Stress and Memory Consolidation

Shira Meir Drexler and Oliver T. Wolf

Abstract This chapter presents stress modulation of learning and memory processes, focusing on the consolidation (and reconsolidation) of emotional memories in health and disease. A stressor is any kind of condition, which presents an environmental demand that exceeds the natural regulatory capacity of the individual. A stressor can be of a physical or psychological nature, tangible or mentally evoked. The subjective state of sensing these possibly adverse conditions is termed 'stress' and it leads to the activation of two systems: the sympathetic nervous system and the hypothalamus-pituitary-adrenal axis. Their end-products of (nor) adrenaline and glucocorticoids mediate different functions but also work in concert to promote an adaptive physiological and behavioral response to the challenge. Stress can either enhance or impair memory, and the timing of the stress relative to the task plays a major role in determining the direction of these effects. The adaptive stress response prioritizes consolidation of potentially dangerous events, therefore while consolidation is enhanced, retrieval is usually impaired. Additional factors, such as stimulus and context characteristics (e.g. emotionality and arousal), stress intensity and duration, also play a role. While in several circumstances can stress hormones lead to strong and persistent maladaptive or traumatic memories, their memory-enhancing and retrieval-impairing properties also make them potential adjuvants for treatment, e.g. in extinction-learning based therapies.

Keywords Emotional memory · Glucocorticoids · Memory reconsolidation · Memory retrieval · Noradrenaline

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Do you remember when did you first hear about the terror attacks on Tuesday, September 11th, 2001? Your answer will probably be 'yes'. You might even remember exact details of the event, such as the time of day, who you were with and where, how you felt, what you thought and said. But do you remember what you had for lunch on Monday, September 10th, 2001, just one day before these events took place? Your answer will probably be 'no'. The reason is that not all memories are created equal. Even years later, stressful events are better remembered than neutral ones.

This chapter will present the stress response and its mediators. Stress modulation of learning and memory processes will be discussed, focusing on the consolidation (and reconsolidation) of emotional memories in health and disease (see also the chapters by Cunningham and Payne on consolidation of emotional memory, and by Kessler, Blackwell and Kehyayan on reconsolidation and posttraumatic stress disorder).

Stress Response

A stressor is any kind of condition, which presents an environmental demand that exceeds the natural regulatory capacity of the animal, in particular when predictability and controllability are at stake (Koolhaas et al. 2011). The stressor can be of a physical or psychological nature, tangible or mentally evoked (Joels and Baram 2009; Joels et al. 2006). It could be the presence of a predator or an aggressive conspecific, an environmental challenge (e.g. flood, earthquake, forest fire) or, for humans nowadays, an important exam or a short deadline at work. The subjective state of sensing these possibly adverse conditions is termed 'stress' and it leads to a complex response, involving a variety of modulators (among them neurotransmitters, peptides and steroid hormones). Different stressors require different responses, and so the nature of the stressor determines the neuronal populations that perceive a potential threat as well as the stress mediators involved in the adaptive response (Joels and Baram 2009). For instance, physical stressors (e.g. cold, blood loss) recruit the brain stem and hypothalamus (Ulrich-Lai and Herman 2009) while psychological stressors (e.g. public speech) recruit brain areas that are involved in emotions (prefrontal cortex (PFC) and amygdala), learning and memory (hippocampus) and decision-making (PFC) (de Kloet et al. 2005). These systems are not segregated and many stressors (e.g. car accident, rape) combine both physical and psychological aspects and responses (Joels and Baram 2009).

This chapter will present the two systems involved in the stress response: the sympathetic nervous system and the hypothalamus-pituitary-adrenal axis (see Fig. 1). Their end-products of (nor)adrenaline and glucocorticoids and their interactions will be the main focus. The two systems mediate different functions but also work in concert to promote an adaptive physiological and behavioral response to the challenge, while suppressing functions that are not of immediate necessity (e.g. growth and reproduction). As the systems are highly conserved among vertebrates,

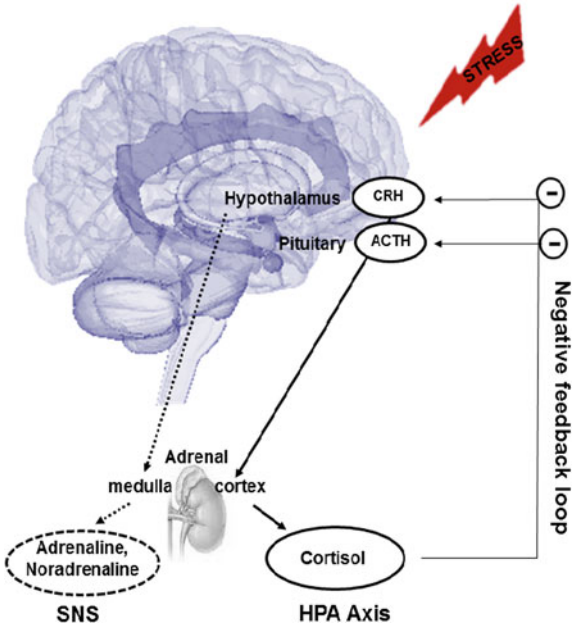

Fig. 1 *The stress response.* The sympathetic nervous system (SNS) and the hypothalamus-pituitary-adrenal (HPA) axis mediate different functions but also work in concert to promote an adaptive physiological and behavioral response to stressors. Their end-products are (nor)adrenaline and cortisol, respectively. Cortisol is also involved in a negative feedback loop, affecting the HPA axis. *ACTH* adrenocorticotropic hormone; *CRH* corticotrophin-releasing-hormone

the use of various animal models is rather common and so evidence from animal and humans studies will be presented interchangeably. For a detailed description of additional stress mediators, see Joels and Baram (2009).

The Sympathetic Nervous System

The sympathetic nervous system (SNS) is fast to respond when facing a threat. This system leads to the secretion of (nor)adrenaline (and other monoamines) from the adrenal medulla. After binding to G-protein coupled receptors in the membrane, they induce rapid but short lasting changes in the neuronal excitability. In some cases, secondary gene-mediated effects occur (Joels and Baram 2009), which are slow in onset but longer lasting. The mostly rapid SNS response promotes physiological (e.g. enhanced metabolism) and behavioral (e.g. increased arousal and vigilance) strategies that help the animal survive the initial phase of the stressful event.

The Hypothalamus-Pituitary-Adrenal Axis

While the SNS response changes neural activity quickly and transiently, the hypothalamus-pituitary-adrenal (HPA) axis mostly leads to a delayed but longer-lasting effect. Following the release of corticotrophin-releasing-hormone (CRH) from the paraventricular nucleus of the hypothalamus, the secretion of adrenocorticotropic hormone (ACTH) from the pituitary stimulates the adrenal cortex to release the steroid hormones glucocorticoids (GCs) to the general circulation. GCs (the main GC is cortisol in humans and corticosterone in rodents) are released in a pulsatile and circadian fashion, with peak concentrations shortly upon awakening and following stress exposure (Joels and Baram 2009; Kirschbaum and Hellhammer 1994). The degree of HPA activation after stress exposure depends on the severity, type and duration of the stressor but also varies between individuals. Genetic factors, personality traits, life history, age, hormonal and health status all affect the HPA response (Joels and Baram 2009; Joels et al. 2006; Kirschbaum and Hellhammer 1994). In addition, the reactivity of the HPA axis differs between males and females and is also altered during the female menstrual cycle (for a review on sex differences in HPA axis response, see Kudielka and Kirschbaum 2005; ter Horst et al. 2012). GCs regulate a wide variety of bodily functions that reinstate the homeostatic control after the temporary disturbance caused by stress. They play a major role in metabolism, and by mobilizing resources to provide energy they help to overcome the increased metabolic demand posed by the challenge. GCs regulate additional systems, such as the immune system, the cardiovascular system as well as affective and cognitive processes (Kudielka and Kirschbaum 2005).

GCs are lipophilic, and therefore can easily enter the brain (McEwen et al. 1968), where their actions facilitate behavior adaptation. In the brain, they bind to two receptor types: Mineralocorticoid (MR) and glucocorticoid (GR) receptors (de Kloet et al. 1998; Joels et al. 2006). Both receptors are co-localized in the hippocampus, amygdala and PFC (de Kloet et al. 2005; Joels and Baram 2009), brain areas that have a fundamental role in learning and memory (McGaugh 2000; Roozendaal 2002). MR are of high affinity, and are mainly present in limbic structures (Reul and de Kloet 1985). They become occupied and activated at lower concentrations, and mediate the initial GCs response to stress. For instance, they modulate appraisal of information and response selection (Lupien and McEwen 1997; Oitzl and de Kloet 1992). The GR, in contrast, are widely present in the brain, but due to their lower affinity become fully occupied only at times of high hormone concentration, e.g. at the circadian peak or following stress exposure (Reul and de Kloet 1985). GR contribute to the HPA negative feedback loop by terminating the stress response. In addition, they mediate the effects of stress on memory consolidation (de Kloet et al. 1998). Until recently, both MR and GR types were thought to lead to changes through gene expression with a delay of more than one hour. However, recent evidence has shown that both receptor types can also alter neuronal functions within minutes via non-genomic pathways (Joels et al. 2008; Joels

and Karst 2012). Membrane-bound MR that reside in the plasma membrane, higher in affinity than the nuclear variant, were suggested to be involved in the fast cognitive effects of stress on memory and executive functions (Otte et al. 2015; Vogel et al. 2015), such as the stress-induced shift from 'cognitive' (i.e. goal-directed) to 'habit' (i.e. stimulus-response) memory system (Schwabe and Wolf 2013). Membrane-bound GR, which regulate the chromatin structure, can allow transient, but potentially stable, effects on transcriptional processes that maintain cellular memory (Roozendaal et al. 2010).

The Effects of Stress on Learning and Memory

How does stress affect memory? If you'd think of the example from the beginning of the chapter (or on any other stressful event you had experienced) you'd probably say that stress enhances memory. In contrast, you might think about a presentation you once held in front of your class, in which you were so stressed you could not remember the answer to an (otherwise simple) question. Indeed, the effects of stress on memory vary, and it can either enhance or impair memory, depending on the timing of the stress with regard to the memory task, on stress intensity and duration, as well as on task-related factors and individual characteristics (Lupien and McEwen 1997; McGaugh and Roozendaal 2002; Shors 2006; Wolf 2008). For additional reviews on GCs effects on memory consolidation and retrieval, see Roozendaal (2002); Wolf (2009).

Stress and Memory Consolidation

The protein-synthesis dependent process of memory consolidation at the cellular level is thought to be accomplished in the first minutes to hours after encoding (Dudai 2004; Kandel 2001). During this period, the memory trace can be affected by a variety of manipulations. Increasing GCs concentrations by stress induction or pharmacological administration after the learning experience enhances the memory for the particular event (de Kloet et al. 1999; Joels et al. 2006). This has been demonstrated in several species for various memory types: for instance, spatial learning (Oitzl et al. 2001) and passive avoidance (Bohus and de Kloet 1981) in rodents, and taste aversion in chicks (Sandi and Rose 1994). For example, rats that were trained in a Morris water maze (a spatial memory task) show elevated circulating GCs concentrations (Oitzl et al. 2001), which are more pronounced when the water temperature is lower (presumably more stressful for the animal compared to lukewarm water). This rise in GCs concentrations is positively correlated with a memory of the platform location in a subsequent test performed one day, or one week, later (Sandi et al. 1997). Preventing GR activity during water maze learning,

either pharmacologically in rats (Oitzl and de Kloet 1992) or genetically in mice (Oitzl et al. 2001) reverses the GCs-mediated performance enhancement.

In humans, post-learning manipulations have demonstrated similar enhancing effects of stress and GCs on memory consolidation. In a typical design, such as demonstrated by Preuß and Wolf (2009), participants are presented with a new learning material (e.g. pictures or words of varying emotional valance). Immediately after learning (with or without immediate recall test), they are exposed to either the stress (e.g. psychosocial stress, cold pressor stress) or the control condition. On the next day, delayed memory recall is tested. While rising the GCs levels by stress exposure facilitates delayed recall in declarative memory tasks (Cahill et al. 2003; Preuß and Wolf 2009) inhibiting GCs activity using steroid synthesis inhibitor during learning of a task impairs the delayed (but not immediate) recall of the learned material (Lupien et al. 2002). The delayed, but not immediate, enhancing effect points to a post-encoding enhancement of memory consolidation by stress and GCs.

Yet not only timing matters. Other task- and stress-related factors play a role in the consequences of stress on memory consolidation (Joels et al. 2006). Even though some studies suggested that GCs enhance consolidation independent of arousal (Abercrombie et al. 2003; Maheu et al. 2004), there is ample evidence demonstrating that (under the same GCs conditions) emotional or arousing events tend to be better remembered than neutral ones. This will be discussed next.

Stimulus Emotionality and Arousal

GCs interact with other modulators (noradrenaline in particular) to enhance the consolidation of emotional and arousing experiences (McGaugh and Roozendaal 2002). In humans, Buchanan and Lovallo (2001) have shown that cortisol treatment prior to encoding of pictures of different emotionality results in enhanced memory for the emotional (whether negative or positive) pictures. In a similar manner, post-learning stress enhances the long-term memory for arousing slides, but not neutral slides (Cahill et al. 2003), and improves the recall of words, in particular emotional ones (Smeets et al. 2008). Noradrenergic arousal can be induced not only by the stimulus itself, but also by the context. For instance, the arousal level in rats is higher in a novel experimental context but decreases following habituation. Exposure of non-habituated (i.e. aroused) rats to a stressor enhanced the long-term memory in a non-aversive task of recognition memory. The effect was opposite (impaired consolidation) in habituated (non-aroused) rats (Maroun and Akirav 2008).

Roozendaal et al. (2006) demonstrated that noradrenergic activation in the basolateral amygdala (BLA) is necessary for GCs-induced effects on emotional memory formation. Unlike GCs, adrenaline does not readily cross the blood-brain barrier, and a peripheral-central pathway mediates its effects on the amygdala. Systemic adrenaline activates β-adrenoreceptors on vagal afferents that terminate in

the nucleus of the solitary tract (NTS). These noradrenergic cell groups project directly to the amygdala and indirectly to the locus coeruleus, leading to noradrenaline secretion. In the BLA, the β-adrenoreceptors directly stimulate cAMP and cAMP-dependent protein kinase A (PKA). GR potentiate the efficacy of this pathway, and may also influence it via coupling with α_1-adrenoreceptors. In addition to interacting with the noradrenergic cascade at postsynaptic levels, GCs alter the levels of available noradrenaline via GR in the noradrenergic cell groups in the NTS. Administrating β-adrenoreceptor antagonist into the BLA blocks GCs-mediated memory enhancement (Roozendaal et al. 1996) while post-training agonists enhance memory consolidation (Liang et al. 1995). Evidence from recent years has also suggested a role for the endocannabinoid system, a lipid-based retrograde signaling system, in mediating this interaction (Atsak et al. 2012). The interaction between GCs and the noradrenergic system, and its contribution to emotional memory enhancement, is thoroughly described by Roozendaal (2002) and is also illustrated in Fig. 2.

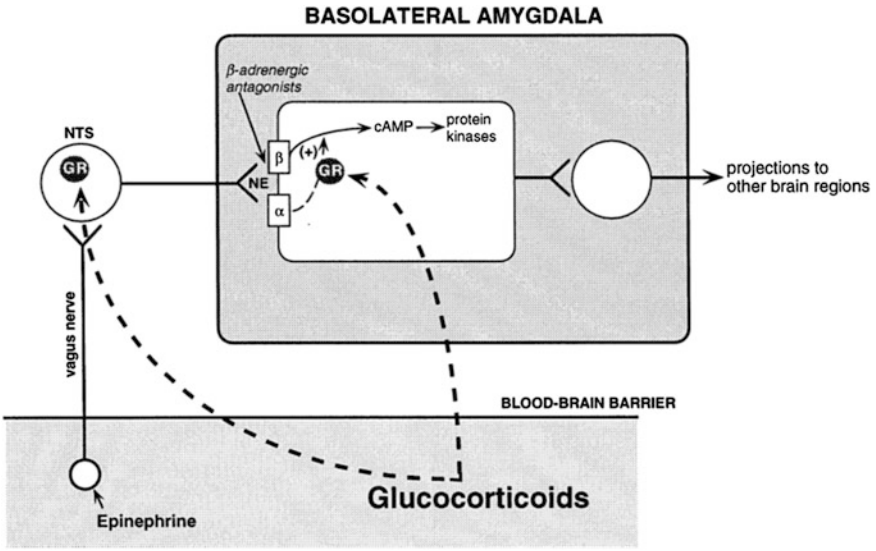

Fig. 2 *The interaction between GCs and the SNS in enhancing memory consolidation*. GCs and the noradrenergic system of the basolateral amygdala (BLA) interact at both presynaptic and postsynaptic sites. Unlike GCs, adrenaline does not readily cross the blood-brain barrier, and a peripheral-central pathway via the vagus nerve mediates its influences on the amygdala. Adrenaline activates β-adrenoreceptors on the NTS, which project directly to the BLA and indirectly to the locus coeruleus, leading to noradrenaline secretion. In the BLA, the β-adrenoreceptor directly stimulates cAMP and cAMP-dependent protein kinase A. GR potentiate this pathway efficacy, and also influence it via coupling with α_1-adrenoreceptors. In addition, GCs alter the levels of available noradrenaline via GR activation in NTS noradrenergic cell groups. *GCs* glucocorticoids; *GR* glucocorticoid receptors; *NTS* nucleus of the solitary tract. Reprinted from *Psychoneuroendocrinology*, 25, B. Roozendaal, "Glucocorticoids and the regulation of memory consolidation", 213–238. Copyright 2000 with permission from Elsevier Science

Stress Intensity

The intensity of stress is another factor determining its effects on memory consolidation. A nonlinear dose-response relationship of neurotransmitters and hormones is common, resulting from different receptor subtypes that operate with specific accessibility, affinity, desensitization and signaling cascades. A dose-response curve, inverted-U shaped, is well documented in the case of GCs (Joels 2006) and is supported by behavioral and electrophysiological studies in animals. For instance, while a moderate rise in GCs concentrations is positively correlated with spatial memory in the Morris water maze (Sandi et al. 1997), too high levels of stress (e.g. very low water temperature) do not lead to further improvement but impair performance (Kim and Diamond 2002). In the hippocampal CA1 pyramidal cells of rats, long-term potentiation (LTP) was found to be affected by GCs in a dose-depended fashion, responding to an inverted U-shaped curve (Diamond et al. 1992; Mesches et al. 1999). Using selective antagonists and agonists for MR and GR, several studies demonstrated that the underlying mechanism is the different affinity of the GCs receptors. Enchanting effects of GCs on memory consolidation were found to depend not only on saturated MR occupancy but also on low to moderate GR occupancy (de Kloet et al. 1998; Roozendaal 2000). However, the dose-dependent effects of GCs have been mainly demonstrated in animals (Joels 2006). Empirical evidence in humans is currently rather sparse. For a detailed review on the inverted U-shaped curve of GCs, see Joels (2006).

Stress Duration

The examples set above concern acute stress, in the context and around the time of the learning experience. The consequences might be significantly different in a brain that has been chronically exposed to stressors. Chronic hyper-(re)activity of the HPA axis can also occur in predisposed individuals and in association to many diseases as well as aging. This can result in dendritic atrophy, reduced neurogenesis and impaired synaptic plasticity in the hippocampus and in the medial PFC. In these cases, learning and memory performances are typically impaired (McEwen 2004; Sapolsky 1999). In the BLA, in contrast, chronic stress leads to robust dendritic growth, which is related to greater anxiety-like behavior (Roozendaal et al. 2009). In a similar way, hypertrophy in the dorsolateral striatum, seen in relation to chronic stress, possibly mediates the bias towards more habitual patterns in instrumental behaviors (Schwabe et al. 2012).

Timing: Consolidation Versus Retrieval

Many students might know this too well: Stress at the time of an exam might lead to a better memory of the stressing test experience itself (when recalled later), while impairing the retrieval of the study material during the exam. Indeed, timing is of critical importance in determining GCs effects on memory. In the short term, GCs and other stress-induced mediators facilitate the strengthening of synaptic contacts involved in the memory formation of the events that led to their release. At the same time, they initiate gene-mediated signals that suppresse any unrelated information from reaching the same brain areas. Indeed, long term memory retrieval is usually impaired by cortisol (de Quervain et al. 2009; Wolf 2009). In most cases this strategy is highly adaptive, prioritizing consolidation of potentially dangerous events over retrieval at times of stress (Diamond et al. 2005; Joels et al. 2006). However, its impairing effects on retrieval might negatively affect performance. In rats that already learned the location of an underwater platform in the Morris water maze, a footshock (i.e. stressor) or injection of corticosterone 30 min before a free swim test lead to performance impairment (de Quervain et al. 1998). In humans, similar impairing effects of stress and GCs were seen in declarative memory tasks (de Quervain et al. 2000; Kuhlmann et al. 2005). Neuroimaging studies have demonstrated that this GCs-induced impairment in declarative memory retrieval is associated with reduced activity of the medial temporal lobe, the hippocampus in particular (de Quervain et al. 2003; Oei et al. 2007).

Stress and Memory Reconsolidation

Stress and GCs have been demonstrated to enhance memory consolidation while impairing retrieval. Do they affect a memory that has been successfully retrieved? The traditional view on memory suggested that memory consolidation is a one-time event, completed shortly after acquisition (McGaugh 1966). This unidirectional view on memory was challenged by Misanin et al. (1968) who suggested that memory reactivation (i.e. retrieval) can cause the memory to re-enter a labile state until re-stabilization (reconsolidation) is completed. The reactivation-dependent lability period was found to last for up to 6 h post-retrieval (Kindt et al. 2009; Schiller et al. 2010), and was suggested to serve as an adaptive mechanism allowing memory update (Alberini 2011; Alberini and LeDoux 2013; Forcato et al. 2014). Various pharmacological agents have been found to affect memory reconsolidation, thereby revealing the mechanisms mediating memory formation and modulation after retrieval. For instance, Nader et al. (2000) demonstrated that reconsolidation is a protein-synthesis-dependent process, while Kindt et al. (2009) showed that reconsolidation of emotional memories is dependent on noradrenergic activity. Both studies pointed to a similarity between reconsolidation after retrieval and

initial consolidation. The possible influence of GCs and stress on memory reconsolidation, however, have been investigated only recently.

Akirav and Maroun (2013) reviewed the different, often conflicting, effects of stress and GCs administration on memory reconsolidation. Several animal studies suggest an impairing effect of either stress induction or GCs administration on memory reconsolidation (Yang et al. 2013). However, both GR agonists (Abrari et al. 2008; Cai et al. 2006) and antagonists (Pitman et al. 2011) were found to impair reactivated memories. The human literature had mainly focused on the effects of stress on reactivated declarative memories. The studies demonstrated either an enhancement (Schwabe and Wolf 2010; Zhao et al. 2009) or impairment (Bos et al. 2014; Coccoz et al. 2011, 2013) of reactivated memories, with conflicting results with regard to the effect on strong emotional memories. Recently, however, Meir Drexler et al. (2015) demonstrated an enhancing effect of cortisol on the reconsolidation of reactivated fear memories in healthy men. The fear conditioning paradigm is a model for stress–and trauma-related disorders, and is often used to investigate the emotional and cognitive mechanisms of aversive memories (Pull 2007). The results of the study suggest a mechanism for emotional memory persistence, and could contribute to the understanding of the persistence of emotional memories in several psychiatric disorders.

Figure 3 provides a summary of the timing-dependent effects of stress on the various memory processes.

Relevance for Psychopathology and Treatment

Due to the enhanced consolidation of highly emotional and stressful events, strong memories are common following an aversive experience. This is a very adaptive mechanism, yet even emotional memories weaken over time. In several circumstances, however, extremely aversive events can lead to maladaptive and traumatic memories. This is seen in post-traumatic stress disorder (PTSD) and anxiety disorders (e.g. phobias). PTSD is characterized by re-experiencing the evet, avoidance of stimuli associated with it, and hyper-arousal (American Psychiatric Association 2013; Yehuda 2002). Re-experiencing symptoms include intrusive daytime recollections, nightmares and flashbacks in which the traumatic event is retrieved. The traumatic memories often keep their vividness and ability to evoke distress for decades or even a lifetime after the event. Anxiety disorders, such as phobias, are characterized by persistent fear that is excessive or unreasonable, cued by the presence or anticipation of a specific stimulus or context (American Psychiatric Association 2013). Exposure to phobic stimuli provokes retrieval of stimulus-associated fear memory that leads to the fear response (de Quervain and Margraf 2008; Fehm and Margraf 2002; Rapee and Heimberg 1997). The strength of the fear memory is a result of over-consolidation due to action of stress hormones at the time of the event (Pitman 1989). In these cases, the aversive event trace remains easily reactivable to an aversive cue or even spontaneously (de Quervain

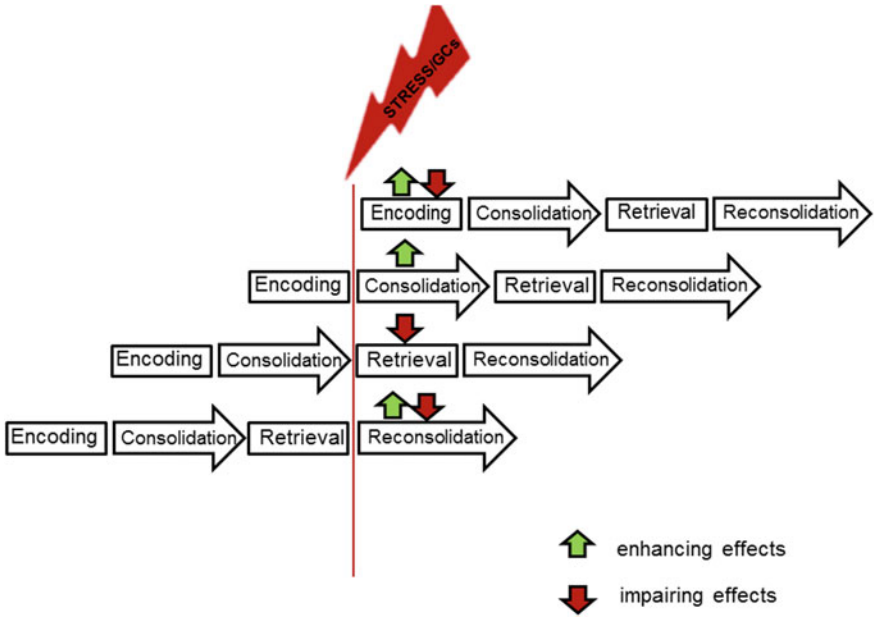

Fig. 3 *The effects of stress and glucocorticoids (GCs) on memory processes*. Stress and GCs effects on memory processes depend on the specific memory phase. Stress induction shortly before encoding typically enhances memory (even though the findings are somewhat heterogeneous). This effect is modulated by the exact timing and the emotionality/relevance of the material. Stress induction after encoding (at the beginning of consolidation) has memory enhancing properties (illustrated with the *green arrow pointing upwards*). Stress before memory retrieval, in contrast, leads to an impairment (illustrated with the *red arrow pointing downwards*). The possible influence of GCs and stress on memory reconsolidation have been investigated only recently with mixed results

and Margraf 2008). The persistence of the memories in the long-term is a possible result of repeated retrievals and enhanced reconsolidation of the fear memory trace at the presence of elevated GCs concentrations (Meir Drexler et al. 2015).

GCs, that can led to robust and maladaptive memories due to their enhancing effect on emotional memory consolidation, can also provide the remedy. Extinction learning occurs when a conditioned responding (e.g. fear) to a stimulus (e.g. spider) is decreased when the reinforcer is omitted (Quirk and Mueller 2008). Extinction is a new learning that creates a fear-inhibiting memory, and is the suggested mechanism underlying various cognitive-behavioral therapies (e.g. exposure therapy) that successfully reduce learned fears (Rachman 1989). As a new learning, it requires consolidation. Due to their memory-enhancing properties, GCs can be used to facilitate the new safety learning in extinction-based therapies (de Quervain and Margraf 2008). In addition, as a result of their retrieval-impairing properties, GCs could partly interrupt the vicious cycle of spontaneous retrieving and reconsolidation of traumatic memories, thereby promote the process of forgetting, a

spontaneous process occurring when memory in not reactivated (de Quervain and Margraf 2008). For a review on GCs, their role in stress-related disorders and their potential for treatment, see de Quervain and Margraf (2008); de Quervain et al. (2009).

Conclusion

Stress leads to the activation of two systems: the sympathetic nervous system and the hypothalamus-pituitary-adrenal axis. Their end-products of (nor)adrenaline and glucocorticoids mediate different functions but also work in concert to promote an adaptive physiological and behavioral response to the challenge. Stress can either enhance or impair memory, and the timing of the stress relative to the task plays a major role in determining the direction of these effects. The adaptive stress response prioritizes consolidation of potentially dangerous events, therefore retrieval during or shortly after stress exposure is usually impaired. Additional factors, such as stimulus and context characteristics (e.g. emotionality and arousal), stress intensity and duration, also play a role. While in several circumstances stress hormones can lead to strong and persistent maladaptive or traumatic memories, their memory-enhancing and retrieval-impairing properties also make them potential adjuvants for treatment, e.g. in extinction-learning based therapies.

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