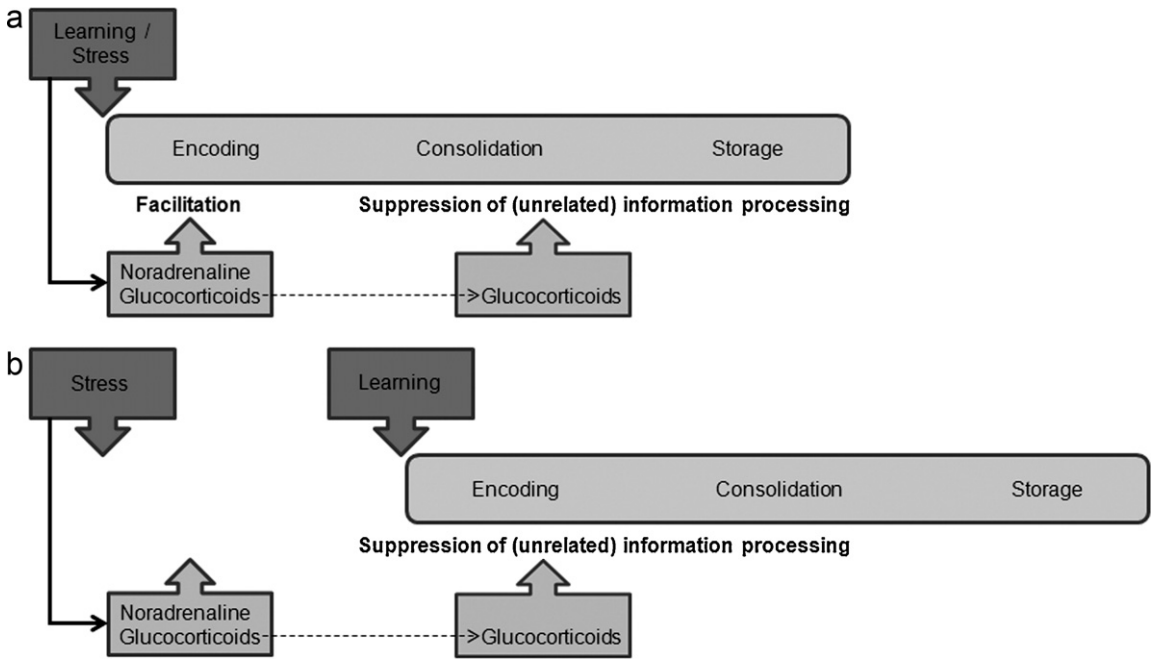

Fig. 2. Opposite effects of stress on learning and memory depend on the timing of the events. (a) If stress is experienced within the context and around the time of the learning experience, catecholamines and non-genomic glucocorticoid actions facilitate encoding processes and thus enhance subsequent memory. (b) If, however, stress is experienced a considerable time before learning, the genomic mode of glucocorticoid action is already active which suppresses information processes and may impair learning of information unrelated to the release of the stress hormones. Figure modified, with permission, from (Joëls et al., 2006).

shortly before, during, or shortly after learning, rapidly acting catecholamine and non-genomic glucocorticoid effects facilitate attentional and other encoding processes. In addition, delayed, genomic glucocorticoid actions suppress competing information processing after learning and hence promote memory consolidation (Buchanan and Lovallo, 2001; Cahill et al., 2003). If, however, an individual is exposed to stress a considerable time before learning and the genomic mode of glucocorticoid action is already active during learning, stress can impede new learning and memory processes. The disruptive effects of stress and glucocorticoids on memory retrieval (Buchanan et al., 2006; De Quervain et al., 1998; Kuhlmann et al., 2005) might be due to the fact that there is often no direct relation between the stressor and the memory test (especially in laboratory settings), i.e., the stressor may be experienced as 'out-of-context'. Alternatively, the stress-induced retrieval impairment could be seen as an indication of a facilitated new learning process, in which the stressful episode is burnt into memory and competing cognitive activities, such as the retrieval of previously learned information, are suppressed (de Kloet et al., 1999; Diamond et al., 2004; Roozendaal, 2002). Similarly, stress after memory retrieval can enhance the storage of the stressful event, leaving fewer capacities for the restabilization of reactivated information and thus impairing reconsolidation (Schwabe and Wolf, 2010b).

Converging lines of evidence from cellular to behavioral levels support this model. Stress hormones like noradrenaline and glucocorticoids may facilitate learning processes at the synaptic level. It is well documented that noradrenaline strengthens synaptic contacts in the hippocampus (Katsuki et al., 1997). Moreover, noradrenaline facilitates the induction of long-term potentiation (Gelinas and Nguyen, 2005; Hopkins and Johnston, 1984; Huang and Kandel, 1996) which is widely considered one of the major cellular mechanisms underlying learning and memory. Glucocorticoids may also exert facilitating effects on hippocampal and amygdala glutamatergic transmission via a rapid, non-genomic mechanism (Karst et al., 2010, 2005). In addition, glucocorticoids can also enhance long-term potentiation. However, the latter effect occurs only if glucocorticoids are present around the time of induction of long-term potentiation (Wiegert et al., 2006). Slow, genomic glucocorticoid actions suppress long-term potentiation in the hippocampus and the amygdala (Diamond et al., 2007; Kavushansky and Richter-Levin, 2006; Kim and Diamond, 2002). Functional differences between early (i.e., non-genomic) and late (i.e., genomic) glucocorticoid actions can also be found at the systems level. For instance, a recent fMRI study in humans showed that glucocorticoids desensitize the amygdala when administered 75 min before the presentation of fearful or happy faces, which may favor vigilance and attention. Amygdala responsivity to fearful – but not happy – faces was normalized again when participants received glucocorticoids 285 min before they saw the faces (Henckens et al., 2010), pointing to a valence-specific effect. Similarly, another fMRI study found enhanced activity in the hippocampus and amygdala shortly after glucocorticoid injection but reduced activity at later time intervals (Lovallo et al., 2010).

Several behavioral studies demonstrate directly that the release of glucocorticoids around the time of learning improves later memory. Rats trained at a low water temperature of 19 °C in the Morris water-maze task, i.e., under stressful conditions that lead to significant increases in corticosterone, showed better long-term memory than rats trained at a water temperature of 25 °C (Sandi et al., 1997). Although these effects seem to be dose dependent (Joëls, 2006; Salehi et al., 2010), pharmacological or genetic interference with the functioning of the glucocorticoid receptor during learning impairs subsequent retention (Oitzl and de Kloet, 1992; Oitzl et al., 2001).

In line with the idea that stress facilitates memory only if there is a convergence between the stress experience and the learning episode in 'time' and (neural) 'space', a recent electroencephalography (EEG) study found that stress shortly before learning neutral and emotionally negative pictures increased the orientation towards negative stimuli, as reflected in a greater magnitude of late positive potentials. Interestingly, these stress-induced changes in brain activity to negative pictures at encoding correlated positively with recall performance 24 h later (Weymar et al., under review). Similarly, stress shortly before the learning of material that was stressor-related or -unrelated and high- or low-arousing enhanced selectively the subsequent memory of the stressor-related high-arousing stimuli (Smeets et al., 2009). However, in another recent study memory for both stressor-unrelated and stressor-related words was impaired when participants were stressed during learning (Schwabe and Wolf, 2010a). These findings suggest that a stressful episode can act as a distractor during learning and that a mere conceptual relatedness between stressor and learning material is not sufficient to enhance memory. It is tempting to speculate that stress at the time of learning promotes particularly the retention of information that is functionally relevant for coping with the stressful experience, such as the location of the escape platform in the water maze.

In summary, this model provides an answer to the question how the opposite effects of stress on memory can be explained: stress enhances memory if it is experienced within the context of the learning episode but impairs memory if it experienced outside the learning context.

3.3. An integrative model

In the previous two sections, we have described two models that explain how stress influences memory processes. One (the 'vertical' view) is based on manipulations of different brain regions (often simultaneously) and makes very specific predictions about the mechanism underlying stress effects on memory. In particular, it postulates that stress effects on memory depend on concurrent glucocorticoid and noradrenergic activity in the basolateral amygdala (Roozendaal, 2002; Roozendaal et al., 2009a). The other one (the 'horizontal' view) is more based on in vitro electrophysiology of brain slices and provides an explanation why stress effects on memory are dependent on the time of the stress exposure, suggesting that stress improves learning around the time of the stress experience via catecholamine and non-genomic glucocorticoid action and that stress impairs learning when it is experienced out of the learning context via genomic glucocorticoid actions (Joëls et al., 2006).

Although the two models differ in their focus (specific mechanism versus changes over time), they share many assumptions. Both models acknowledge the critical role of the (basolateral) amygdala and its modulatory influences on other brain areas for the effects of stress on memory. In both models, noradrenaline and glucocorticoids are the key players and both models assume that glucocorticoids may exert rapid, non-genomic as well as slow, genomic actions and that these different modes of glucocorticoid action have different effects on memory processes.

Indeed, there is evidence that the two proposed mechanisms operate hand in hand (Joëls et al., 2011). Noradrenaline and glucocorticoids are both required to enhance inhibitory avoidance memory in rats (Roozendaal et al., 1999), as predicted by the 'vertical' view. However, they do so only if the two stress mediators rise at about the same time. If glucocorticoids rise considerably earlier than noradrenaline, the memory-facilitating effect of noradrenaline is suppressed (Borrell et al., 1984), as predicted by the 'horizontal' view. A recent study in humans yielded similar findings (Zoladz et al., 2011). Here, participants were stressed before

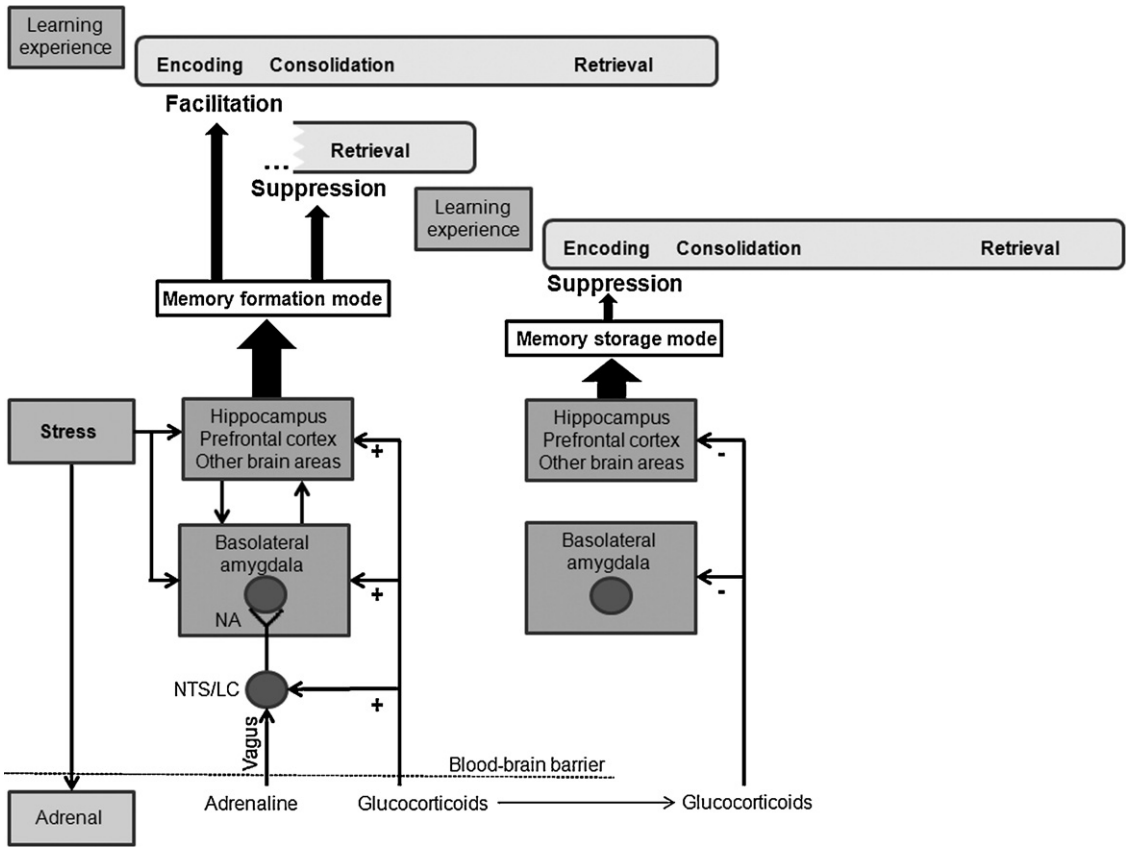

Fig. 3. Integrative model of stress effects on memory. Rapid catecholamine and non-genomic glucocorticoid effects interact in the basolateral amygdala to shift other brain areas into a 'memory formation' mode. The memory formation mode facilitates the processing of events present around the time of the stressful experience but suppresses other cognitive operations such as memory retrieval. With time, genomic glucocorticoid actions become active which promote a 'memory storage mode' that reduces interference with memory consolidation by suppressing the encoding of new information. NA – noradrenaline; NTS – nucleus tractus solitarius; LC – locus coeruleus.

they learned neutral and emotionally arousing material. Critically, the interval between stress and learning was either short (no delay) or relatively long (30 min). Overall, stress affected solely the memory for emotionally arousing material, which is in line with the hypothesis that stress effects require noradrenergic activation in the amygdala. The direction of the stress effect, however, depended critically on the timing of the stress exposure. Stress immediately before learning enhanced memory 24 h later, whereas stress 30 min prior to learning reduced the recall performance. Moreover, positive correlations between heart rate as an indicator of autonomic nervous system activity and memory occurred in the group that was stressed immediately before learning. In the group that was stressed 30 min before learning, heart rate and salivary cortisol levels correlated negatively with memory.

Integrating the two models and based on the evidence reviewed above, the following picture emerges: stressful experiences lead to the secretion of catecholamines and glucocorticoids. Fast catecholamine and non-genomic glucocorticoid actions interact in the basolateral amygdala to shift the activity of other brain areas, such as the prefrontal cortex, the hippocampus or the caudate nucleus, into a 'memory formation mode'. Although the basolateral amygdala appears to be the central mediator of catecholamine and glucocorticoid actions on memory processes (Roozendaal et al., 2009a), these stress hormones exert also direct effects on brain regions such as the prefrontal cortex and hippocampus which contribute to the initiation of the memory formation mode (Diamond et al., 2007). In the memory formation mode, perception, attention, encoding, and the early consolidation of ongoing events is enhanced; the cognitive capacities of the organism are directed at coping with the current stressor and its storage into memory. Competing cognitive operations, such as the retrieval of previous experiences, are suppressed. As time after the stressful episode proceeds, catecholamine levels return to baseline and genomic glucocorticoid actions are exerted. They shift the organism into a 'memory storage mode' in which the threshold for the processing of new material (and possibly the retrieval of old material) that is unrelated to the stressful experience is increased. Thus, the storage mode reduces interference and promotes the long-term storage of events that were experienced under stress. This integrative model is summarized in Fig. 3.

4. Stress effects on memory: current trends

So far, we were referring mainly to the influence of acute stress on hippocampus- and basolateral amygdala-dependent memory processes. In the following, we will give a brief overview of recent research focusing on the influence of stress on different (i.e., non-hippocampal) memory systems and the influence of stress during early life on later cognitive functioning, respectively.

4.1. Stress effects on striatum-dependent learning and memory

In everyday life, "memory" is mostly used to refer to hippocampus-dependent episodic memory. Similarly, research on stress and memory has focused mainly on hippocampus-dependent memory processes over the past decades (for a review see Lupien and Lepage, 2001). However, memory is no single entity, it is composed of multiple hippocampal and non-hippocampal memory systems (Squire, 2004) and there is evidence that stress may also affect the consolidation of hippocampus-independent

forms of memory (Miranda et al., 2008; Roozendaal et al., 2010). One of the non-hippocampal memory systems that has received increased attention in recent years is the striatum. For a long time, the striatum was considered primarily a motor area but there is by now a broad consensus that it has also mnemonic functions (Graybiel, 2008; Packard and Knowlton, 2002; White, 1997).

Is striatum-dependent memory influenced by stress? Although stress hormone receptors are only moderately expressed in the striatum (Morimoto et al., 1996), recent evidence indicates that stress and glucocorticoids affect striatum-dependent behavior. Corticosterone infusion directly into the dorsal striatum immediately after inhibitory avoidance learning enhanced subsequent memory for the task (Medina et al., 2007). Intra-striatal corticosterone injections left contextual memory unaffected, suggesting that corticosterone may have strengthened memory for procedural or implicit aspects of the training. This idea is supported by another study (Quirarte et al., 2009) in which corticosterone was injected into the dorsal striatum before rats were trained on either a spatial version of the water maze, that requires hippocampus-based spatial memory (Morris et al., 1986), or on a cued version that is known to depend on dorsal striatum-based stimulus-response memory (Packard and Knowlton, 2002). Corticosterone injections into the dorsal striatum enhanced memory for the cued version but not for the spatial version, indicating that glucocorticoids act in the (dorsal) striatum to enhance the consolidation of stimulus-response memories. The effects of stress hormones on striatum-dependent memory require an intact basolateral amygdala (Packard and Teather, 1998) and the infusion of a β-adrenoceptor antagonist into the basolateral amygdala prevented the effects of glucocorticoid injections into the striatum (Quirarte et al., unpublished data), thus suggesting that the mechanism underlying stress effects on striatum-dependent memory is very similar to the one underlying stress effects on hippocampus-dependent memory. Comparable evidence from humans is largely missing. Closing this gap is one of the challenges for future human research on stress and memory.

4.2. Stress and the quality of memory

Multiple memory systems are not independent but may interact (Kim and Baxter, 2001). The nature of these interactions can be cooperative (Voermans et al., 2004) or competitive (Poldrack and Packard, 2003). Competitive interactions can be observed, for example, in a fixed location-visible platform water maze task, in which rodents are trained to find a fixed, submerged platform that is marked with a pole. Rats could use either the relationship between several extramaze cues (i.e., a hippocampus-dependent spatial strategy) or the association with the pole (i.e., a neostriatum-dependent stimulus-response strategy) to locate the escape platform. A test trial, in which pole and platform are relocated to another quadrant, reveals the used strategy: swimming to the quadrant where the platform had been during training indicates spatial learning, whereas swimming to the novel location of pole and platform indicates stimulus-response learning. Most interestingly, rats that were stressed before training in such a fixed location-visible platform paradigm used significantly more often a stimulus-response strategy than non-stressed controls (Kim et al., 2001; Packard and Wingard, 2004). This stress-induced shift towards more stimulus-response learning can be blocked by a mineralocorticoid receptor antagonist (Schwabe et al., 2010a), which suggests that this receptor might operate as a switch between spatial and stimulus-response memory systems.

These findings were recently translated to humans (Schwabe et al., 2007). Participants were exposed to a psychosocial stressor before they were trained to locate a 'win-card' out of four cards in a 3D model of a room. The 'win-card' could be identified via multiple room cues, i.e., via a spatial strategy, or via the association with a single, proximal cue, i.e., via a stimulus-response strategy. Relocating the 'win-card' and the proximal cue in a test trial revealed the used strategy: choosing the card in the old position of the 'win-card' was interpreted as a spatial strategy, choosing the card next to the novel position of the cue was interpreted as a stimulus-response strategy. As in rats, stress prior to learning favored the use of stimulus-response memory over spatial memory. The effects obtained after chronic stress or acute glucocorticoid administration were highly comparable (Schwabe et al., 2008b, 2009a).

The modulatory influence of stress on the use of multiple memory systems is not limited to spatial versus stimulus-response memory. Recent evidence shows that stress may also change the systems used during instrumental learning. Instrumental learning, i.e., learning how to achieve a desired state, can be controlled by two systems operating in tandem: (i) a prefrontal cortex-dependent goal-directed system that encodes the causal relationship between an action and the motivational value of the outcome; and (ii) a dorsolateral striatum-dependent habit system that learns the association between an action and preceding stimuli, without any link to the value of the outcome that is engendered by the action (Balleine and Dickinson, 1998; Dickinson, 1985). Stress before learning renders instrumental action insensitive to changes in the value of the outcome and thus habitual (Schwabe and Wolf, 2009b). There is evidence that this stress-induced shift from goal-directed to habit learning may also require concurrent glucocorticoid and noradrenergic activity, similar to stress effects on hippocampus-dependent memory (Roozendaal et al., 2006a). The parallel administration of glucocorticoids and the α_2-adrenoceptor antagonist yohimbine mimicked the stress effect on instrumental action, whereas glucocorticoid or yohimbine administration alone had no effect (Schwabe et al., 2010b). A recent rodent study reported that chronic stress may bias instrumental action in rats towards more habitual action and that this shift is accompanied by opposite structural changes in the structures underlying goal-directed and habitual action, respectively, with atrophy in the prefrontal cortex and hypertrophy in the dorsolateral striatum (Dias-Ferreira et al., 2009). However, it seems rather unlikely that a single stress or glucocorticoid exposure may have similar effects at the neural level.

These findings demonstrate that stress affects not only *how much* we learn and remember, i.e., the quantity of memory, but also *how* we learn and *what* we remember, i.e., the quality of our memory (for a review see Schwabe et al., 2010c).

4.3. Effects of early life and prenatal stress on memory

The effects of stress on brain and behavior may be long-lasting, particularly if stress is experienced in critical periods of brain development such as childhood and youth (Lupien et al., 2009; Oitzl et al., 2010). Rats exposed to fragmented or low maternal care during the early postnatal period (i.e., a severe stressor for a rat pup) showed significant changes in hippocampal structure and synaptic plasticity later in life (Brunson et al., 2005; Champagne et al., 2008). These changes were accompanied by impairments in various hippocampus-dependent tasks (Bredy et al., 2004; Brunson et al., 2005; Oitzl et al., 2000; Toki et al., 2007). However, although early life stress has negative effects on later synaptic plasticity and memory when tested under normal conditions, this pattern may be reversed when rats are tested under high stress conditions. After administration of a high dose of corticosterone, adult offspring of low-caring mothers showed enhanced long-term potentiation. Furthermore, adult offspring from low-caring mothers performed better than offspring from high-caring mothers in a

highly stressful fear conditioning task (Champagne et al., 2008). Similar results were obtained after maternal deprivation: adult rats that were deprived for 24 h at postnatal day 3 exhibited – compared to controls – impaired LTP and learning under non-stressful conditions but improved functionality with stress-like corticosterone levels (Oomen et al., 2010). These findings suggest that early life stress may prepare the organism for optimal cognitive functioning in high stress environments (Oitzl et al., 2010).

In addition to early life stress, maternal distress during pregnancy may alter subsequent brain functioning of the offspring (for a review see Weinstock, 2008). Prenatal stress may result in reduced hippocampal cell proliferation, impaired long-term potentiation in the hippocampus, and impaired performance in the Morris water-maze task (Lemaire et al., 2006; Yaka et al., 2007; Yang et al., 2006). Moreover, prenatal stress may also affect the 'quality' of memory by changing the contributions of hippocampus-dependent and dorsal striatum-based memory systems to behavior. For instance, adult offspring from mothers that were exposed to ethanol during gestation used in a fixed location-visible platform water maze task significantly more often a dorsal striatum-based stimulus-response strategy than control rats (Sutherland et al., 2000).

Obviously, it is rather difficult to assess the influence of early life or prenatal stress on memory in humans. There are, however, studies that suggest an influence of early life or prenatal stress on cognitive functioning in humans, too. For example, children of mothers who experienced a natural disaster or other stressors during pregnancy exhibited reduced cognitive abilities at the age of 5–7 years (Gutteling et al., 2006; Laplante et al., 2008). In the face of these findings and other findings that relate early life or prenatal stress to an increased vulnerability to psychopathology (for reviews see Cottrell and Seckl, 2009; Gunnar and Quevedo, 2007; Loman and Gunnar, 2010), studying the influence of early life or prenatal stress on brain and cognition appears to be an important avenue for future research.

5. Concluding remarks

Stress affects memory in various ways. Depending on the timing of the stress exposure, stress can impair or improve (hippocampus-dependent) memory processes. It has been previously suggested that these effects require simultaneous noradrenergic and glucocorticoid activity in the basolateral amygdala (Roozendaal et al., 2006b) and that the direction of the stress effects on memory depends on whether stress is experienced within or outside the context of the learning episode (Joëls et al., 2006). Collectively, these models propose that catecholamines and glucocorticoids interact in the basolateral amygdala to induce a 'memory formation mode' that enables the organism to effectively encode the experiences made under stress. The further consolidation of these experiences in long-term memory is promoted by a 'memory storage mode' that is initiated by genomic glucocorticoid actions sometime after the stress experience has come to an end.

Recent years have seen considerable advances in our understanding of stress effects on memory. For instance, it has become increasingly clear that stress affects not only hippocampus-dependent memory but also striatum-dependent memory as well as the interactions between multiple memory systems (Schwabe et al., 2010c). Furthermore, it has been shown that stress may pre-program memory performance in later life when it is experienced in critical periods of (brain) development (Lupien et al., 2009; Oitzl et al., 2010). Despite these advances, many questions remain. How can the reported dose-dependencies in the effects of stress and stress hormones on memory be explained? Is the retrieval of previously learned material only impaired during the 'memory formation mode' or also during the 'memory storage mode'? What is the neural basis of the modulatory effects of stress on multiple memory systems and are these effects also dependent on the timing of the stress exposure? How can glucocorticoids exert opposite effects in different brain areas? How do the modulatory influences of the basolateral amygdala on other brain areas, such as the hippocampus, interact with the effects that glucocorticoids and other stress mediators exert in these areas directly? Why does stress change memory in some individuals but not (or to a lesser extent) in others? Answering these and other questions seems to be necessary to get a complete picture of how stress shapes memory to prepare the organism for similar challenges in the future.

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