CHAPTER 8

Stress, fear, and memory in healthy individuals

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8.1 Introduction

Life-threatening experiences such as car accidents, assaults, or natural disasters usually produce powerful and intrusive memories. In vulnerable individuals, these overly strong memories may persist and lead to the debilitating condition of posttraumatic stress disorder (PTSD). In addition to strongly encoded emotional memories, impoverished memory functioning or disruptions in memory have been associated with exposure to stress. These two, apparently opposing, memory processes have also been identified as key memory impairments in PTSD patients, in the form of highly emotional traumatic memories that are easily triggered and general memory impairments (American Psychiatric Association, 2013).

In this chapter, we summarize the research findings on the impact of acute stress on memory functioning in healthy individuals, which may shed light on the underlying neurobiological processes related to these two apparently distinct memory processes.

The strength of traumatic memories has been related to the action of hormones and neurotransmitters that are released during the traumatic event (Pitman, 1989; Pitman et al., 2012). Although such extreme experiences are relatively rare, we all experience stress in varying degrees and forms every day, with work-related stress, financial problems, relationship distress, or chronic illness being only a few examples. Albeit less intense, it is assumed that the biological responses to everyday stress are highly similar to the physiological responses to life-threatening stress experiences. The stress response begins when the prefrontal cortex (PFC) and limbic structures, in particular the amygdala and the hippocampus, appraise a situation or a stimulus as a potential threat (i.e., a stressor) to the organism. These brain areas are intimately

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linked to the hypothalamus, the control center of two major stress response systems of the body: the rapidly acting sympathetic nervous system and the hypothalamus–pituitary–adrenal (HPA) axis (Joëls & Baram, 2009; see Figure 8.1 and Chapters 9 and 11). When prefrontal and limbic structures signal that a situation is threatening, the hypothalamus rapidly activates the sympathetic nervous system, which triggers, within seconds, the release of epinephrine and norepinephrine from the adrenal medulla. Although these catecholamines

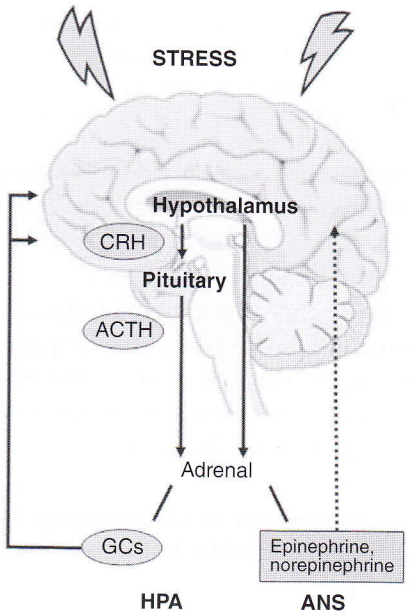

Figure 8.1 Circuits activated by stress. If a situation is perceived as a threat for the physiological or psychological integrity of the organism, the brain activates two lines of defense mechanisms that serve to adapt to the demand and to restore balance: the rapidly acting autonomic nervous system (ANS) and the slower hypothalamic–pituitary–adrenal (HPA) axis. The first line of defense sets in immediately after the stressor occurs when the amygdala activates the hypothalamus. Activation of the hypothalamus in turn stimulates the sympathetic arm of the ANS, which secretes norepinephrine at its postganglionic nerve endings. Among the effector organs of the ANS is the adrenal medulla, which releases epinephrine and norepinephrine. Autonomic activation can indirectly (via the vagal nerve, solitary tract nucleus, and locus coeruleus) lead to the release of norepinephrine in the brain. The second line of defense is initiated by the secretion of corticotropin-releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus. CRH causes the secretion of β-endorphin and adrenocorticotropic hormone (ACTH) from the anterior pituitary, which is transported in the bloodstream to the cortex of the adrenal glands, inducing the secretion of glucocorticoids. Glucocorticoids exert negative feedback via receptors at the pituitary and hypothalamus, thereby reducing the enhanced activity of the HPA axis. (Reproduced from Schwabe et al., 2010b.)

cannot cross the blood–brain barrier, they exert indirect effects on the brain via the vagus nerve, which then further activates central noradrenergic systems, particularly the locus coeruleus and the nucleus tractus solitarius (Williams & Clayton, 2001). In addition to the activation of the sympathetic nervous system, the hypothalamus also triggers the HPA axis by releasing corticotropin-releasing hormone (CRH). CRH provokes the secretion of another hormone, adrenocorticotropic hormone (ACTH), from the pituitary. ACTH, in turn, stimulates the release of glucocorticoids (mainly cortisol in humans and corticosterone in rodents) from the adrenal cortex. Glucocorticoids are steroid hormones that can cross the blood–brain barrier. Through binding to glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs) in the brain, glucocorticoids modulate, in concert with norepinephrine and other hormones and neurotransmitters that are released in response to stressors, learning and memory processes by acting on various brain areas, including the hippocampus, amygdala, and PFC. Understanding how stress, through these stress mediators, may yield strongly consolidated emotional memories and impaired memory functioning could enhance our understanding of the pathogenesis of PTSD and potentially open the door to novel treatment approaches.

In this chapter, we first focus on the impact of stress and stress hormones on human episodic memory, i.e., memory for events that can be explicitly stated and tested, such as the memory for your last birthday party. Next, we review stress effects on human fear conditioning, an important model of PTSD, where fear memories can be established without explicit awareness of the learning process. In the third part of this chapter, we will summarize recent findings showing that stress may alter the contributions of multiple memory systems to learning, thus promoting a shift from flexible, "cognitive" to rather rigid, "habit" learning and memory. Finally, we discuss the implications of these findings on stress and memory in healthy humans for trauma memory, the core feature of PTSD. Findings related to neuropsychological studies of memory function in PTSD patients are covered elsewhere in this book (see Chapter 12).

8.2 Time-dependent effects of stress on episodic memory in healthy humans

When learning, storing, and retrieving new information, the hippocampus and adjacent medial temporal lobe regions are the key locus of episodic memory in the brain (Dickerson & Eichenbaum, 2010; Tulving & Markowitsch, 1998). At the same time, the hippocampus is one of the brain areas with the highest density of GRs and MRs (de Kloet et al., 1998; McEwen et al., 1986), suggesting that it is particularly sensitive to stress and glucocorticoid effects. Indeed, there is converging evidence from neurophysiological, neuroimaging, and behavioral

studies showing that stress and stress hormones affect hippocampal activity and functionality (Diamond et al., 2007; Kim et al., 2001; Pruessner et al., 2008; de Quervain et al., 2003; Schwabe et al., 2009a). Hippocampus-dependent learning and memory processes may be enhanced or impaired by stress, depending on whether or not stress occurs around the time and within the context of a learning episode (Joëls et al., 2006). In a stressful situation, the hippocampus turns to a 'memory formation mode' during which strong memories are created for everything that is related to the stressor. When the stress situation is over, the hippocampus appears to shift to a "memory storage mode" that is dedicated to the consolidation of the memories of the stressful event (Schwabe et al., 2012a). The prioritized encoding and storage of memories of stressful experiences is obviously adaptive; our survival may depend on remembering these stressful episodes from our past. However, the superior memory for information related to a stressor may come at the cost or detriment of stressor-unrelated memory processes. In the following sections, we discuss the effect of stress on every stage of a memory – encoding, consolidation, retrieval, and post-retrieval reconsolidation – in more detail (see also Figure 8.2).

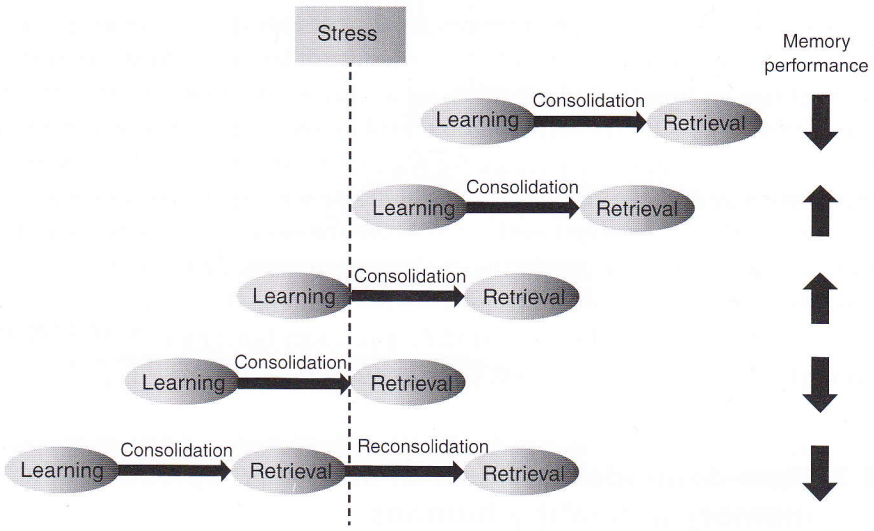

Figure 8.2 Time-dependent effects of stress on hippocampus-dependent episodic memory. Stress before learning may enhance memory when it occurs within the context of a learning experience (e.g., shortly before or during learning), whereas stress out of the learning context (e.g., relatively long before learning) impairs memory. Stress shortly after learning strengthens subsequent memory, particularly for emotionally arousing information. Conversely, stress before retention testing typically reduces retrieval performance, again particularly for emotionally arousing information. In addition, stress may also interfere with the re-stabilization ("reconsolidation") of memories after retrieval. (Reproduced from Schwabe & Wolf, 2013.)

8.2.1 Stress and memory encoding

One of the challenges in investigating the specific effects of stress on memory encoding is that stress effects on encoding can hardly be disentangled from those on memory consolidation, and in some studies the stress effects may influence encoding, consolidation, and retrieval. Studies in which participants were exposed to a (unrelated) stressor before encoding yielded heterogeneous results, with some studies reporting enhanced (Henckens et al., 2009; Nater et al., 2007; Schwabe et al., 2008; Van Stegeren et al., 2010), and others impaired, subsequent memory performance (Elzinga et al., 2005; Kirschbaum et al., 1996; Lupien et al., 1997). Several factors have been proposed to account for these discrepant findings. For example, it has been suggested that stress has different effects on the encoding of neutral and emotional material (Payne et al., 2006; Tops et al., 2003) or that the direction of the stress effects depends on the stressor intensity and the associated glucocorticoid level (Abercrombie et al., 2003). Based on models derived from neurophysiological studies in rodents (Diamond et al., 2007; Joëls et al., 2006), it has recently been argued that the time of the stress exposure relative to the learning episode might be the critical factor that determines whether stress before learning enhances or impairs memory. It is assumed that catecholamines and rapid, non-genomic glucocorticoid actions enhance the memory for currently ongoing events, whereas the slowly developing genomic glucocorticoid actions impair memory formation (Joëls et al., 2006, 2011). Such a biphasic effect of glucocorticoids on the hippocampus was recently confirmed in the human brain (Lovallo et al., 2010). Moreover, a recent behavioral study reported that memory was impaired when healthy subjects were stressed 30 minutes before learning, but enhanced when subjects were exposed to the stressor shortly before learning (Zoladz et al., 2011). In line with these findings, other studies showed that psychosocial stress shortly before or during learning enhanced the retention of material that is conceptually related to the stress situation, such as stressor-related, high-arousal words (Smeets et al., 2007, 2009). However, stress around the time of learning may not necessarily boost memory. If stress is not related to the learning experience, it may act as a distractor and result in severely impaired memory (Schwabe & Wolf, 2010a). In sum, many factors determine how exactly stress affects memory encoding, and the details are still not fully understood.

8.2.2 Stress and memory consolidation

Compared with neutral events, emotionally arousing experiences are typically very well remembered (Christianson, 1992; McGaugh, 2000; Winograd & Neisser, 1992). Understanding how the superior memory for emotional material is created has important implications for the intrusive traumatic memories that typically develop in PTSD. The emotional memory enhancement is thought to be

a result of the influence of adrenal hormones on amygdala activity, which in turn promotes consolidation processes in other brain regions such as the hippocampus. For instance, amygdala activity during encoding correlates significantly with the strength of emotional memories (Cahill et al., 1996) and amygdala dysfunction abolishes the superior memory for emotional material (Cahill et al., 1995). Adrenergic activity is critical for the superior memory for an emotionally arousing event. For instance, studies showed a correlation between the level of the plasma metabolite of norepinephrine, 3-methoxy-4-hydroxyphenylglycol (MHPG), and the strength of emotional memory formation in the context of a pharmacological challenge (Southwick et al., 2002). Blocking the activity of norepinephrine by means of the β-adrenergic antagonist propranolol eliminates both the emotional memory enhancement and the associated increase in amygdala activity (Cahill et al., 1994; Strange & Dolan, 2004), and hence is theoretically an interesting treatment for direct use after exposure to a traumatic event. In line with the idea that hormones and neurotransmitters that are released in response to stress facilitate memory consolidation, stress and elevated glucocorticoid or epinephrine levels shortly after training also enhance subsequent memory (Andreano & Cahill, 2006; Beckner et al., 2006; Cahill & Alkire, 2003; Cahill et al., 2003). The enhancing effects of stress on memory consolidation are particularly pronounced for emotionally arousing material (Cahill et al., 2003). Moreover, glucocorticoids appear to be most effective in individuals who are emotionally aroused (Abercrombie et al., 2006). These latter findings corroborate the view that glucocorticoids interact with emotional arousal-induced noradrenergic activation to boost memory consolidation, which has been convincingly shown in rodents (Roozendaal et al., 2006a,b).

8.2.3 Stress and memory retrieval

Stress or the administration of glucocorticoids shortly before retention testing is often associated with reduced memory performance (de Quervain et al., 2000; Kuhlmann et al., 2005; Schwabe & Wolf, 2009a, 2014; Tollenaar et al., 2008, 2009; but for indications of enhanced retrieval during or after stress, see Hupbach & Fieman, 2012; Schilling et al., 2013; Schönfeld et al., 2014; Schwabe et al., 2009b), suggesting that memory retrieval is, in contrast to memory consolidation, impaired by stress. The disruptive effect of stress or glucocorticoids on retrieval performance is paralleled by reduced activity in the PFC and the hippocampus during retention testing (Kukolja et al., 2008; Oei et al., 2007). Emotionally arousing memories are, again, particularly sensitive to the influence of stress and stress hormones (Buchanan et al., 2006; Kuhlmann et al., 2005). Blocking the arousal-related noradrenergic activity pharmacologically with a β-adrenergic antagonist prevents the impact of stress on memory retrieval (de Quervain et al., 2007; Schwabe et al., 2009b), whereas it does not affect retrieval *per se* (Tollenaar et al., 2009). Thus, there is strong evidence that the impairing

effect of stress on memory retrieval requires, as with the enhancing effect on memory consolidation, concurrent glucocorticoid and noradrenergic activation.

8.2.4 Stress and memory reconsolidation

The past 15 years have seen renewed interest in the idea that the reactivation of a consolidated memory during retrieval returns this memory to an unstable state again from which it needs to be stabilized anew during a process of "reconsolidation" (Dudai, 2006; Nader & Hardt, 2009). Recent evidence suggests that stress may affect memory also when administered after retrieval, i.e., during reconsolidation. The direction of these effects, however, is not yet fully clear. One study reported that stress during reconsolidation enhances subsequent memory (Coccoz et al., 2011), similar to stress during initial consolidation. Other studies, however, showed that stress after retrieval impairs updating of memory traces (Schmidt et al., 2014) and disrupts the re-stabilization of memories during reconsolidation, resulting in impaired subsequent recall (Schwabe & Wolf, 2010c; Zhao et al., 2009). Given the potential opportunity to modify unwanted memories after their reactivation, stress hormone effects on memory reconsolidation might be particularly interesting in the context of PTSD and are therefore an important avenue for future research.

8.3 Stress and fear conditioning in humans

In addition to the episodic memory of the traumatic event, conditioned fear is an important part of the trauma memory (see Chapter 4). Fear conditioning processes are thought to play a major role in the development of anxiety disorders in general (Mineka & Oehlberg, 2008; Mineka & Zinbarg, 2006) and fear conditioning is one of the most important models of fear learning relevant to PTSD (Graham & Milad, 2011; Mineka & Oehlberg, 2008). During fear conditioning, an individual learns that a neutral stimulus is reliably paired with an aversive event (unconditioned stimulus, UCS) leading to a fear response (unconditioned response). As a result of these pairings, the initially neutral stimulus alone can trigger the fear response and is now referred to as a conditioned stimulus (CS). The CS can be a cue (cue-dependent conditioning) or a context (context-dependent conditioning). Because human fear conditioning studies have used mainly cue-dependent conditioning, we will focus mainly on this form of conditioning (for context-dependent conditioning in animals, see Maren et al., 2013; for the effects of development on fear learning, see Chapter 4).

Repeated presentations of the CS without the UCS result in fear extinction during which fear memories are suppressed. Exposure to phobic stimuli and situations, or trauma-related memories in the case of PTSD, is based

on fear extinction and represents the most effective therapeutic strategy to treat anxiety disorders (Foa & Kozak, 1986; Vervliet et al., 2013). However, after extinction, the fear is not gone, it is just not expressed. Return of fear is often observed when individuals are exposed to the CS after a delay (spontaneous recovery), after a change in context (renewal), or after unsignalled presentations of the UCS (reinstatement; see Bouton, 2004).

It is well established that the amygdala is the central structure for fear conditioning in the brain, both in humans and other animals (LeDoux, 2000). Moreover, the anterior cingulate cortex, the insula, the ventromedial PFC (vmPFC), and the hippocampus are important parts of the fear and extinction network (Mechias et al., 2010; Sehlmeyer et al., 2009). Interestingly, abnormalities in this fear circuitry have been repeatedly found in PTSD patients (Elzinga & Bremner, 2003; Etkin & Wager, 2007). In the following sections, we review the findings regarding the impact of stress and stress hormones on fear memory formation, extinction, and the return of fear.

8.3.1 Stress and fear memory formation

How stress affects fear acquisition in healthy individuals remains controversial; some studies reported enhanced, others reduced, conditioned fear memory after stress. Part of these discrepancies is the result of differences in the timing of the stress experience. For instance, autonomic activity setting in rapidly after stressor onset appears to be associated with enhanced conditioned fear (Antov et al., 2013). In line with these findings, pharmacological elevations in noradrenergic stimulation by the α_2-adrenoreceptor antagonist yohimbine strengthens subsequent fear memory, as indicated by slower extinction learning, heightened fear retrieval after reinstatement, and increased fear reacquisition (Soeter & Kindt, 2011). In contrast to the influence of autonomic arousal, the delayed cortisol response to a stressor appears to be negatively correlated with fear memory formation (Antov et al., 2013). This is in line with findings that the cortisol response 30 minutes after stress exposure is negatively associated with amygdala activation (Oei et al., 2012). However, it is important to note that there is accumulating evidence for significant sex differences in stress effects on fear conditioning, in line with animal data (Dalla & Shors, 2009; Shors, 2004). For instance, stress induction 1 hour before fear conditioning enhanced fear responses in men but appeared to inhibit fear memory in women (Jackson et al., 2006). Similarly, stress-induced cortisol elevations after fear conditioning strengthen fear memory consolidation in men but not in women (Zorawski et al., 2005, 2006). Exposure to psychosocial stress led to the same pattern of results: stress attenuated conditioned fear responses in men, but enhanced fear responses in women taking oral contraceptives (Merz et al., 2013).

Pharmacological studies suggest that glucocorticoids may further modulate fear conditioning processes differently in men and women sex-dependently.

Cortisol attenuated fear contextualization and increased fear generalization in women taking oral contraceptives, whereas the opposite pattern was observed in men (Van Ast et al., 2012). More specifically, in women, cortisol enhanced fear towards cues signaling danger in threatening and safe contexts, as well as towards safety signals in a threatening context. Such deficits in fear contextualization may constitute a vulnerability factor in the development of anxiety and trauma-related disorders such as PTSD. Moreover, it has been consistently shown that pharmacological elevations of cortisol diminish fear responses in men and free-cycling women, but increase fear in women taking oral contraceptives (Merz et al., 2010, 2012; Stark et al., 2006; Tabbert et al., 2010). Neuroimaging revealed that glucocorticoid administration and stress affected the fear network, including the amygdala and the hippocampus (Henckens et al., 2010, 2012; de Quervain et al., 2003), which are critical for the formation of emotional memories (Cahill & McGaugh, 1998; McGaugh, 2000). Cortisol also exerted sex hormone status-related effects in areas involved in fear expression and regulation, such as the anterior cingulate or the orbitofrontal cortex. Further evidence points to sex-dependent effects of stress hormones, particularly on amygdala activity. For example, noradrenergic stimulation led to increased amygdala activity in response to fearful faces in women but to decreased amygdala responses in men (Schwabe et al., 2013a). In line with these findings, rapid cortisol effects reduced amygdala responsivity to fearful faces (Henckens et al., 2010) and also impaired resting state functional connectivity of the amygdala to the hippocampus in men (Henckens et al., 2012).

Taken together, autonomic activity and rapid, non-genomic glucocorticoid actions appear to enhance fear memory formation. However, when stress hormone concentrations peak shortly before or during acquisition they inhibit transiently the fear circuit surrounding the amygdala and the hippocampus in general, but increase fear in women taking oral contraceptives. Slowly developing, genomic glucocorticoid effects, on the other hand, seem to enhance fear acquisition again. How exactly stress hormones evoke these opposite fear response patterns is still not fully understood.

8.3.2 Stress, extinction, and the return of fear

The majority of human studies on the influence of stress on fear conditioning processes have focused on fear acquisition, yet over the past few years also fear extinction and the subsequent return of fear received increasing attention. For example, cortisol administration before fear learning has been shown to reduce activation of the amygdala or the hippocampus during subsequent extinction learning in women taking oral contraceptives (Tabbert et al., 2010). However, here, cortisol effects on fear acquisition and extinction could not be separated. To overcome this problem, in a recent functional magnetic resonance imaging experiment, cortisol was given directly after fear learning, 45 minutes before

fear extinction took place (Merz et al., 2014). The results showed that cortisol increased electrodermal fear responses during extinction in men, which was paralleled by attenuated activation of the amygdala, medial PFC, and nucleus accumbens. These findings suggest that cortisol disrupted the interplay between these structures, which may have delayed fear extinction. Whereas this study used a 1-day design in which fear acquisition und extinction were separated only by a short delay, another recent study in healthy humans tested how stress alters extinction of a conditioned fear memory that was acquired 1 day before (Bentz et al., 2013). Here, stress reduced fear retrieval expressed as UCS expectancy in men, but not in women. However, this effect was evident only at the first CS presentation in the extinction session as well as in another test on a third day, indicating that stress inhibited fear retrieval rather than that it affected extinction learning. These findings parallel experiments in phobic patients, who benefit from cortisol intake prior to exposure sessions, which are based on the principle of extinction learning (de Quervain et al., 2011; Soravia et al., 2006; see below).

Several further attempts have been made to enhance extinction learning and to prevent the return of fear mainly by pharmacological alterations of noradrenergic activity (see Holmes & Quirk, 2010, for an overview of the animal literature). Pharmacologically increased noradrenergic activity before exposure therapy attenuates fear at a 1-week follow-up in acrophobic patients (Powers et al., 2009). In line with findings in episodic memory (discussed earlier), it is tempting to speculate that yohimbine made extinction memories more arousing and thus better consolidated.

Building on the proposed lability of memories after their reactivation (Nader & Hardt, 2009), several recent studies aimed to tackle fear memories during reconsolidation. Administration of the β-adrenergic antagonist propranolol given either before or after fear memory reactivation by a single CS presentation reduced the return of fear in subsequent reinstatement and renewal protocols, even 1 month later (Soeter & Kindt, 2010, 2012a,b).

Taken together, augmentation of (nor)adrenergic transmission seems to promote consolidation of fear extinction. Neuroimaging studies exploring the neural underpinnings of the effects of norepinephrine are still largely missing. The animal literature, however, suggests an enhancement of the excitability of neurons in the vmPFC (Mueller & Cahill, 2010).

8.4 Stress-induced modulation of multiple memory systems

The previous two sections dealt with stress effects on single memory systems, mainly the hippocampus and the amygdala. Stress may affect the performance of these systems and thus alter quantitative memory parameters such as the

number of remembered items or the strength of the fear memory. Over the past few years, evidence has accumulated suggesting that stress affects not only how much we learn or remember in a given situation but also how we learn and which strategies we use during learning (Schwabe et al., 2010b).

Many tasks can be solved in different ways; they can be acquired by distinct memory systems that differ in the mode of operation and the type of information that is processed (Squire, 2004). Stress may have a critical impact on which of these systems is engaged during learning. Route learning, for example, may be supported by a hippocampus-dependent spatial memory system that learns the relationship between multiple cues in the environment and by a dorsal striatum-dependent stimulus–response (S–R) memory system that associates a single stimulus with a certain response (McDonald & White, 1993; Packard et al., 1989). In line with earlier rodent data (Kim et al., 2001; Packard & Wingard, 2004), stress before learning promotes in humans S–R learning at the expense of spatial learning (Schwabe et al., 2007). Glucocorticoids seem to play an important role in the switch between flexible, "cognitive" spatial learning and rather rigid, "habitual" S–R learning (Bohbot et al., 2011; Schwabe et al., 2009c). Probabilistic classification learning may also be subserved by a hippocampal and a striatal system (Foerde et al., 2006; Knowlton et al., 1996) and which memory controls learning can also be influenced by stress. Stress before classification learning favors striatum-dependent "procedural" learning over hippocampus-dependent "declarative" learning (Schwabe & Wolf, 2012). Neuroimaging data confirmed that stress shifted classification learning from hippocampal to striatal control and suggested that this shift may be due to an impairment of the hippocampus-dependent system (Schwabe & Wolf, 2012). The shift from hippocampus-dependent to striatum-dependent memory is orchestrated by the amygdala, as indicated by findings showing that stress increases amygdala connectivity with the dorsal striatum, whereas amygdala connectivity with the hippocampus decreases after stress (Schwabe et al., 2013b).

Instrumental learning can also be controlled by two separate memory systems: a PFC-based "goal-directed" system that encodes the association between an action and the outcome that is engendered by the action; and a dorsolateral striatum-based "habit" system that associates a response with preceding stimuli (Balleine & O'Doherty, 2010; Dickinson, 1985). Stress promotes habit learning (Schwabe & Wolf, 2009b, 2010b). This stress-induced bias towards habits is correlated with the cortisol increase in response to stress and can be prevented by a β-adrenergic antagonist (Schwabe et al., 2011), suggesting that stress effects on the engagement of goal-directed and habit systems necessitate, in same way as stress effects on hippocampal memory (Roozendaal et al., 2006a), simultaneous glucocorticoid and noradrenergic activation. Corroborating this conclusion, pharmacological elevations of both glucocorticoid and noradrenergic activity

resulted in habitual learning, whereas behavior remained goal-directed when only one of the two stress response systems was stimulated (Schwabe et al., 2010a, 2012b). At the neural level, habit learning after concurrent glucocorticoid and noradrenergic activity is associated with sensitivity of prefrontal areas to changes in the motivational value of an outcome (Schwabe et al., 2012b).

In sum, stress may modulate the engagement of multiple memory systems in a manner that favors "habit" over "cognitive" memory and this appears to be due to an impairment of "cognitive" memory systems, thus allowing "habit" systems to dominate behavior (Schwabe & Wolf, 2013).

8.5 Stress and memory in healthy subjects: implications for PTSD

Stress affects how much we learn and remember. Emotionally arousing events are typically remembered much better than neutral events. Moreover, stress during or shortly after a learning experience may enhance episodic or fear memory, particularly when the content is related to the stressor, whereas memory retrieval appears to be impaired by stress (Roozendaal et al., 2006a; Schwabe et al., 2012a). In addition to these stress effects on quantitative memory performance, stress may also modulate the engagement of multiple memory systems in a manner that facilitates rather rigid, inflexible memory processes at the expense of flexible but cognitively demanding memory processes (Schwabe & Wolf, 2013). These different stress effects on memory may help to explain the apparently opposing memory processes in PTSD patients, who suffer from strong intrusive, trauma-related memories on the one hand, but show general memory impairments or distortions for information that is unrelated to the traumatic event, on the other.

The extreme stress during a traumatic experience leads to a strong release of glucocorticoids and catecholamines. As described earlier, these stress mediators promote the formation of lasting memories, in particular if stress occurs in the context of the learning episode, as is the case during a traumatic experience. Thus, the action of stress hormones during the trauma may result in an "overconsolidation" of the traumatic event, through episodic memory processes and fear conditioning (Elzinga & Bremner, 2003; Pitman, 1989; Pitman et al., 2012), resulting in memories that are easily triggered by a wide range of reminders. In addition, the extreme stress during a traumatic experience may alter the recruitment of multiple memory systems in memory formation. Based on research in healthy individuals (Schwabe, 2013), it can be predicted that the stressful experience favors the engagement of habit or S–R memory that is subserved by the striatum over PFC- or hippocampus-dependent cognitive memory. In addition to the fear conditioning processes, the aberrant engagement of habit

or S–R memory processes may be reflected in the strong emotional responding to single trauma-related cues (e.g., odors or sounds) that is often observed in PTSD patients (Liberzon et al., 1999; Pissiota et al., 2002). Furthermore, the predominance of striatum-based habit memory under stress, at the expense of hippocampal learning, could also account for the disorganization of trauma memory and why it is often difficult for PTSD patients to integrate the traumatic experience into autobiographical memory (Ehlers & Clark, 2000), which is part of hippocampus-dependent memory. Moreover, stress alters the neurocircuitry of fear, which might explain the aberrant fear response in PTSD. Interestingly, the stress-induced alterations in fear memory appear to be more pronounced in women, who also show a higher prevalence of PTSD than men (Kilpatrick et al., 2013). These examples show that the research on stress effects on memory may enhance our understanding of the neurobiological basis of stress-related disorders such as PTSD.

In addition, however, the findings regarding the impact of stress on memory might also open the door to novel treatment approaches for PTSD. For instance, based on evidence indicating that stress and glucocorticoids impair memory retrieval (Buchanan et al., 2006; de Quervain et al., 2000), it has been hypothesized that stress hormones could also reduce trauma memory retrieval (de Quervain & Margraf, 2008).

It has been shown that glucocorticoids may attenuate phobic fear (Mouthaan et al., 2014; Soravia et al., 2006; de Quervain et al., 2011). There is also some evidence that glucocorticoids may indeed reduce memory-related PTSD symptoms, such as intrusive re-experiencing or nightmares (Aerni et al., 2004). Another strategy makes use of the fact that stress or glucocorticoid effects on memory necessitate noradrenergic arousal (McGaugh, 2000; Roozendaal et al., 2006a), suggesting that blockade of noradrenergic activity might prevent the "overconsolidation" of memory. Indeed, there is some evidence that pharmacological blockade of norepinephrine action by the β-adrenergic antagonist propranolol shortly after a potentially traumatic event reduces PTSD symptoms 3 months later (Pitman et al., 2002; Vaiva et al., 2003). However, trauma memory formation can only be interfered with in a short time window after the traumatic event when clinical treatment is often not available, which limits the practical utility of modifications of initial trauma memory formation. An alternative strategy to circumvent this problem could be the modification of traumatic memories after their reactivation, i.e., during reconsolidation. Memory modification during reconsolidation provides an opportunity to change consolidated, seemingly robust, memories (Nader & Hardt, 2009). In line with evidence from healthy subjects showing that propranolol during fear reactivation can erase subsequent fear (Kindt et al., 2009), propranolol during or after trauma reactivation has been shown to reduce subsequent intrusions (Brunet et al., 2008, 2011), a pathological hallmark of PTSD.

These results are certainly preliminary and much more research is needed to determine the potential use of stress hormone manipulations in the treatment of traumatic memories. Only the first steps have been taken on the long road to the development of novel treatment strategies for PTSD and it is unclear whether it will be successful. However, in light of the suffering associated with PTSD, these efforts are worthwhile.

References

Abercrombie HC, Kalin NH, Thurow ME et al. (2003) Cortisol variation in humans affects memory for emotionally laden and neutral information. *Behav Neurosci* 117, 505–516.

Abercrombie HC, Speck NS, Monticelli RM (2006) Endogenous cortisol elevations are related to memory facilitation only in individuals who are emotionally aroused. *Psychoneuroendocrinology* 31, 187–196.

Aerni A, Traber R, Hock C et al. (2004) Low-dose cortisol for symptoms of post-traumatic stress disorder. *Am J Psychiatry* 161, 1488–1490.

American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders: DSM-V*. American Psychiatric Press, Washington, DC.

Andreano JM, Cahill L (2006) Glucocorticoid release and memory consolidation in men and women. *Psychological Sci* 17, 466–470.

Antov MI, Wölk C, Stockhorst U (2013) Differential impact of the first and second wave of a stress response subsequent fear conditioning in healthy men. *Biol Psychol* 94, 456–468.

Balleine BW, O'Doherty JP (2010) Human and rodent homologies in action control: corticostriatal determinants of goal-directed and habitual action. *Neuropsychopharmacology* 35, 48–69.

Beckner VE, Tucker DM, Delville Y et al. (2006) Stress facilitates consolidation of verbal memory for a film but does not affect memory retrieval. *Behavioral Neurosci* 120, 518–527.

Bentz D, Michael T, Wilhelm FH et al. (2013) Influence of stress on fear memory processes in an aversive differential conditioning paradigm in humans *Psychoneuroendocrinology* 38, 1186–1197.

Bohbot VD, Gupta M, Banner H et al. (2011) Caudate nucleus-dependent response strategies in a virtual navigation task are associated with lower basal cortisol and impaired episodic memory. *Neurobiol Learn Mem* 96, 173–180.

Bouton ME (2004) Context and behavioral processes in extinction. *Learn Mem* 11, 485–494.

Brunet A, Orr SP, Tremblay J et al. (2008) Effect of post-retrieval propranolol on psychophysiologic responding during subsequent script-driven traumatic imagery in post-traumatic stress disorder. *J Psychiatr Res* 42, 503–506.

Brunet A, Poundja J, Tremblay J et al. (2011) Trauma reactivation under the influence of propranolol decreases posttraumatic stress symptoms and disorder: 3 open-label trials. *J Clin Psychopharmacol* 31, 547–550.

Buchanan TW, Tranel D, Adolphs R (2006) Impaired memory retrieval correlates with individual differences in cortisol response but not autonomic response. *Learn Mem* 13, 382–387.

Cahill L, Alkire MT (2003) Epinephrine enhancement of human memory consolidation: interaction with arousal at encoding. *Neurobiol Learn Mem* 79, 194–198.

Cahill L, Babinsky R, Markowitsch HJ et al. (1995) The amygdala and emotional memory. *Nature* 377, 295–296.

Cahill L, Gorski L, Le K (2003) Enhanced human memory consolidation with post-learning stress: interaction with the degree of arousal at encoding. *Learn Mem* 10, 270–274.

Cahill L, Haier RJ, Fallon J et al. (1996) Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Proc Natl Acad Sci USA* 93, 8016–8021.

Cahill L, McGaugh JL (1998) Mechanisms of emotional arousal and lasting declarative memory. *Trends Neurosci* 21, 294–299.

Cahill L, Prins B, Weber M et al. (1994) Beta-adrenergic activation and memory for emotional events. *Nature* 371, 702–704.

Christianson SA (1992) *The Handbook of Emotion and Memory*. L. Erlbaum Associates, Hillsdale, NJ.

Coccoz V, Maldonado H, Delorenzi A (2011) The enhancement of reconsolidation with a naturalistic mild stressor improves the expression of a declarative memory in humans. *Neuroscience* 185, 61–72.

Dalla C, Shors TJ (2009) Sex differences in learning processes of classical and operant conditioning. *Physiol Behav* 97, 229–238.

de Kloet ER, Vreugdenhil E, Oitzl MS et al. (1998) Brain corticosteroid receptor balance in health and disease. *Endocrine Rev* 19, 269–301.

de Quervain DJ, Aerni A, Roozendaal B (2007) Preventive effect of ß-adrenoceptor blockade on glucocorticoid-induced memory retrieval deficits. *Am J Psychiatry* 164, 967–969.

de Quervain DJ, Bentz D, Michael T et al. (2011) Glucocorticoids enhance extinction-based psychotherapy. *Proc Natl Acad Sci USA* 108, 6621–6625.

de Quervain DJ, Henke K, Aerni A et al. (2003) Glucocorticoid-induced impairment of declarative memory retrieval is associated with reduced blood flow in the medial temporal lobe. *Eur J Neurosci* 17, 1296–1302.

de Quervain DJ, Margraf J (2008) Glucocorticoids for the treatment of post-traumatic stress disorder and phobias: a novel therapeutic approach. *Eur J of Pharmacol* 583, 365–371.

de Quervain DJ, Roozendaal B, Nitsch RM et al. (2000) Acute cortisone administration impairs retrieval of long-term declarative memory in humans. *Nature Neurosc* 3, 313–314.

Diamond DM, Campbell AM, Park CR et al. (2007) The temporal dynamics model of emotional memory processing: a synthesis on the neurobiological basis of stress-induced amnesia, flashbulb and traumatic memories, and the Yerkes-Dodson law. *Neural Plasticity* 2007, 60803.

Dickerson BC, Eichenbaum H (2010) The episodic memory system: neurocircuitry and disorders. *Neuropsychopharmacology* 35, 86–104.

Dickinson A (1985) Actions and habits: the development of behavioral autonomy. *Phil Trans R Soc Lond B: Biological Sciences* 308, 67–78.

Dudai Y (2006) Reconsolidation: the advantage of being refocused. *Current Opin Neurobiol* 16, 174–178.

Ehlers A, Clark DM (2000) A cognitive model of posttraumatic stress disorder. *Behav Res Therapy* 38, 319–345.

Elzinga BM, Bakker A, Bremner JD (2005) Stress-induced cortisol elevations are associated with impaired delayed, but not immediate recall. *Psychiatry Res* 134, 211–223.

Elzinga BM, Bremner JD (2003) Are the neural substrates of memory the final common pathway in PTSD? *J Affect Disord* 70, 1–17.

Etkin A, Wager TD (2007) Functional neuroimaging of anxiety: A meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. *Am J Psychiatry* 164, 1476–1488.

Foa EB, Kozak MJ (1986) Emotional processing of fear: exposure to corrective information. *Psychol Bull* 99, 20–35.

Foerde K, Knowlton BJ, Poldrack RA (2006) Modulation of competing memory systems by distraction. *Proc Natl Acad Sci USA* 103, 11778–11783.

Graham BM, Milad MR (2011) The study of fear extinction: implications for anxiety disorders. *Am J Psychiatry* 168, 1255–1265.

Henckens MJ, van Wingen GA, Joëls M et al. (2012) Corticosteroid induced decoupling of the amygdala in men. *Cerebral Cortex* 22, 2336–2345.

Henckens MJAG, Hermans EJ, Pu Z et al. (2009) Stressed memories: How acute stress affects memory formation in humans. *J Neurosci* 29, 10 111–10 119.

Henckens MJAG, van Wingen GA, Joels M et al. (2010) Time-dependent effects of corticosteroids on human amygdala processing. *J Neurosci* 30, 12 725–12 732.

Holmes A, Quirk GJ (2010) Pharmacological facilitation of fear extinction and the search for adjunct treatments for anxiety disorders – the case of yohimbine. *Trends Pharmacol Sci* 31, 2–7.

Hupbach A, Fieman R (2012) Moderate stress enhances immediate and delayed retrieval of educationally relevant material in healthy young men. *Behav Neurosci* 126:819–825.

Jackson ED, Payne JD, Nadel L et al. (2006) Stress differentially modulates fear conditioning in healthy men and women. *Biol Psychiatry* 59, 516–522.

Joëls M, Baram TZ (2009) The neuro-symphony of stress. *Nat Rev Neurosci* 10, 459–466.

Joëls M, Fernandez G, Roozendaal B (2011) Stress and emotional memory: a matter of timing. *Trends Cogn Sci* 15, 56–65.

Joëls M, Pu Z, Wiegert O et al. (2006) Learning under stress: how does it work? *Trends Cogn Sci* 10, 152–158.

Kilpatrick DG, Resnick HS, Milanak ME et al. (2013) National estimates of exposure to traumatic events and PTSD prevalence using DSM-IV and DSM-5 criteria. *J Traum Stress* 26, 537–547.

Kim J, Lee H, Han J et al. (2001) Amygdala is critical for stress-induced modulation of hippocampal long-term potentiation and learning. *J Neurosci* 21, 5222–5228.

Kindt M, Soeter M, Vervliet B (2009) Beyond extinction: erasing human fear responses and preventing the return of fear. *Nat Neurosci* 12, 256–258.

Kirschbaum C, Wolf OT, May M et al. (1996) Stress- and treatment-induced elevations of cortisol levels associated with impaired declarative memory in healthy adults. *Life Sci* 58, 1475–1483.

Knowlton BJ, Mangels JA, Squire LR (1996) A neostriatal habit learning system in humans. *Science* 273, 1399–1402.

Kuhlmann S, Piel M, Wolf OT (2005) Impaired memory retrieval after psychosocial stress in healthy young men. *J Neurosci* 25, 2977–2982.

Kukolja J, Thiel CM, Wolf OT et al. (2008) Increased cortisol levels in cognitively challenging situations are beneficial in young but not older subjects. *Psychopharmacology* 201, 293–304.

LeDoux JE (2000) Emotion circuits in the brain. *Ann Rev Neurosci* 23, 155–184.

Liberzon I, Taylor SF, Amdur R et al. (1999) Brain activation in PTSD in response to trauma-related stimuli. *Biol Psychiatry* 45, 817–826.

Lovallo WR, Robinson JL, Glahn DC et al. (2010) Acute effects of hydrocortisone on the human brain: an fMRI study. *Psychoneuroendocrinology* 35, 15–20.

Lupien SJ, Gaudreau S, Tchiteya BM et al. (1997) Stress-induced declarative memory impairment in healthy elderly subjects: relationship to cortisol reactivity. *J Clin Endocrinol Metab* 82, 2070–2075.

Maren S, Phan KL, Liberzon I (2013) The contextual brain: implications for fear conditioning, extinction, and psychopathology. *Nature Reviews Neuroscience* 14, 417–428.

McDonald RJ, White NM (1993) A triple dissociation of memory systems: hippocampus, amygdala, and dorsal striatum. *Behav Neurosci* 107, 3–22.

McEwen BS, de Kloet ER, Rostene W (1986) Adrenal steroid receptors and actions in the nervous system. *Physiol Rev* 66, 1121–1188.

McGaugh JL (2000) Memory-a century of consolidation. *Science* 287, 248–251.

Mechias M-L, Etkin A, Kalisch R (2010) A meta-analysis of instructed fear studies: Implications for conscious appraisal of threat. *NeuroImage* 49, 1760–1768.

Merz CJ, Hermann A, Stark R et al. (2014) Cortisol modifies extinction learning of recently acquired fear in men. *Soc Cogn Affect Neurosci* 9, 1426–1434.

Merz CJ, Tabbert K, Schweckendiek J et al. (2010) Investigating the impact of sex and cortisol on implicit fear conditioning with fMRI. *Psychoneuroendocrinology* 35, 33–46.

Merz CJ, Tabbert K, Schweckendiek J et al. (2012) Oral contraceptive usage alters the effects of cortisol on implicit fear learning. *Hormon Behav* 62, 531–538.

Merz CJ, Wolf OT, Schweckendiek J et al. (2013) Stress differentially affects fear conditioning in men and women. *Psychoneuroendocrinology* 11, 2529–2541.

Mineka S, Oehlberg K (2008) The relevance of recent developments in classical conditioning to understanding the etiology and maintenance of anxiety disorders. *Acta Psychol* 127, 567–580.

Mineka S, Zinbarg R (2006) A contemporary learning theory perspective on the etiology of anxiety disorders - It's not what you thought it was. *Am Psychol* 61, 10–26.

Mouthaan J, Sijbrandij M, Luitse JS et al. (2014) The role of acute cortisol and DHEAS in predicting acute and chronic PTSD symptoms. *Psychoneuroendocrinology* 45, 179–186.

Mueller D, Cahill SP (2010) Neuroadrenergic modulation of extinction learning and exposure therapy. *Behav Brain Res* 208, 1–11.

Nader K, Hardt O (2009) A single standard for memory: the case for reconsolidation. *Nat Rev Neurosci* 10, 224–234.

Nater UM, Moor C, Okere U et al. (2007) Performance on a declarative memory task is better in high than low cortisol responders to psychosocial stress. *Psychoneuroendocrinology* 32, 758–763.

Oei NY, Elzinga BM, Wolf OT et al. (2007) Glucocorticoids decrease hippocampal and prefrontal activation during declarative memory retrieval in young men. *Brain Imaging Behav* 1, 31–41.

Oei NY, Veer IM, Wolf OT et al. (2012) Stress shifts brain activation towards ventral 'affective' areas during emotional distraction. *Soc Cogn Affect Neurosci* 7, 403–412.

Packard M, Hirsh R, White NM (1989) Differantial effects of fornix and caudate nucleus lesions on two radial maze tasks: evidence for multiple memory systems. *J Neurosci* 9, 1465–1472.

Packard M, Wingard JC (2004) Amygdala and "emotional" modulation of the relative use of multiple memory systems. *Neurobiol Learn Mem* 82, 243–252.

Payne JD, Jackson ED, Ryan L et al. (2006) The impact of stress on neutral and emotional aspects of episodic memory. *Memory* 14, 1–16.

Pissiota A, Frans O, Fernandez M et al. (2002) Neurofunctional correlates of posttraumatic stress disorder: a PET symptom provocation study. *Eur Archiv Psychiatr Clin Neurosci* 252, 68–75.

Pitman RK (1989) Post-traumatic stress disorder, hormones, and memory. *Biol Psychiatry* 26, 221–223.

Pitman RK, Rasmusson AM, Koenen KC et al. (2012) Biological studies of post-traumatic stress disorder. *Nat Reviews Neuroscience* 13, 769–787.

Pitman RK, Sanders KM, Zusman RM et al. (2002) Pilot study of secondary prevention of post-traumatic stress disorder with propranolol. *Biol Psychiatry* 51, 189–142.

Powers MB, Smits JAJ, Otto MW et al. (2009) Facilitation of fear extinction in phobic participants with a novel cognitive enhancer: A randomized placebo controlled trial of yohimbine augmentation. *J Anxiety Disord* 23, 350–356.

Pruessner JC, Dedovic K, Khalili-Mahani N et al. (2008) Deactivation of the limbic system during acute psychosocial stress: evidence from positron emission tomography and functional magnetic resonance imaging studies. *Biol Psychiatry* 63, 234–240.

Roozendaal B, Okuda S, De Quervain DJ et al. (2006a) Glucocorticoids interact with emotion-induced noradrenergic activation in influencing different memory functions. *Neuroscience* 138, 901–910.

Roozendaal B, Okuda S, Van der Zee EA et al. (2006b) Glucocorticoid enhancement of memory requires arousal-induced noradrenergic activation in the basolateral amygdala. *Proc Natl Acad Sci USA* 103, 6741–6746.

Schilling TM, Kölsch M, Larra MF et al. (2013) For whom the bell (curve) tolls: cortisol rapidly affects memory retrieval by an inverted u-shaped dose-response relationship. *Psychoneuroendocrinolgy* 38, 1565–1572.

Schmidt PI, Rosga K, Schatto C et al. (2014) Stress reduces the incorporation of misinformation into an established memory. *Learn Mem* 21, 744–747.

Schönfeld P, Ackermann K, Schwabe L (2014) Remembering under stress: different roles of autonomic arousal and glucocorticoids in memory retrieval. *Psychoneuroendocrinology* 39, 249–256.

Schwabe L (2013) Stress and the engagement of multiple memory systems: integration of animal and human studies. *Hippocampus* 23, 1035–1043.

Schwabe L, Bohringer A, Chatterjee M et al. (2008) Effects of pre-learning stress on memory for neutral, positive and negative words: Different roles of cortisol and autonomic arousal. *Neurobiol Learn Mem* 90, 44–53.

Schwabe L, Bohringer A, Wolf OT (2009a) Stress disrupts context-dependent memory. *Learn Mem* 16, 110–113.

Schwabe L, Höffken O, Tegenthoff M et al. (2011) Preventing the stress-induced shift from goal-directed to habit action with a beta-adrenergic antagonist. *J Neurosci* 31, 17317–17325.

Schwabe L, Höffken O, Tegenthoff M et al. (2013a) Opposite effects of noradrenergic arousal on amygdala processing of fearful faces in men and women. *Neuroimage* 73, 1–7.

Schwabe L, Joëls M, Roozendaal B et al. (2012a) Stress effects on memory: an update and integration. *Neurosci Biobehav Rev* 36, 1740–1749.

Schwabe L, Oitzl MS, Philippsen C et al. (2007) Stress modulates the use of spatial and stimulus-response learning strategies in humans. *Lear Mem* 14, 109–116.

Schwabe L, Oitzl MS, Richter S et al. (2009c) Modulation of spatial and stimulus-response learning strategies by exogenous cortisol in healthy young women. *Psychoneuroendocrinology* 34, 358–366.

Schwabe L, Römer S, Richter S et al. (2009b) Stress effects on declarative memory retrieval are blocked by a β-adrenoceptor antagonist in humans. *Psychoneuroendocrinology* 34, 446–454.

Schwabe L, Tegenthoff M, Höffken O et al. (2010a) Concurrent glucocorticoid and noradrenergic activity shifts instrumental behavior from goal-directed to habitual control. *J Neurosci* 30, 8190–8196.

Schwabe L, Tegenthoff M, Höffken O et al. (2012b) Simultaneous glucocorticoid and noradrenergic activity disrupts the neural basis of goal-directed action in the human brain. *J Neurosci* 32, 10146–10155.

Schwabe L, Tegenthoff M, Höffken O et al. (2013b) Mineralocorticoid receptor blockade prevents stress-induced modulation of multiple memory systems in the human brain. *Biol Psychiatry* 74, 801–808.

Schwabe L, Wolf OT (2009a) The context counts: Congruent learning and testing environments prevent memory retrieval impairment following stress. *Cogn Affect, and Behav Neurosci* 9, 229–236.

Schwabe L, Wolf OT (2009b) Stress prompts habit behavior in humans. *J Neurosci* 29, 7191–7198.

Schwabe L, Wolf OT (2010a) Learning under stress impairs memory formation. *Neurobiol Learn Mem* 93, 183–188.

Schwabe L, Wolf OT (2010b) Socially evaluated cold pressor stress after instrumental learning favors habits over goal-directed action. *Psychoneuroendocrinology* 35, 977–986.

Schwabe L, Wolf OT (2010c) Stress impairs the reconsolidation of autobiographical memories. *Neurobiol Learn Mem* 94, 153–157.

Schwabe L, Wolf OT (2012) Stress modulates the engagement of multiple memory systems in classification learning. *J Neurosci* 32, 11042–11049.

Schwabe L, Wolf OT (2013) Stress and multiple memory systems: from 'thinking' to 'doing'. *Trends Cogn Sci* 17, 60–68.

Schwabe L, Wolf OT (2014) Timing matters: temporal dynamics of stress effects on memory retrieval. *Cogn Affect? Behav Neurosci* 14, 1041–1048.

Schwabe L, Wolf OT, Oitzl MS (2010b) Memory formation under stress: Quantity and quality. *Neurosci Biobehav Rev* 34, 584–591.

Sehlmeyer C, Schöning S, Zwitserlood P et al. (2009) Human fear conditioning and extinction in neuroimaging: A systematic review. *PLoS ONE* 4, e5865.

Shors TJ (2004) Learning during stressful times. *Learn Mem* 11, 137–144.

Smeets T, Giesbrecht T, Jelicic M et al. (2007) Context-dependent enhancement of declarative memory performance following acute psychosocial stress. *Biol Psychol* 76, 116.123.

Smeets T, Wolf OT, Giesbrecht T et al. (2009) Stress selectively and lastingly promotes learning of context-related high arousing information. *Psychoneuroendocrinolgy* 34, 1152–1161.

Soeter M, Kindt M (2010) Dissociating response systems: Erasing fear from memory. *Neurobiol Learn Mem* 96, 30–41.

Soeter M, Kindt M (2011) Noradrenergic enhancement of associative fear memory in humans. *Neurobiol Learn Mem* 96, 263–271.

Soeter M, Kindt M (2012a) Erasing fear for an imagined threat event. *Psychoneuroendocrinology* 37, 1769–1779.

Soeter M, Kindt M (2012b) Stimulation of the noradrenergic system during memory formation impairs extinction learning but not the disruption of reconsolidation. *Neuropsychopharmacology* 37, 1204–1215.

Soravia LM, Heinrichs M, Aerni A et al. (2006) Glucocorticoids reduce phobic fear in humans. *Proc Natl Acad Sci USA* 103, 5585–5590.

Southwick SM, Horner B, Morgan CA et al. (2002) Relationship of enhanced norepinephrine activity during memory consolidation to enhanced long-term memory in humans. *Am J Psychiatr* 159, 1420–1422.

Squire LR (2004) Memory systems of the brain: a brief history and current perspective. *Neurobiol Learn Mem* 82, 171–177.

Stark R, Wolf OT, Tabbert K et al. (2006) Influence of the stress hormone cortisol on fear conditioning in humans: Evidence for sex differences in the response of the prefrontal cortex. *NeuroImage* 32, 1290–1298.

Strange BA, Dolan RJ (2004) β-adrenergic modulation of emotional memory-evoked human amygdala and hippocampus responses. *Proc Natl Acad Sci USA* 101, 11454–11458.

Tabbert K, Merz CJ, Klucken T et al. (2010) Cortisol enhances neural differentiation during fear acquisition and extinction in contingency aware young women. *Neurobiol Learn Mem* 94, 392–401.

Tollenaar MS, Elzinga BM, Spinhoven P et al. (2008) Long-term outcomes of memory retrieval under stress. *Behavioral Neurosci* 122, 697–703.

Tollenaar MS, Elzinga BM, Spinhoven P et al. (2009) Immediate and prolonged effects of cortisol, but not propranolol, on memory retrieval in healthy young men. *Neurobiol Learn Mem* 91, 23–31.

Tops M, van der Pompe GA, Baas D et al. (2003) Acute cortisol effects on immediate free recall and recognition of nouns depend on stimulus-valence. *Psychophysiology* 40, 167–173.

Tulving E, Markowitsch HJ (1998) Episodic and declarative memory: role of the hippocampus. *Hippocampus* 8, 198–204.

Vaiva G, Ducroca F, Jezequel K et al. (2003) Immediate treatment with propranolol decreases posttraumatic stress disorder two months after trauma. *Biol Psychiatry* 54, 947–949.

Van Ast VA, Vervliet B, Kindt M (2012) Contextual control over expression of fear is affected by cortisol. *Frontiers Behav Neurosci* 6, 67.

Van Stegeren AH, Roozendaal B, Kindt M et al. (2010) Interacting noradrenergic and corticosteroid systems shift human brain activation patterns during encoding. *Neurobiol Learn Mem* 93, 56–65.

Vervliet B, Craske MG, Hermanns D (2013) Fear extinction and relapse: state of the art. *Ann Rev Clin Psychol* 9, 215–248.

Williams CL, Clayton EC (2001) Contribution of brainstem structures in modulating memory storage processes. In: Gold PE, Greenough WT (eds) *Memory Consolidation: Essays in Honor of James L McGaugh*. American Psychological Association, Washington DC, pp. 141–163.

Winograd E, Neisser U (1992) *Affect and Accuracy in Recall: Studies in "Flashbulb Memories"*. Cambridge University Press, New York.

Zhao LY, Zhang XL, Shi J et al. (2009) Psychosocial stress after reactivation of drug-related memory impairs later recall in abstinent heroin addicts. *Psychopharmacology* 203, 599–608.

Zoladz PR, Clark B, Warnecke A et al. (2011) Pre-learning stress differentially affects long-term memory for emotional words, depending on temporal proximity to the learning experience. *Physiol Behav* 103, 467–476.

Zorawski M, Banding NQ, Kuhn CM et al. (2006) Effects of stress and sex on acquisition and consolidation of human fear conditioning. *Learn Mem* 13, 441–450.

Zorawski M, Cook CA, Kuhn CM et al. (2005) Sex, stress and fear: Individual differences in conditioned learning. *Cogn Affect Behav Neurosci* 5, 191–201.