Chapter 9.9

Memory and Stress

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Abstract

Stressful events have a major impact on memory. In this chapter, I will discuss classic and more recent findings suggesting that stress may have distinct effects on different stages of memory – encoding, consolidation, retrieval, and reconsolidation – and that these effects are closely linked to the precisely timed action of hormones and neurotransmitters that are released in response to stress. In addition to these time-dependent changes in memory performance after stress, I will discuss evidence showing that stress modulates the engagement of multiple memory systems in a manner that facilitates rather simple but rigid 'habit' memory, at the expense of cognitively more demanding forms of memory. I will further argue that this shift towards habit memory may be adaptive for performance under stress but result in rather inflexible memories. Finally, I will discuss some implications of stress-induced changes in memory.

Keywords: stress, memory, glucocorticoids, hippocampus, amygdala, dorsal striatum, multiple memory systems, encoding, consolidation, retrieval

9.9.1 Introduction

Stressful events are ubiquitous in everyday life. They may range from the many daily hassles, such as getting stuck in the traffic when late, to major life events, including the death of a beloved one. Although clearly distinct in their intensity and long-term consequences, what these situations have in common is that they threaten the organism's homeostasis, its inner balance (1, 2). Such threats, or stressors, trigger the release of numerous neurotransmitters, hormones and other neuromodulators. Through the action of these stress mediators on the brain, stress may exert a significant impact on a broad range of cognitive functions (3-8).

This chapter will focus on the impact of acute stress on memory processes. Although it is primarily dedicated to stress-induced changes in human memory, I will also repeatedly refer to findings in non-human animals because particularly studies in rodents provided critical insights into how stress alters memory processes; the vast majority of the human studies on stress and memory build on these insights. Since the impact of stress on memory depends critically on the activity of the body's stress response systems, in the first part of this chapter I will briefly portray the central and peripheral stress response systems of the body. In terms of stress-induced changes in memory, I will distinguish effects on quantitative aspects of memory (*how much is remembered*) from those on the quality or nature of memory (*what is remembered*). In part two of this chapter, I will review stress effects on quantitative memory performance. Here, I will show that stress may have different effects on memory depending on the stage of memory – encoding, consolidation, retrieval or reconsolidation. In part three, I will summarize evidence indicating that stress may bias the engagement of multiple memory systems and thus affect the quality of memory. Finally, I will discuss the implications of stress-induced changes in memory for cognitive adaptation under stress as well as for clinical and educational contexts.

9.9.2 Basics of the physiological stress response

The stress response is characterized by a remarkable complexity. It includes a multitude of different stress mediators that act in concert to enable a rapid adaptation to internal and external demands as well as to reinstate homeostasis. Threat-related information from all sensory systems is conveyed to the brain. The precise nature of the stress response, however, depends on the type of stressor (and several additional factors (9)). For instance, physical stressors that involve an immediate threat to homeostasis, such as blood loss, cold, or respiratory distress, rapidly recruit the brainstem and hypothalamic regions. By contrast, psychological stressors that require interpretation by higher brain structures, such as embarrassment or deadlines, are channeled through limbic forebrain structures, which then provide descending input to the hypothalamus and brainstem nuclei (10, 11). A key structure that integrates ascending and descending stress signals is the paraventricular nucleus (PVN) of the hypothalamus. The PVN directly regulates two major stress response systems: the sympathetic nervous system and the hypothalamus-pituitary-adrenal (HPA) axis (Figure 1).

The actions of these stress response systems have classically been described as two temporal "waves" of stress responses. Within seconds after stressor onset, the first wave sets in, when the sympathetic branch of the autonomic nervous system is activated. This sympathetic activation represents the "fight-or-flight"-response first described by Walter Cannon (12) more than a century ago and includes, for instance, increases in heart rate, pupil dilation and respiration. Moreover, sympathetic activation triggers the release of adrenaline (mainly from the adrenal medulla) and noradrenaline (mainly from sympathetic nerves but also from the adrenal medulla). Notably, peripheral adrenaline and noradrenaline cannot cross the blood-brain-barrier but exert indirect effects on the brain via the vagus nerve (13), which then modulates the activity of noradrenergic brainstem nuclei (in particular, the locus coeruleus and nucleus tractus solitarius). In addition to these peripheral effects, sympathetic activation

increases the release of monoamines, such as noradrenaline, dopamine and serotonin, in several brain regions, including the amygdala, hippocampus, and prefrontal cortex (PFC), with critical implications for the cognitive processing of the ongoing stressor. Beyond monoamines, stress also induces a rapid release of a number of neuropeptides, including corticotropin-releasing hormone (CRH), vasopressin and oxytocin, which may all contribute to the behavioral stress response (9, 14). Importantly, this first wave of the stress response wanes quickly, typically within minutes after the stressor is over, and its effects are rather short-lived (albeit there is some evidence that rapid monoamine activation might also lead to sustained genomic changes, (15)).

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More long-lasting stress effects are accomplished through the delayed, second wave of the stress response, which is closely linked to the activity of the HPA axis. This hormonal cascade starts when stress signals from ascending brainstem pathways or descending limbic inputs lead to the secretion of CRH in the hypothalamic PVN. CRH acts on the anterior pituitary to facilitate the release of adrenocorticotrophic hormone (ACTH), which in turn stimulates the synthesis and secretion of glucocorticoids (mainly cortisol in humans and corticosterone in rodents) from the adrenal cortex. Glucocorticoids are steroid hormones that can pass the blood-brain-barrier and thus directly act on the brain. They reach peak levels about 30 minutes after the onset of a stressful event and are thought to be a driving force in stress effects on cognition and behavior (4, 8, 16-20).

Glucocorticoids exert their actions via two receptor types that differ in expression and affinity: mineralocorticoid receptors (MR) and glucocorticoid receptors (GR). High-affinity

MR are expressed mainly in the hippocampus and to a lesser extent in the amygdala and PFC, whereas the low-affinity GR are abundantly expressed throughout the brain (1, 21). Traditionally, both MR and GR were assumed to exist only as intracellular receptors mediating slow genomic changes by activating responsive genes, which develop after one or two hours but may last for several hours to even days or weeks. More recent evidence, however, challenged this view and showed that there is also a membrane-bound MR (and possibly also GR, (22)) that may induce rapid, non-genomic (i.e., gene-independent) effects on brain, cognition and behavior (8, 23, 24). Interestingly, the membrane-bound MR appears to have a lower affinity than its intracellular counterpart, which is almost fully saturated by tonic glucocorticoid concentrations, and is thus responsive to stress-induced increases in glucocorticoids (25). In light of the biphasic action of glucocorticoids via intracellular and membrane-bound receptors, the temporal profile of the stress response may best be characterized as consisting of, at least, three waves: (i) a rapid but short-lasting first wave involving sympathetic activation, monoamines and neuropeptides, (ii) a second wave that sets in within minutes after stressor onset and is based on non-genomic glucocorticoid actions, and (iii) a third wave that begins only hours after stressor onset, when genomic glucocorticoid actions have developed. Importantly, these temporal waves of the stress response appear to have distinct effects on brain areas critical for memory formation and retrieval (26-28).

9.9.3 Stress and memory performance: how much do we remember?

The investigation of stress effects on learning and memory has a longstanding tradition in animal research. First reports on the impact of stress mediators, such as adrenaline, on memory performance date back to the first half of the last century (29-32). In humans, research on stress and memory began in the early-1990s, with first studies showing that cortisol may affect

memory performance (33, 34). Since then, there has been an explosion in the number of studies investigating stress effects on human learning and memory. A key finding of these studies is that whether stress enhances or impairs memory depends critically on the memory stage affected by stress. Accordingly, I will portray the impact of stress on memory separately for the major stages of a memory – encoding, consolidation, retrieval, and reconsolidation. Because research has so far mostly focused on hippocampus-dependent episodic or semantic memory, I will limit the present review to this form of memory. Evidence that stress affects also non-hippocampal forms of memory, such as dorsal striatal memory is, however, accumulating, in both rodents and humans (35-40). For these memories, the direction of the stress effects appears to be dependent on the memory stage as well, similar to what is known for hippocampal memory. Moreover, beyond long-term memory, acute stress is known to have a significant influence on working memory. More specifically, most studies agree that stress disrupts working memory performance (41-45).

9.9.3.1 Stress and memory encoding

In order to investigate the impact of stress on memory, participants are typically exposed to either a stressor or a non-stressful control procedure. Over the past decades, several standardized procedures have been developed to induce stress in a laboratory setting. The most prominent of these procedures is the Trier Social Stress Test (TSST, (46)), a psychosocial stressor that mimics a job interview in which participants are required to give, while being videotaped, a free speech and complete a mental arithmetic task in front of a cold and non-reinforcing panel. Another frequently used stress protocol is the Socially Evaluated Cold Pressor Test (SECPT; (47)), an extension of the classical Cold Pressor Test (48) by socio-evaluative elements. Here, participants are asked to immerse their hand for three minutes into

ice water, while being videotaped and evaluated by a rather could and neutral experimenter. Both, the TSST and the SECPT are known to result in significant increases in subjective stress rating, autonomic nervous system activity, and cortisol (49, 50). It should be noted that an experience of stress is per definition associated with an increase in subjective and physiological arousal. The effects of emotional arousal on memory are discussed in chapter XYZ. Furthermore, critical interaction between stress-induced glucocorticoids and emotional arousal will be discussed in section 9.9.3.5.

In several studies, healthy participants were exposed to a stressor (or control manipulation) shortly before performing a learning task in order to assess the impact of stress on memory encoding. The findings of these studies have been rather inconsistent. While some studies showed that stress before learning reduces subsequent recall, the integration of contextual features into the memory trace or late positive potentials (LPP), an EEG marker of selective attention (51-53), others suggested that stress prior to encoding facilitates later memory (54-57). For instance, one study showed that stress before learning made memories more resistant to distortions through misinformation (58). Furthermore, stress before encoding has been shown to strengthen event-related potentials implicated in enhanced memory formation (59, 60). Although these studies diverge with respect to the direction of the stress effect on encoding, many of them link the observed effect to stress-induced increases in cortisol (53, 61, 62). Direct evidence for cortisol-driven changes in memory comes from studies that manipulated cortisol pharmacologically before encoding. However, even the findings on the impact of elevated cortisol before learning on subsequent memory were inconsistent, with some studies reporting beneficial (63, 64) and others detrimental effects (53, 65).

How can the remarkable heterogeneity of the findings on the influence of stress (even when the same stress protocol was used) and cortisol on encoding be explained? Some authors argued that there may be gender differences in the impact of stress on memory encoding. Yet,

although some studies suggested differential effects of stress before learning in women compared to men (35, 66, 67), potential gender differences cannot explain the majority of the inconsistent findings, as stress effects on encoding differed also in the same gender. Alternatively, the emotionality of the encoded material has been suggested as a source of the inconsistent findings. Specifically, stress before encoding was reported to strengthen later memory of emotionally arousing stimuli but to impair memory for neutral material (68, 69). However, while several studies showed beneficial effects of stress or cortisol specifically for emotionally arousing material (56, 59, 66), the pattern of results was not consistent across studies (51, 60, 70). Finally, based on the temporal dynamics of the major stress response systems, in particular the sympathetic nervous system and HPA axis, it has been suggested that the temporal distance between stress exposure and learning may be a critical factor for the direction of the stress effect (71). In line with this idea, stress a few minutes before learning appeared to enhance memory (55, 72-74), whereas stress about 30 minutes before learning impaired subsequent memory (66, 72). Although the temporal distance may not account for all of the discrepant findings and opposite results were reported even for comparable intervals between stress exposure and encoding (53, 54), the temporal proximity is closely linked to another critical factor: the actual relatedness between stressor and learning.

A stressful encounter is, of course, itself a learning experience that is encoded and the existing evidence shows unanimously that stressful events themselves are well remembered. A classic rodent study conducted more than 20 years ago showed that subsequent memory for a water maze task can be modulated by varying the water temperature (i.e. stress level). The lower the water temperature (i.e. the higher the stress level), the better the memory for this experience (75). In line with these rodent data, human studies showed that memory for a stressful encounter is significantly better than memory for a non-arousing control situation (76, 77). Even learning within the (temporal) context of a stressful encounter may boost learning

(55, 78), unless the stressor acts as distractor, which profoundly impairs later memory (79). Neuroimaging data suggest that the enhanced encoding under stress is linked to increased activity of visual and inferotemporal areas and, surprisingly, reduced hippocampal activity (78). Amygdala-hippocampal crosstalk at rest, however, appears to facilitate subsequent memory for events encoded under stress (80).

Thus, stress may have distinct effects on memory depending on the extent to which the stressor and learning episode overlap. In a recent study from our lab, we aimed to track the impact of stress on encoding across time (76). To this end, participants first underwent a psychosocial stressor (or control manipulation) and then went on a two-hour tour through a zoo. Both during the stressor and during the zoo tour, participants were wearing a camera that took several pictures per minute. These pictures were used in a memory test one week later, enabling us to test memory as a function of the temporal distance to stressor onset. Our findings showed enhanced memory for two time intervals (Figure 2): the stressful episode itself and a period about half an hour after the stressor, after cortisol levels had reached a plateau.

In sum, although there is a considerable inconsistency in the literature on stress and memory encoding, the conclusion that stress has none or at least no systematic effect on encoding may be premature. Studies that were directed at testing stress effects on encoding differed on many critical dimensions, with the emotionality of the stimulus material and the temporal proximity and relatedness between stressor and learning situation being just a few, so that these studies are hardly comparable. Moreover, some studies tested recall shortly after encoding, when stress response systems were still active (53, 54), which raises the possibility that stress affected memory retrieval in addition to or rather than encoding. Although stress effects on encoding cannot be disentangled from those on either consolidation or retrieval, depending on whether memory is tested immediately after encoding or later, research suggests

that material encoded under stress (or shortly after a stressful event) is typically well remembered.

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9.9.3.2 Stress and memory consolidation

The effects of stress before or during encoding may reflect a combination of encoding and consolidation effects because stress mediators, such as cortisol, often remain elevated after encoding, during early consolidation. In order to isolate stress effects on memory consolidation, individuals need to be exposed to a stressful event shortly after encoding and at least several hours before retention testing. The vast majority of studies that did expose participants to a stressor after encoding showed, in line with evidence from rodent studies (19), that post-encoding stress enhances subsequent memory (81-85). A recent meta-analysis of the literature on stress and memory confirmed the facilitating effect of stress on consolidation (86). This facilitating effect was closely linked to stress-induced increases in cortisol and sympathetic arousal (82, 87, 88). Further, a pharmacological elevation of cortisol concentrations after encoding has been shown to be sufficient to boost subsequent memory (89).

Interestingly, many studies reported enhancing stress effects specifically for the consolidation of emotionally arousing material ((81, 82, 85, 90); but see, for example, (91) for an effect on neutral material). This specificity is generally in line with the 'tag-and-capture' hypothesis, which assumes that memory traces are tagged during encoding and that tagged traces can later capture plasticity-related products that facilitate memory storage (92, 93). One recent study tested such a tagging mechanism for stress effects on consolidation and showed that stress-induced cortisol made memories more dependent on hippocampal and amygdala

activity during encoding (87). In other words, the cortisol response to stress seemed to promote specifically the storage of information that was considered most relevant by the organism during prior encoding. Moreover, one study suggested that stress enhances memory specifically when the stressful event occurs in the same spatial context as prior encoding (94), thus facilitating the relatedness or integration of stressful encounter and learning experience. Although such a contextual account is intriguing, previous studies showed that stress enhances consolidation also when experienced in a different context than prior encoding (82, 91). Elucidating the exact conditions that may be required for the memory enhancement to occur remains a challenge for future research.

Beyond possible contextual boundary conditions for a stress-induced consolidation enhancement, several studies suggested that the enhancing effects of stress on consolidation are gender specific. In particular, whereas stress after encoding enhanced memory in men, it did not affect consolidation in women (91, 95). Initial evidence further suggested that such gender differences may be linked to an interaction of stress with sex hormones (90). Gender differences in the impact of stress on consolidation may be highly relevant given differences between men and women in the prevalence of disorders such as posttraumatic stress disorder (PTSD; (96)), in which stress effects on memory formation are critical. However, further research is needed to show how robust the suggested gender differences in the impact of stress on memory consolidation are, as several studies did not report such differences (81, 84), and to elucidate the mechanisms that may contribute to such differences.

9.9.3.3 Stress and memory retrieval

It is commonly assumed that stress exerts opposite effects on memory consolidation and retrieval: while stress promotes memory consolidation, it appears to impair memory retrieval

(19, 20, 28, 97). Initial evidence for a stress-induced retrieval impairment was presented by a study in which elderly humans that underwent stressor shortly before retention testing showed a memory impairment relative to a non-stressful control condition (98). The interest in the impact of stress on memory retrieval, however, was spurred by a landmark study in rodents published one year later. In this study, rats were significantly impaired in their memory for a previously learned water maze task when exposed to a stressor before retention testing (17). This retrieval deficit was specifically observed if retention testing took place about 30 minutes after the stressor, when corticosterone reached peak levels. The critical role of glucocorticoids in the stress-induced retrieval impairment was demonstrated in elegant follow-up experiments. In particular, the stress-induced retrieval deficit disappeared when the stress-induced secretion of corticosterone was blocked pharmacologically with the glucocorticoid synthesis inhibitor metyrapone and the retrieval deficit recurred when metyrapone was combined with the pharmacological administration of corticosterone. These findings were successfully translated to humans. To date, quite a number of studies reported stress-induced retrieval impairments in humans (82, 84, 99-101) and several of these studies suggested that these impairments are particularly pronounced for the retrieval of emotionally arousing material (82, 100, 101).

Very recently, fMRI was combined with sophisticated multivariate analysis techniques to elucidate how the stress-induced retrieval deficit is represented in the human brain (102). This study showed that stress before and concurrent with memory testing disrupts the relationship between hippocampal activation, reinstatement in cortical representation areas and memory performance. Furthermore, stress reduced the involvement of the (posterior) hippocampus and the recruitment of large-scale frontoparietal networks during retrieval. In line with findings in rodents (17, 19, 103), cortisol appeared to play a key role in the stress-induced retrieval impairment in humans. The retrieval impairment after stress was particularly pronounced in individuals showing a pronounced cortisol response to stress (82, 101, 104) and

a pharmacological administration of cortisol was sufficient to produce this retrieval deficit (105, 106). Evidence from a study using positron emission tomography (PET) indicated that cortisol exerts its detrimental influence on memory retrieval by reducing retrieval-related activation in medial temporal lobe areas (107).

Moreover, stress appears to unfold its influence on memory retrieval in a time-dependent manner, closely linked to the action of cortisol. A series of experiments varied the time interval between stress exposure and recall testing in order to unravel the role of the different temporal waves of the stress response (see section 9.9.2) in the modulation of memory retrieval. Interestingly, when retrieval took place under stress, before cortisol levels were elevated, and the testing situation was the source of stress, stress did not impair retrieval and the sympathetic stress response tended even to facilitate retrieval performance (108). However, if retention testing took place 25 minutes later, when cortisol levels were already significantly increased, and out of the context of the stressful encounter, stress impaired retrieval and this impairment was directly correlated with the magnitude of the cortisol response (108). Moreover, when the interval between stress exposure and retention testing was extended to 90 minutes, when cortisol levels had returned to baseline but genomic cortisol actions presumably developed, there was a retrieval impairment that was even stronger than the deficit observed after 25 minutes, when non-genomic cortisol actions prevailed (109). Together these data provide striking evidence for a role of cortisol in the stress-induced impairment in memory retrieval and this impairment may last longer than the acute rise in cortisol. At the same time, the early sympathetic nervous system response to stress (108) or stress without significant increase in cortisol (104) might even facilitate memory retrieval.

Although the predominant view holds that stress or cortisol administration impairs memory retrieval, it should also be noted that several studies did not find such an impairment but reported even enhanced memory retrieval after stress (73, 83, 110-113). The source of these

discrepant findings remains still rather unclear; specific characteristics of the tested samples, the magnitude of the stress response or other methodological differences are likely candidates to explain these differences. Moreover, there is initial evidence that the relationship between the learning and testing situations may have a significant impact on stress-induced changes in memory retrieval. For instance, it is well known that if the retrieval context is congruent with the encoding context it may provide retrieval cues that promote memory performance (114-116). Thus, it might be predicted that the congruency between the learning and testing situations may attenuate the stress-induced retrieval deficit. Indeed, when the learning context was enriched by a specific odor and testing took place in the same (spatial) context with this odor present, the stress-induced retrieval deficit was completely abolished (117). Likewise, it has recently been shown that retrieval practice after encoding, known to boost subsequent memory (118, 119), may protect against detrimental effects of stress on memory retrieval (120) but see (102) for a study that did not find a protective effect of memory strength against disruptive effects of stress on retrieval. These findings point to the intriguing possibility that stress-induced retrieval deficits can be prevented by leveraging psychological mechanisms known to aid memory.

9.9.3.4. Stress and post-retrieval processes

Stress and cortisol may not only impair the immediate retrieval but can also affect the long-term recall of memories retrieved under stress (121, 122). These findings suggest that stress induces not only a transient retrieval impairment but, given that stress mediators such as cortisol remain often elevated long after retrieval, may also affect post-retrieval processes related to subsequent memory. Over the past two decades, evidence has accumulated to suggest that memories re-enter a labile state again after their retrieval, from which they need to be

stabilized anew during a process call reconsolidation (123-129). Critically, it is assumed that reactivated memories can be modified during reconsolidation and several studies in rodents and humans suggested that stress mediators, such as glucocorticoids and catecholamines, may be involved in the post-reactivation stabilization or modification of memories (130-135).

Accordingly, several studies aimed at investigating the impact of stress on memory reconsolidation and hence exposed individuals to stress shortly after memory retrieval. These studies indicated that stress may indeed alter memory after retrieval, i.e. the proposed reconsolidation process. The direction of this effect, however, is still debated: whereas some studies suggested that post-retrieval stress impairs reconsolidation and long-term memory (136-139), others suggested that stress enhances reconsolidation, similar to its impact on initial consolidation (140-144). To date, the factors that contribute to these inconsistencies remain elusive. Potential stress effects on reconsolidation, however, may have tremendous implications, in particular for clinical contexts. Reconsolidation-based treatments might provide a unique opportunity to alter unwanted memories, for instance in addiction or PTSD (145-148). Furthermore, trauma reactivation, an integral part of therapeutic interventions, is often experienced as highly stressful by PTSD patients, which may have considerable effects on subsequent trauma memory. Given these far-reaching implications of stress-induced changes in post-retrieval reconsolidation, understanding the mechanisms that give rise to stress-related changes in reconsolidation as well as the factors contributing to the present heterogeneity in the findings is important.

9.9.3.5. Stress and memory performance: mechanistic insights

In sum, it is by now widely accepted that stress may have opposite effects on different stages of memory. In particular, stress appears to enhance memory consolidation but to impair

memory retrieval. Although stress effects on consolidation and retrieval are opposite, they seem to share a common mechanism. Elegant studies in rodents showed that stress effects on both memory consolidation and retrieval require concurrent activity of glucocorticoids and noradrenaline in the basolateral amygdala (BLA), which then modulates memory processes in other brain areas such as the hippocampus (103, 149). For instance, it has been shown that the pharmacological blockade of noradrenergic arousal in the BLA or the inactivation of the BLA eliminates glucocorticoid effects on memory (150, 151). Likewise, glucocorticoids are ineffective in rats that are habituated to the testing context (152) but glucocorticoid effects can be reinstated by the parallel administration of the α2-adrenceptor antagonist yohimbine, which increases noradrenergic stimulation (153).

While this memory modulation model is mainly based on rodent data, several findings in humans support this model. First, stress effects on both consolidation and retrieval seem to be particularly pronounced for emotionally arousing material that is associated with increased noradrenergic activity (81, 101). Second, stress-induced cortisol enhanced memory consolidation only when the rise in cortisol was paralleled by subjective arousal (154). Third, pharmacological studies demonstrated that the effects of stress and glucocorticoids can be abolished by the β-adrenoceptor antagonist propranolol (111, 155), suggesting the stress and glucocorticoid effects require simultaneous noradrenergic activation in humans as well. Finally, an fMRI study indicated that participants with a high cortisol response to stress showed higher amygdala activity while viewing emotionally arousing pictures than participants showing a lower cortisol response (156).

The critical role of the glucocorticoid-noradrenaline interaction for stress effects has been established over the past 25 years. More recently, however, evidence has been accumulated to suggest that this model might need a modification by incorporating the endocannabinoid system as an important player. The endocannabinoid system is a lipid

signaling system that modulates neurotransmitter release in the brain (157). Endocannabinoid receptors are expressed in brain areas critical for stress and memory, including the amygdala and the hippocampus (158). Accordingly, several studies implicated endocannabinoids in stress response and the modulation of learning and memory (159-161). Most importantly, the endocannabinoid system, in interaction with glucocorticoids, has been suggested to modulate noradrenergic circuits and hence memory processes (159, 161). For instance, it has been shown that intra-BLA injections of an endocannabinoid receptor antagonist blocked the enhancing effect of systemic glucocorticoid injections on consolidation, suggesting that endocannabinoid signaling in the BLA is required for glucocorticoid effects on consolidation (162). Moreover, blockade of endocannabinoid receptor activity within the BLA was shown to completely prevent glucocorticoid interactions with the noradrenergic system in regulating memory consolidation (163). Further evidence indicated that the effect of endocannabinoids is critically dependent on the arousal level of the testing conditions, with high arousal conditions being necessary for the endocannabinoid effects (164). Another study provided direct evidence that endocannabinoids play a role in regulating glucocorticoid effects on noradrenergic activity that results in impaired retrieval (165). Based on these data, a model has been proposed in which glucocorticoids bind to membrane-bound receptors in the BLA, which in turn activate a G-protein cascade leading to the synthesis of endocannabinoids. Endocannabinoids may then inhibit the release of GABA, which disinhibits noradrenaline release, resulting in increased β-adrenoceptor stimulation linked to both enhanced consolidation and impaired retrieval (166).

Testing this model in humans is complicated by the fact that pharmacological manipulations of the endocannabinoid system are not safe in humans (160, 167). However, a recent study used a behavioral genetics approach to target the role of endocannabinoids in stress effects on human memory (168). This study genotyped healthy participants for a polymorphism of the gene coding the endocannabinoid CB1 receptor and exposed then to a stressor or control

manipulation before they encoded neutral and emotionally arousing stimuli in the MRI scanner. Memory for those stimuli was tested 24hrs later. The results of this study showed that memory performance correlated with the activity of and connectivity between hippocampus and amygdala in stressed participants, however, depending on the CB1 receptor polymorphism.

It is by now widely accepted that stress effects on memory rely on an interaction of glucocorticoids and noradrenergic arousal (modulated, most likely, by endocannabinoids). However, how can we explain the opposite effects of stress on memory consolidation and retrieval? And why are the stress effects on memory encoding so heterogeneous? These questions are addressed by another model, which assumes that stress effects on memory depend critically on whether stress is experienced in the context of the learning episode or not (4). Stress would facilitate learning when it is experienced in the context and around the time of the event that needs to be remembered. Learning out of the context of the stressful encounter, however, would impair subsequent memory. Moreover, it is assumed that stress would impair cognitive processes that are not directly relevant for the ongoing stressor, such as the retrieval of unrelated material. These differential effects of stress were linked to the different temporal waves of the physiological stress response (see section 9.9.2.). Specifically, catecholamines and rapid, non-genomic actions of glucocorticoids via membrane-associated receptors were thought to facilitate learning and memory. The delayed, genomic glucocorticoid actions were assumed to increase the threshold for mnemonic processing and hence to impair both the encoding of new information and the retrieval of unrelated material. Support for this model comes from neurophysiological data showing that both noradrenaline and rapid glucocorticoid actions may facilitate synaptic plasticity processes (169-172), whereas delayed glucocorticoid actions impair plasticity (173-175). Furthermore, this model is in line with rodent and human data suggesting that memory is typically enhanced for the stressful episode itself (75-77) as well as for events encoded shortly after stress (72, 73), when catecholamine and early

glucocorticoid actions prevail. Studies that elevated glucocorticoid concentrations at different time points provided further direct evidence for distinct effects of rapid compared to slow glucocorticoid actions. As predicted by the model, glucocorticoid administration several hours before testing reduced task-related activity in the amygdala and hippocampus (176, 177). Further behavioral evidence showed that a glucocorticoid increase shortly before a task impaired the contextualization of memories and left working memory unaffected, whereas glucocorticoid elevations hours before testing enhanced both of these functions (178, 179). Moreover, stress effects on memory retrieval appeared to be critically dependent on whether sympathetic arousal or non-genomic or genomic glucocorticoid actions were predominant at the time of retention testing (108, 109). Time-dependent effects of glucocorticoids were also reported in a study that assessed changes in hippocampal and amygdala activity after cortisol injection. Here, cortisol led to a rapid rise followed by a delayed decrease in hippocampal and amygdala activity (180). Beyond time-dependent changes in the activity of single brain areas, it has also been suggested that stress induces a reconfiguration of large-scale brain networks (181). In particular, stress was thought to rapidly favor a salience network, at the expense of an executive control network and that the preferential recruitment of these networks reverses after stress subsides and genomic glucocorticoid actions have developed (26).

These two models are not mutually exclusive but the proposed mechanisms are assumed to operate hand in hand (27). For instance, glucocorticoids and noradrenaline may enhance inhibitory avoidance memory in rats (182), but they do so only when these stress mediators rise at about the same time. If glucocorticoids rise considerably earlier than noradrenaline, the memory enhancing influence of noradrenaline is suppressed (183). Based on these prior models, an integrative model has been proposed that distinguishes two modes of mnemonic processing during and after stress: a memory formation mode and a memory storage mode ((28); Figure 3). According to this model, rapid catecholamine and non-genomic glucocorticoid

actions interact in the BLA, which then shifts other brain areas, including the hippocampus and PFC, into a 'memory formation' mode. These BLA-mediated effects are complemented by direct effects of stress mediators on the hippocampus and PFC. In the memory formation mode, perception, attention, encoding, and the early consolidation of ongoing events are 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 unrelated material, are suppressed. As time after the stressful event proceeds, the rather short-lived catecholamine activity returns to baseline and the delayed, genomic glucocorticoid effects develop. In particular the latter shift the organism into a memory storage mode. In this mode, the threshold for processing stressor-unrelated information is increased, thus protecting the memory of the stressful episode itself from interference.

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9.9.4 Stress and the modulation of multiple memory systems: what do we remember?

For more than two decades, research on stress and memory focused primarily on stress-induced changes in quantitative performance, expressed for example as number of items recalled or latencies to a certain goal location, within a single memory system, mainly the hippocampus. Memory, however, is not a single entity. There are multiple memory systems that differ with respect to the underlying neural substrate, the information processed, and the mode of operation (184-187). These memory systems are often active in parallel and process information simultaneously (187-189). Accumulating evidence suggests that stress may have a critical impact on the preferential engagement of these memory systems. In particular, it has been demonstrated across tasks and species that stress favors rather simple but rigid ('habitual')

forms of memory, at the cost of flexible but cognitively more demanding ('cognitive') forms of learning and memory (8, 190-195). By modulating the engagement of multiple memory systems, stress may – in addition to its effects on quantitative memory performance – affect the nature of learning and memory, i.e. how we approach a task, which strategies we use during learning and what we remember from past experiences.

9.9.4.1 Stress and multiple memory systems: spatial navigation

Very first evidence for a stress-induced shift in the balance of multiple memory systems came from a landmark study in rodents almost 20 years ago (196). In this study, rats were trained in a fixed location-visible platform water maze task that could be acquired by a hippocampus-based spatial memory system and a dorsal striatum-based stimulus-response (S-R) memory system. The chosen strategy was revealed in a test trial, in which platform and cue were relocated. Compared to non-stressed controls, rats exposed to a stressor before training used the S-R memory system significantly more often, at the cost of the spatial memory system. This study provided the first evidence that stress may bias the relative engagement of multiple memory systems during learning. Follow-up experiments showed that systemic or intra-amygdala injections of anxiogenic drugs are sufficient to produce this effect (197, 198). Further, glucocorticoids were shown to favor S-R over spatial learning in a circular hole board task (199).

These initial findings in rodents were subsequently translated to humans. In particular, one study exposed healthy participants to a psychosocial stressor or a control manipulation shortly before they were trained to find a win-card in a wooden 3D model of a room (200). Critically, the location of this win-card could be learned through its association with a single proximal cue (S-R strategy) or by using the relationship between multiple room cues (spatial

strategy). Same as in rats, stress favored S-R learning at the expense of spatial learning. To elucidate the involved brain mechanisms, a subsequent study combined fMRI with a virtual spatial learning task that allowed distinguishing hippocampus-dependent spatial from dorsal striatum-dependent S-R learning (201). This study replicated the stress-induced bias towards more S-R learning and showed that the stress-induced increase in cortisol was associated with enhanced functional connectivity between amygdala and dorsal striatum.

While these studies induced stress before learning, rodent data suggested that stress may modulate the engagement of multiple memory systems also at retrieval. Specifically, the administration of an anxiogenic drug before a retention test for a dual-solution water maze task biases memory towards the S-R system as well (202). Thus, stress seems to affect not only which memory system is used during task acquisition but also which of several parallel memory traces is reactivated and guided behavior during retrieval. Moreover, there is some evidence that – beyond the effect of acute stress – chronic stress may favor S-R over spatial memory processes (203). Likewise, stress during critical periods of brain development may have a critical impact on the preferential engagement of spatial and S-R memory in adulthood (204, 205).

9.9.4.2 Stress and multiple memory systems: classification learning

During (probabilistic) classification learning, individuals have to learn how to classify stimuli based on trial-by-trial feedback. Converging lines of evidence from fMRI studies in healthy participants and neuropsychological studies in patients with medial temporal lobe or basal ganglia dysfunctions indicate that classification learning can be supported by a hippocampus-based and a dorsal-striatum-based memory system (188, 206-209). There is even some evidence to suggest that these systems compete for control of learning (188), raising the

question which system gets the upper hand. Accumulating evidence suggests that stress may be a factor that biases hippocampal and dorsal striatal systems during classification learning. A first study testing the impact of stress on the control of classification learning showed that stress prior to learning reduced explicit task knowledge and biased learning strategies from hippocampal towards dorsal striatal strategies (210). This stress-induced shift in 'systems' learning was paralleled by a reduction in hippocampal activity. Moreover, fMRI data indicated that classification performance was correlated with hippocampal activity in non-stressed controls but with dorsal striatal activity in stressed participants, further suggesting that stress shifted the control of learning from the hippocampus to the dorsal striatum. Subsequent studies replicated this basic pattern of results and further pointed to the amygdala as a mediator of this stress-induced shift (211, 212). Specifically, stress seemed to increase amygdala connectivity with the dorsal striatum, whereas it decreased amygdala connectivity with medial temporal lobe structures (211, 212).

Notably, not all individuals are equally likely to demonstrate a shift from hippocampal to dorsal striatal learning and memory after stress. First evidence suggests that genetic variants of the glucocorticoid and noradrenergic system may explain at least part of this variance and affect hippocampal and striatal activity as well as the connectivity of these regions with the amygdala during classification learning (211, 213). Recently, a study in humans tested the impact of glucocorticoids and noradrenergic arousal on the preferential recruitment of hippocampal and striatal memory systems during retrieval in a classification learning task (214). This study showed, in line with previous evidence (215), a practice-related bias from hippocampal to dorsal striatal learning strategies which was, in placebo controls, even more pronounced after a night of sleep (216). Administration of hydrocortisone or the α2-adrenceptor antagonist yohimbine, however, abolished this further shift towards dorsal striatal learning and thus led to even more hippocampal memory relative to placebo. Although the

direction of this stress (hormone) effect was somewhat surprising, these findings suggest that stress hormones may not only affect the memory system engaged during acquisition but also the control of memory retrieval, in line with rodent data from the domain of spatial navigation.

9.9.4.3 Stress and multiple memory systems: other forms of learning

Beyond spatial navigation and classification learning, there are several other task domains that can be supported, at the same time, by multiple memory systems. For instance, in instrumental learning and memory a PFC-dependent, goal-directed system can be distinguished from a dorsolateral striatum-dependent habit system. Whereas the goal-directed system acquires the causal relationship between an action and an outcome, the habit system learns associations between responses and preceding stimuli, independent of the outcome engendered by the response (217, 218). A conceptually related distinction is that between model-based and model-free learning (219). Similar to the stress-induced shift from hippocampal to striatal control in spatial navigation and classification learning, stress appears to have a decisive effect on which of these different learning and memory systems guides behavior. In particular, it has been demonstrated repeatedly in healthy humans that stress may favor habitual responding, at the expense of goal-directed control (220-222). These findings are very well in line with rodent data showing a similar shift after either acute or chronic stress (223, 224). The stress-induced bias towards habitual responding appears to be present already in infants (225), suggesting that this effect may occur very early in life. Further studies suggested that stress favors habits in particular in individuals showing a pronounced cortisol response to stress (226), as well as in those with a low baseline working memory capacity (227, 228). While these studies exposed individuals to stress before acquisition, one study stressed participants after acquisition, shortly before the critical test of goal-directed versus habitual control of performance and reported a

very similar bias towards habitual responding (229). This finding suggests that stress may affect not only the mode of task acquisition but also the expression of instrumental behavior.

In another form of conditioning - classical fear conditioning - an unconditioned stimulus may be associated with another stimulus or with the context in which learning takes place (i.e. the conditioned stimulus), corresponding to cue-dependent and context-dependent conditioning, respectively. While cue-dependent fear conditioning relies mainly on the amygdala, context-dependent fear learning also depends on the hippocampus (230, 231). Recently, stress has been shown to modulate the balance of cued and contextual fear learning in a virtual task that allowed both forms of fear conditioning (232). More specifically, stress prior to fear learning in this task completely abolished contextual fear learning and made cue-dependent fear learning more resistant to extinction, even when the conditioned stimulus was relocated to another, previously safe context. Similarly, there is evidence that stress may strengthen amygdala-dependent delay conditioning but impair hippocampus-dependent trace conditioning and that this change in conditioning is linked to reduced hippocampal activity (233).

Together, these findings provide strong evidence that stress promotes, across tasks and domains of learning and memory, a shift from more flexible but cognitively demanding forms of learning and memory to simpler but more rigid ones ((8, 234); Figure 4).

- Please insert Figure 4 about here –

9.9.4.4 Stress and multiple memory systems: mechanistic insights

As for stress effects on performance within a single memory systems, there also is strong evidence for a critical involvement of glucocorticoids in driving stress-induced changes in the engagement of multiple memory systems (199, 223, 226, 232, 235), although the relationship between glucocorticoid activity and memory bias may not necessarily be linear (236, 237). These rapid glucocorticoid effects appear to be mediated by the membrane-associated MR (8). Pharmacological blockade of the MR abolished the stress-induced shift from hippocampal to dorsal striatal memory in both rodents and humans (199, 238). Further, a haplotype linked to enhanced expression of the MR appeared to facilitate the stress-induced shift from 'cognitive' to 'habitual' control of classification learning (213).

Glucocorticoids, however, do not act in isolation. Increased noradrenergic activation may similarly alter the balance of multiple memory systems (197, 202, 216) and the stress-induced shift towards 'habitual' memory is not only modulated by an MR-related gene variant but also by a polymorphism of the gene coding the α2-adrenoceptor (211). In rats, the glucocorticoid-induced shift towards habit memory was abolished by a parallel injection of a β-adrenergic receptor antagonist (239), suggesting that glucocorticoids require concurrent noradrenergic activity to unfold their effects. The idea that stress effect on the modulation of multiple memory systems necessitate simultaneous glucocorticoid and noradrenergic activity is also supported by studies on the impact of stress on the control of human instrumental learning. In these studies, the β-adrenergic receptor antagonist propranolol blocked the stress-induced shift from goal-directed to habitual control of learning (221), whereas the combined administration of hydrocortisone and the α2-adrenoceptor antagonist yohimbine, which leads to increased noradrenergic stimulation, was sufficient to provoke this shift (240, 241).

Glucocorticoids and catecholamines may modulate the brain areas involved in 'cognitive' and 'habitual' forms of learning and memory in opposite directions. For instance, stress may increase dorsal striatal activation and decrease hippocampal activation during classification learning (210, 211, 238). Likewise, combined hydrocortisone and yohimbine administration reduced prefrontal activity associated with goal-directed learning in humans (241) and glucocorticoid injections directly into the dorsolateral striatum were sufficient to promote habit memory in rats (235). The actions of stress mediators directly on areas such as the dorsal striatum, hippocampus and PFC may facilitate a shift towards 'habitual' memory in two ways, by directly strengthening habitual memory and by releasing habit memory from the inhibitory control of 'cognitive' systems (190, 242, 243).

In addition to these direct stress effects on brain areas critical for 'cognitive' or 'habitual' memory, there is evidence for a modulatory role of the amygdala. As noted in section 9.9.3.5, a modulatory role of the amygdala in stress effects on memory performance is well established (103, 153). Rodent studies that injected anxiogenic drugs directly into the amygdala and observed a shift from 'cognitive' to 'habit' memory suggested a similar role of the amygdala in the stress-induced modulation of multiple memory systems (197). In line with such an involvement of the amygdala, several fMRI studies showed that stress facilitates amygdala connectivity with the dorsal striatum and, at the same time, decreases amygdala crosstalk with the hippocampus and adjacent areas (201, 211, 238). Interestingly, these opposite changes in connectivity with the amygdala were particularly sensitive to the pharmacological blockade of the MR (201, 238). Together, these findings suggest that (i) the amygdala may orchestrate the engagement of multiple memory systems under stress, and (ii) this amygdala modulation is driven by glucocorticoids acting via the MR, presumably in interaction with adrenergic arousal.

In terms of the mechanisms underlying stress effects on the relative balance of multiple memory systems, it is important to note that most studies focused on a time interval between stress and learning (or retrieval) when cortisol levels peaked. Whether there are time-dependent effects of stress, known to be highly relevant for stress effects on the formation and retrieval of hippocampal memory, is currently unclear.

9.9.4.1 Stress and multiple memory systems: consequences for performance

A particularly intriguing finding in the research on the stress-induced modulation of multiple memory systems is that the shift towards 'habitual' forms of memory goes along with fully intact memory performance. Stressed subjects that shifted towards habit memory were comparable to non-stressed controls in their classification learning performance or latency to find a goal location (196, 199, 200, 210, 211). Severe impairments, however, were observed in individuals who kept using 'cognitive' memory systems despite stress or in which the shift towards habit memory was pharmacologically blocked (199, 238). This pattern of results points to the fascinating possibility that the bias towards 'habitual' memory may be highly adaptive to rescue performance under stress (8, 192). If, however, the shift from 'cognitive' towards 'habit' memory is successful and performance remains unaffected, what are the behavioral consequences of this stress-induced shift?

It is commonly assumed that 'cognitive' memory is flexible and allows a transfer of knowledge to novel situations, whereas 'habit' memory is characterized by its rigidity (184, 186). Given this assumption, does the rescue of memory performance under stress come at the cost of the flexibility of memory? Early studies suggested that stress results in more gist-like memory representations that lack specificity (244). Similarly, both stress and the rapid action of glucocorticoids have been shown to impede the integration of contextual details into the

memory trace (52, 179). More direct evidence for the idea that stress creates rather inflexible memories comes from a study that used the famous misinformation paradigm (245) to test whether stress affects the incorporation of new (in this case, misleading) information into an existing memory (246). In this study, stress 'protected' memory from biases through misinformation, which might point to a reduced capacity to update memories in light of new information (alternatively, the reduced misinformation effect might be due to impaired encoding of the misleading information). Furthermore, the generalization across past experiences has been proposed to be a memory process that is particularly sensitive to the functioning of the 'cognitive' hippocampus-based system (247, 248). Recent evidence shows that stress or increased noradrenergic arousal may disrupt this generalization capacity (249, 250). Finally, a series of experiments suggested that stress may interfere with the integration of new information into existing knowledge. More specifically, it is well known that prior knowledge may promote the encoding and retrieval of related material, an effect referred to as schema-based memory (251, 252). Stress or glucocorticoid administration has been shown to reduce individuals' ability to benefit from prior knowledge during learning (253). Subsequent fMRI studies linked this deficit to reduced hippocampal activity and difficulties in the separation of brain networks implicated in the processing of schema-congruent and novel information, respectively (254, 255).

In sum, these studies suggest that – beyond the well-known enhancement of memory formation and impairment of retrieval – stressful events may alter the nature and flexibility of memory (256). This inflexibility may at least partly be owing to a shift from 'cognitive' to 'habitual' control of memory.

9.9.5 Memory and stress: implications and conclusion

Research on the modulation of memory started more than a century ago, with the famous studies of Lashley and colleagues in rodents (31). Based on this influential work, other researchers began to investigate the role of stress mediators, such as catecholamines, in memory formation (30). Human research on stress and memory began only relatively recently, about 30 years ago. Since then, considerable progress has been made in understanding to what extent stressful events may alter memory processes and which mechanisms are involved in these effects. Key insights, provided by rodent and human studies, were that stress may have different, even opposite effects on different memory stages (in particular, stress may enhance consolidation but impair retrieval; (17, 19)) and that stress effects are due to the concerted action of glucocorticoids and noradrenergic arousal (103, 149). Further, there are timing-dependent differences in the impact of stress related to the temporal profile of action of major stress mediators, with stress within the context of learning enhancing memory formation and stress out of the learning episode impairing memory formation (4, 27). Such stress effects are not limited to hippocampus-dependent memory but were shown to occur in other memory systems, such as the dorsal striatum, as well (36, 38). Beyond changes in a single memory system, stress was further shown to induce a reconfiguration of large-scale brain networks (26, 181) which may set the stage for a shift from 'cognitive' to 'habitual' forms of memory (8, 234). This bias towards 'habit' memory - which was shown in spatial navigation, classification learning, instrumental learning and Pavlovian fear conditioning - may change the nature of learning and memory, reflected, for instance, in a reduced capacity to integrate contextual details into the memory trace, to integrate new information with existing memories or to generalize experiences to new situations (256).

All of these stress-induced changes in memory may be, in general, highly adaptive, facilitating coping with the ongoing stressor as well as the preparation for similar events in the

future. For instance, the enhanced consolidation after stress creates lasting memories for the stressful encounter, which may be beneficial for coping with similar future stressors. The stress-induced retrieval deficit for stressor-unrelated events, on the other hand, may reduce distraction from the ongoing event. Similarly, the preferential use of well-established habits and routines may save cognitive resources and promote performance under stress. However, although being generally adaptive, these stress-induced changes may come at the cost of the flexibility of memory and have significant implications for several applied contexts. Stress, for instance is highly prevalent in educational contexts and may result in retrieval deficits during examinations, a decreased ability to link elements of knowledge or to a deficit in transferring knowledge to new contexts (257). Moreover, stress-induced changes in memory may play a prominent role in several stress-related psychopathologies, including major depression, anxiety disorders, addiction or PTSD. For example, the overly strong memory for traumatic events, a hallmark feature of PTSD, has been related to an over-consolidation due to the excessive release of stress hormones during the trauma (258) or to building strong associations between single trauma-related cues and fear (192, 194).

In the face of these far-reaching consequences, it is crucial to elucidate the mechanisms underlying the impact of stress on memory. The past decades have seen quite some progress in our understanding of the mechanisms involved in stress effects on memory and first attempts have been made to translate these mechanistic insights to the clinic (for a review, see (20)). For instance, leveraging the detrimental effect of glucocorticoids on memory retrieval, hydrocortisone administration has been shown to reduce indices of trauma memory in PTSD patients and subjective fear in patients with spider or social phobia (259, 260). However, despite the considerable progress in the research on stress and memory over the past decades, there are still several inconsistencies in the literature that are difficult to explain (e.g. regarding stress effects on encoding) and several puzzling questions still need to be addressed. Recently,

several new biological players have been introduced to the field of stress and memory. In particular endocannabinoids were suggested to be an important ingredient in stress effects on memory (20, 163, 165) and a prediction error signal was proposed as a cognitive mechanism contributing to altered memory for aversive events (261, 262). These and other developments to come may promise to further enhance our understanding of exactly how stressful events change our memories.

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Figures

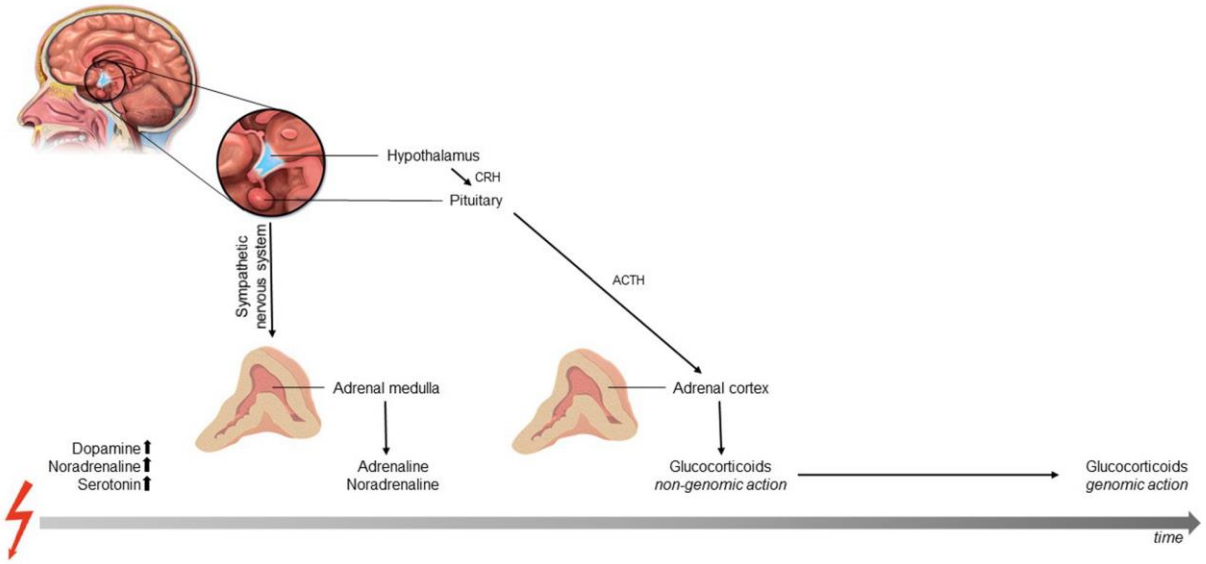

Figure 1: Physiological response to stressful events. Within seconds after the onset of a stressful encounter, dopamine, serotonin and noradrenaline are released in the brain. Moreover, the activation of the sympathetic nervous system, triggered by the hypothalamus, results in the secretion of adrenaline and noradrenaline from the adrenal medulla. In addition, the hypothalamus activates the hypothalamus-pituitary-adrenal axis, leading the release of corticotrophin releasing hormone (CRH), which stimulates the release of the adrenocorticotrophic hormone (ACTH) from the pituitary. ACTH, in turn, triggers the secretion of glucocorticoids (mainly cortisol in humans) from the adrenal cortex. Through binding to mineralocorticoid receptors (MR) and glucocorticoid receptors (GR), glucocorticoids may exerts rapid, non-genomic and slow, genomic actions.

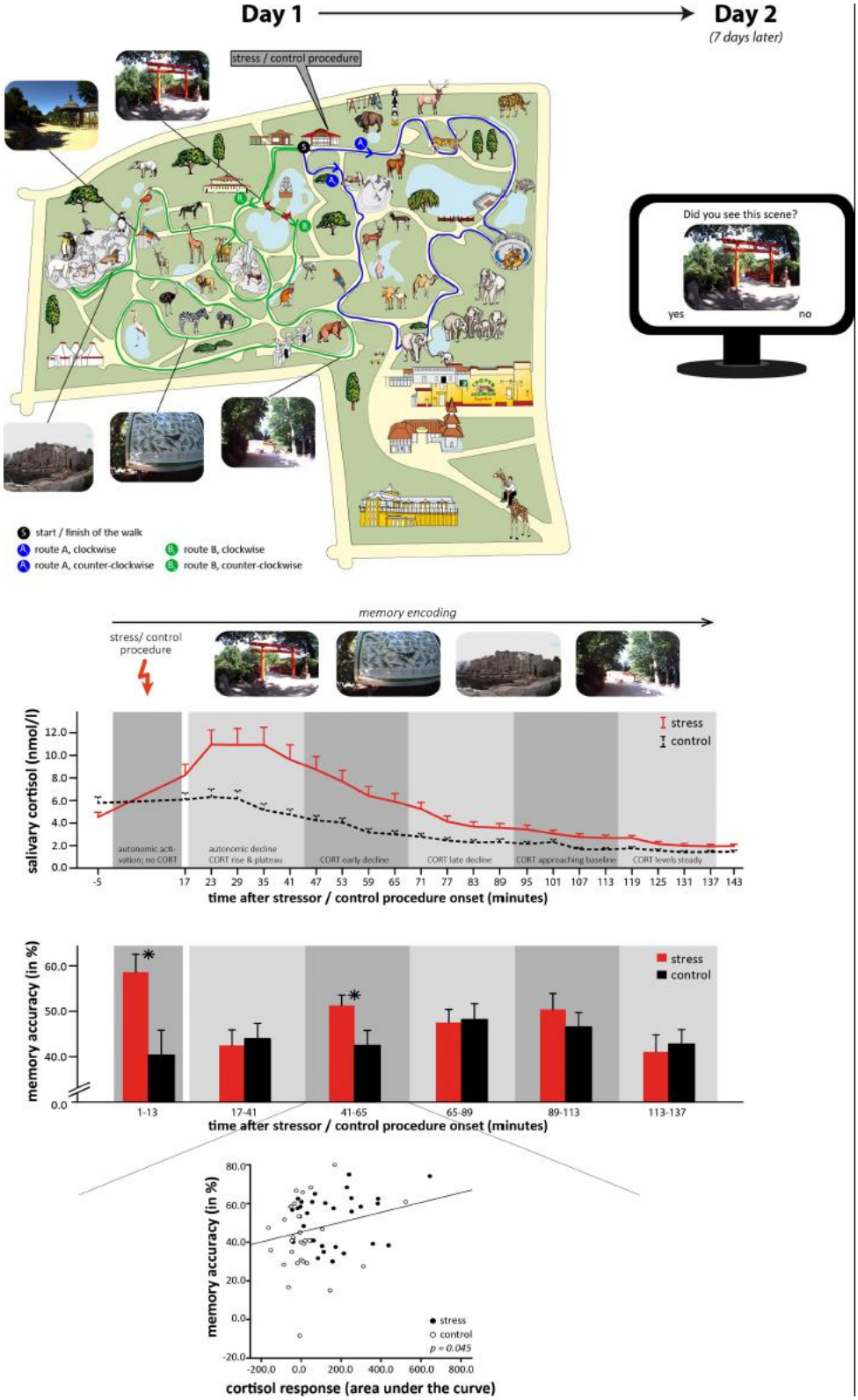

Figure 2: Study tracking the impact of stress on memory formation across 2 hours. (A) Participants were first exposed to a psychosocial stressor (or control manipulation) and then went on a two-hour tour through a zoo. During the experimental treatment and the tour through

the zoo, pictures were taken by a camera with a high frequency. One week later, participants' recognition memory for the scenes encoded during and in the aftermath of the stressor was tested. (B) The stress exposure resulted in a pronounced cortisol increase. (C) Memory performance was enhanced, relative to controls, for the stressful event itself and for scenes encoded after the stress-induced cortisol increased had reached a plateau. (D) This latter enhancement was directly associated with the magnitude of the cortisol response. Modified, with permission, from (76).

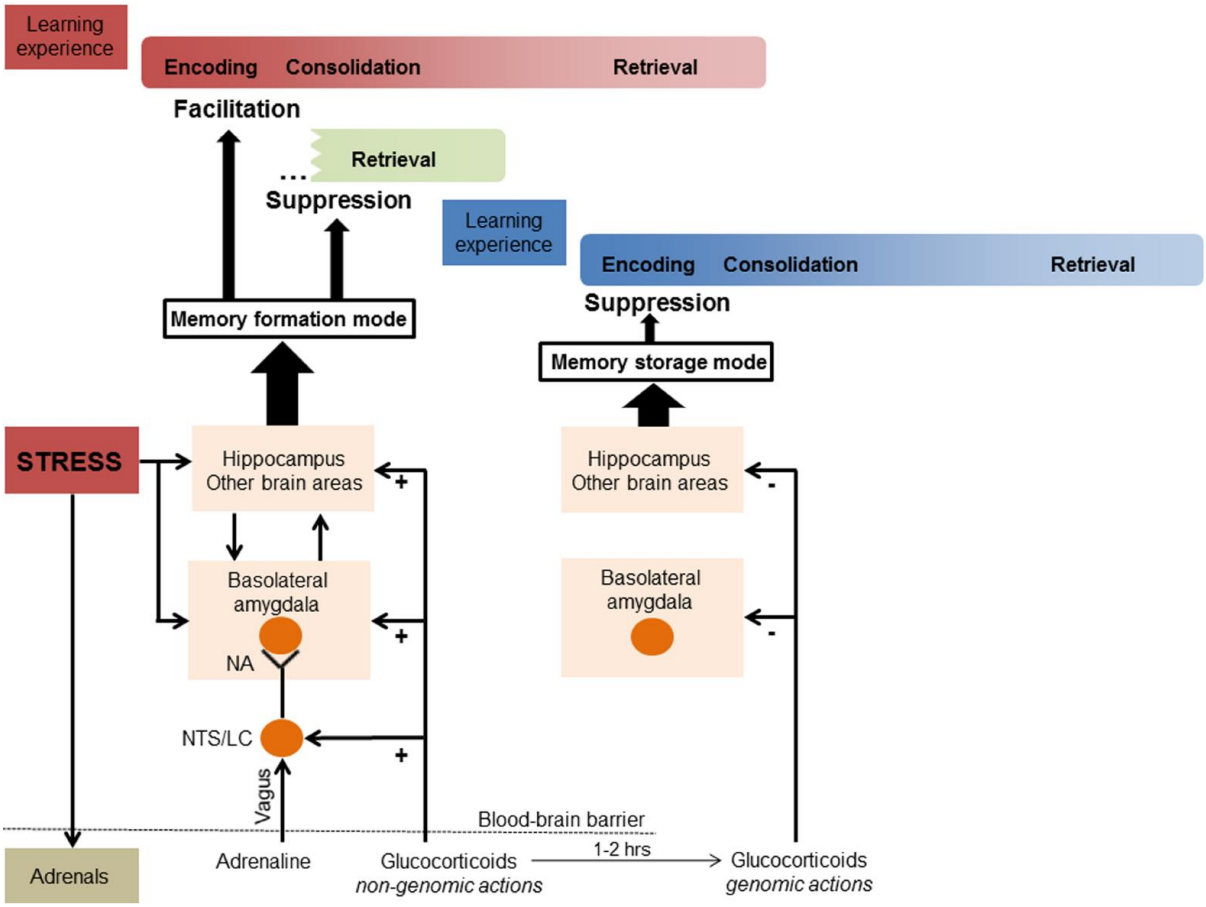

Figure 3: Integrative model of the impact of stress on memory process in the hippocampus (and, most likely, other brain areas). Rapid catecholamine and non-genomic glucocorticoid effects interact in the basolateral amygdala to shift the hippocampus (and, presumably, other areas such as the dorsal striatum) into a 'memory formation' mode. During this memory formation stage, the processing of events present around the time of the stressful experience is facilitated, whereas other cognitive operations such as memory retrieval or the encoding of events that are unrelated to the stressor are suppressed. With time, non-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 solitaries; LC – Locus coeruleus. Reproduced, with permission, from (234).

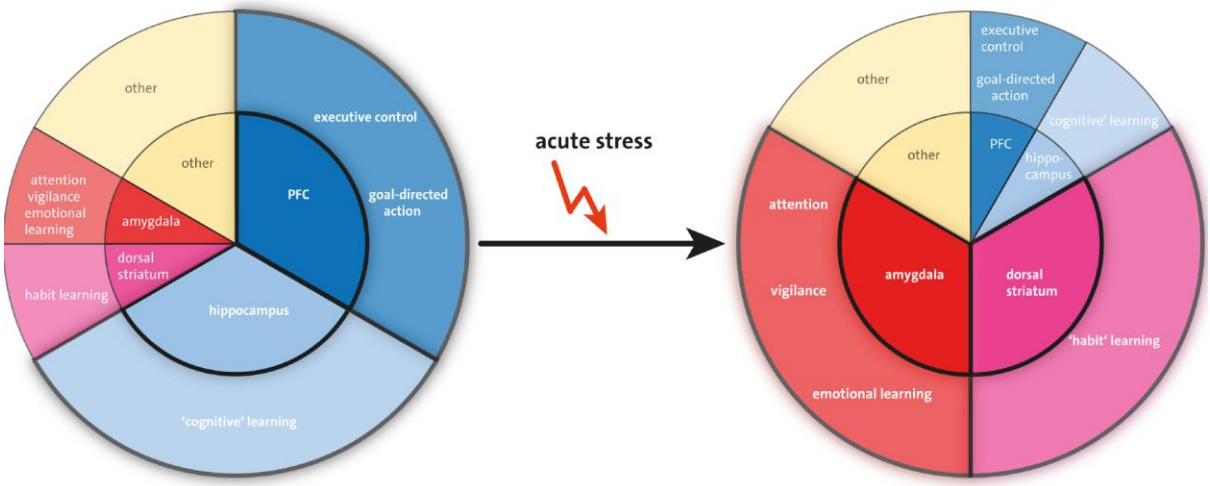

Figure 4: Stress-induced modulation of multiple memory systems. Circles represent hypothetically available cognitive and neural resources, respectively. Left: At rest, resources are predominantly allocated to the hippocampus and the prefrontal cortex, allowing executive control processes, goal-directed actions, and cognitively more demanding types of learning and memory (‘cognitive’ memory). Right: Stress induces, most likely through the MR, a shift in resource allocation towards the amygdala and the dorsal striatum, supporting increased vigilance and more efficient ‘habit’ learning. At the same time, less resources are available for cognitively more demanding processes mediated by the hippocampus or the prefrontal cortex under stress. Figure modified, with permission, from (8).