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The influence of stress hormones on emotional memory: Relevance for psychopathology

Oliver T. Wolf *

Department of Psychology, University of Bielefeld, Postfach 10 01 31, D-33501 Bielefeld, Germany

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Abstract

Substantial progress within recent years has led to a better understanding of the impact of stress on emotional memory. These effects are of relevance for understanding and treating psychopathology. The present selective review describes how emotional memory is modulated through stress hormones. Acute as well as chronic effects are discussed and information from rodent models is compared to human experimental studies and clinical observations. Finally, the relevance of these findings for emotional memory disturbances in psychiatric disorders is exemplified by discussions on neuroendocrine alterations in depression, post traumatic stress disorder and phobias.
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1. Overview

Most psychiatric disorders are characterized by emotional memory or emotional learning disturbances. Brain regions involved in these processes are the two medial temporal lobe structures, amygdala and hippocampus, and several brain regions within the prefrontal cortex (PFC; LaBar & Cabeza, 2006). These learning and memory alterations are not just secondary symptoms but are key components of these disorders. For example, PTSD patients experience vivid flashbacks in which they relive the trauma (Nemeroff et al., 2006; Rauch, Shin, & Phelps, 2006; see also Holmes & Bourne, 2008). Patients with major depression in contrast have a memory bias with a preferred storage and retrieval of negative information (Leppanen, 2006). Finally phobic patients display an exaggerated conditioned fear response which they cannot control cognitively (Centonze, Siracusano, Calabresi, & Bernardi,

2005). The examples illustrate that emotional memory dysfunctions appears to underlie several psychiatric disorders.

In this context, actions of neuroendocrine stress mediators are of relevance. The goal of the present review is thus to highlight the influence of stress hormones on emotional memory and emotional learning. Starting from a basic science perspective, experimental work on animals and humans will be reviewed. Afterwards potential clinical implications are outlined using depression, PTSD and phobias as examples. Two systems will be considered: The hormones of the sympathetic nervous system (SNS; adrenalin and noradrenalin) and the hormones of the hypothalamus pituitary adrenal (HPA) axis (CRH, ACTH, and cortisol/corticosterone). These stress responsive systems interact at multiple levels in the periphery and the brain. Together they influence emotional memory in a complex manner.

2. The neuroendocrinology of stress

Most often stress is used to refer to a state in which the individual perceives a real or anticipated challenge to homeostasis, which requires some sort of adaptive response

* Tel.: +49 (0)521 106 4433; fax: +49 (0)521 106 6422.
E-mail address: oliver.wolf@uni-bielefeld.de

(De Kloet, Joels, & Holsboer, 2005; McEwen, 1998). A stressor is the specific event which induces the stress. It can be physical (e.g. thirst, pain) or psychological (e.g. fear or work overload) in nature. A stressor can be acute (an upcoming oral exam) or chronic (constant work overload, inadequate housing conditions, etc.). The subjective evaluation of the stressor and the evaluation of available coping resources is important in determining the individual impact of a stressor (Lazarus, 1993; Mason, 1968a; Ursin & Eriksen, 2004).

When a stressor is encountered the organism responds with secretion of neuroendocrine mediators. These hormones interact with affective and cognitive processes in order to facilitate adaptation (De Kloet et al., 2005; Herbert et al., 2006; McEwen, 1998). The process of maintaining stability through change has been termed allostasis, which is in the short run adaptive and beneficial, but can in the long run oppose a health burden on target systems in periphery and brain (McEwen, 2000, 2003).

The first rapid response is orchestrated by the SNS. Initiated by the hypothalamus, neurons in the spinal cord signal to the adrenal medulla. This results in a rapid release of adrenalin and noradrenalin. These hormones lead to physical alterations, typical of 'feeling stressed' (e.g. increases in heart rate, breathing frequency and sweat production; De Kloet et al., 2005; Mason, 1968b). Adrenalin and noradrenalin cannot easily pass the blood brain barrier, but can stimulate the vagus nerve, which causes an increased noradrenergic tone in the brain by its action on regions in the brain stem (locus coeruleus and nucleus of the solitary tract). These regions stimulate several brain areas most importantly the amygdala (Roozendaal, Okuda, de Quervain, & McGaugh, 2006).

A second slower response is orchestrated by the HPA axis. Here corticotrophin releasing hormone (CRH) together with vasopressin is released from the paraventricular nucleus of the hypothalamus into the portal blood system. In addition to its neuroendocrine function CRH also acts outside the hypothalamus as a neurotransmitter in the CNS and is a regulator of the anxiety system (Dunn & Berridge, 1990; Mitchell, 1998). On reaching the pituitary, CRH stimulates adrenocorticotrophin (ACTH) release into the peripheral blood stream. ACTH initiates the secretion of glucocorticoids (GCs; corticosterone in most laboratory animals, cortisol in humans) from the adrenal cortex (Charney, 2004; De Kloet et al., 2005). Increasing cortisol levels cause a negative feedback by their action at several levels of the HPA axis (pituitary and hypothalamus) but also by influencing the hippocampus, the amygdala and the prefrontal cortex (PFC; De Kloet, Vreugdenhil, Oitzl, & Joels, 1998; Gold, Drevets, Charney, & Drevets, 2002; Jacobson & Sapolsky, 1991). In contrast to the catecholamines, naturally occurring GCs (like all other steroid hormones) can pass the blood brain barrier. In the brain GCs can act via two different intracellular receptors (sometimes referred to as type I or mineralocorticoid (MR) and type II or glucocorticoid (GR) receptor), which differ in their distribution and affinity (De Kloet et al., 1998; Herbert et al., 2006; Joels, 2001). Moreover, GCs can exert rapid nongenomic effects, which sometimes also depend on the MR receptor (De Kloet et al., 2005; Karst et al., 2005). GCs can influence neuronal excitability, neuronal plasticity, dendritic remodeling and neurogenesis (De Kloet et al., 2005; Herbert et al., 2006; Joels, 2001; McEwen, 2003). Besides, multiple neurotransmitter systems like the cholinergic, noradrenergic, serotonergic and dopaminergic system are influenced by GCs (Charney, 2004; De Kloet et al., 2005; Herbert et al., 2006; Joels, 2001; McEwen, 2003). In addition, the effects of GCs on the CNS are modulated at multiple additional levels (see Karssen et al., 2001; Seckl & Walker, 2004). In sum, GCs can have rapid as well as long-lasting effects on the function and structure of the brain.

3. Emotional memory

Emotional information is processed differently than neutral information. Examples can be found at the level of stimulus perception but also in the domains of attention, working memory or long-term memory (Dolan, 2002; LaBar & Cabeza, 2006; Ohman, 2005; Phelps, 2004). The evolution of such a privileged processing assures that information most relevant to survival is given high priority. This is adaptive under normal circumstances but becomes maladaptive in the case of psychiatric disorders (Dolan, 2002; LaBar & Cabeza, 2006; Ohman, 2005; Phelps, 2004). In fact, several psychiatric disorders are characterized by alterations in emotional memory or emotional learning.

This review will put its focus on episodic memory, which is a system concerned with the explicit and voluntary storage and retrieval of specific events (LaBar & Cabeza, 2006). In addition, working (short-term) memory and associative emotional learning exemplified by fear conditioning will be touched upon.

3.1. Episodic memory

A long-lasting body of research has demonstrated that emotional material is remembered better than neutral material (LaBar & Cabeza, 2006). Some researchers suggest that the emotional arousal (ranging from high to low) is more important than the emotional valence (ranging from positive to negative). Arousal appears to be closer linked to the activity of the amygdala, which is especially important for emotional processing (Kensinger, 2004; LaBar & Cabeza, 2006). The analysis of the valence of a specific stimulus appears to be processed predominantly in prefrontal regions of the brain (Kensinger, 2004).

In human experimental studies subjects remember emotional pictures, words or stories better than neutral ones. The temporal development of this phenomenon is, however, still debated. The initial pioneering studies from

Kleinsmith and Kaplan suggested that retrieval of emotional material is initially poorer in immediate recall tests but then 'builds up' over time so that delayed retrieval is superior (Kleinsmith & Kaplan, 1963). Other researchers have reported that emotional and neutral material is retrieved equally well in immediate recall tests while the advantage of emotional material becomes only obvious with longer delays (days to weeks, Quevedo et al., 2003). In contrast, it has also been reported that memory for emotional material is enhanced for immediate and delayed retrieval tests (Kuhlmann & Wolf, 2006b; Payne et al., 2006). Specifics of the learning material, the learning instructions and the number of retrieval tests might be able to explain some of the variance (Christianson, 1992; LaBar & Cabeza, 2006).

Animal studies have indicated that the amygdala is important for the emotional facilitation of memory. Noradrenergic activation of the basolateral nucleus (BLA) is crucial for the modulation of memory traces, which are stored in other brain areas (e.g. the hippocampus (McGaugh, Cahill, & Roozendaal, 1996)). Thus the amygdala provides a memory trace with an 'emotional stamp'. Studies with patients have illustrated that the amygdala is crucial for emotional memory in humans (Cahill, Babinsky, Markowitsch, & McGaugh, 1995) and here especially for central aspects (the gist) (Adolphs, Tranel, & Buchanan, 2005). Also pharmacological studies revealed that blockade of the beta-adrenergic system impairs emotional memory (Cahill, Prins, Weber, & McGaugh, 1994). This occurs in the absence of effects on the perceived subjective emotionality of the learning material. Similarly stimulation of the central noradrenergic system by pharmacological agents or by vagus nerve stimulation leads to enhanced emotional memory (Clark, Naritoku, Smith, Browning, & Jensen, 1999; Ghacibeh, Shenker, Shenal, Uthman, & Heilman, 2006; Southwick et al., 2002). Imaging studies using positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) showed that amygdala activity is associated with emotional memory facilitation (Cahill et al., 1996; Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000). Moreover, beta blockade led to a blunted amygdala response to emotional stimuli, which was associated with poorer memory of this material (Strange & Dolan, 2004; van Stegeren et al., 2005). Thus there is solid empirical evidence that noradrenergic activation in the amygdala leads to enhanced memory consolidation via its interaction with the hippocampus (LaBar & Cabeza, 2006; Phelps, 2004).

In this context sex differences have been observed. In imaging studies activity of the right amygdala was associated with emotional memory consolidation in men, while in women such a correlation was observed with the left amygdala (Cahill, 2003, 2006). Also sex specific effects were reported for the impact of beta blockade on memory (Cahill & van Stegeren, 2003). These sex specific effects might be caused by a sex specific cerebral lateralization for emotional memory.

In contrast to the well understood chain of events underlying emotional memory consolidation, retrieval is less understood. A role of the amygdala in emotional episodic or autobiographical memory retrieval has been suggested (Buchanan, Tranel, & Adolphs, 2005; Dolcos, LaBar, & Cabeza, 2005), but this issue remains controversial (LaBar & Cabeza, 2006; Phelps, 2004). Also the role of adrenergic activation in this context is debated (Murchison et al., 2004; Przybyslawski, Roullet, & Sara, 1999; Roozendaal, Hahn, Nathan, de Quervain, & McGaugh, 2004).

4. Acute stress

After having established the neuroanatomy of declarative emotional memory and the critical role of the adrenergic system, the question arises as to what effects the hormones of the HPA axis, namely corticosterone and cortisol exert. First the effects of acute stress will be summarized. The impact of chronic stress will be discussed later.

4.1. Acute stress and episodic memory in animals and humans

Decades of animal research have characterized the beneficial effects of GCs on memory consolidation (De Kloet, Oitzl, & Joels, 1999; Roozendaal, 2000). Increasing GC levels during learning lead to enhanced memory consolidation (e.g. Sandi, Loscertales, & Guaza, 1997). This results in better retrieval days or weeks later. Roozendaal and McGaugh have dissected the underlying mechanisms. GCs interact with noradrenergic activation in the BLA in modulating memory consolidation in other brain areas (Roozendaal, Okuda, et al., 2006). The BLA is activated by noradrenergic input from the brain stem, which reflects in part increased activity of the vagus nerve. For the effects of GCs, noradrenergic activation in the BLA is a prerequisite. BLA lesions as well as beta blockade prevent the effects of GCs agonists on memory consolidation (Roozendaal, Okuda, et al., 2006).

In humans beneficial effects of GCs or stress exposure on (emotional) memory consolidation were found in several studies, even though the findings are not consistent. It was observed that pre-learning GC treatment (Buchanan & Lovallo, 2001; Kuhlmann & Wolf, 2006b) or immediate post learning stress (Beckner, Tucker, Delville, & Mohr, 2006; Cahill, Gorski, & Le, 2003) enhanced memory consolidation resulting in enhanced retrieval days to weeks later. In some studies this effect was specific to arousing material (Buchanan & Lovallo, 2001; Cahill et al., 2003; Kuhlmann & Wolf, 2006b), while in other studies effects were more global (Abercrombie, Kalin, Thurow, Rosenkranz, & Davidson, 2003; Beckner et al., 2006; Maheu, Joober, Beaulieu, & Lupien, 2004). However, there are also studies which failed to find beneficial effects on consolidation (Rimmele, Domes, Mathiak, & Hautzinger, 2003). In line with the experimental studies outlined above, basal cortisol levels were associated with enhanced long term

but not short-term memory for emotional faces (Putman, Van Honk, Kessels, Mulder, & Koppeschaar, 2004). Studies observing a specific effect of GCs on the consolidation of emotional material support the hypothesis that arousal (leading to noradrenergic activation in the BLA) is a prerequisite for the effects of GCs on memory consolidation. This model is in line with a stress study reporting that cortisol elevations were only associated with enhanced memory consolidation in those subjects which reported to be emotionally aroused (Abercrombie, Speck, & Monticelli, 2005). It is also in line with a recent functional imaging study which found that subjects with higher endogenous cortisol levels had significantly stronger amygdala responses to emotional slides, when compared to subjects with lower cortisol levels (van Stegeren et al., 2006 see also van Stegeren, 2008). Thus, today, we have corroborative evidence from animal and human studies that glucocorticoids lead to enhanced memory consolidation. This effect appears to be especially pronounced for arousing material (see Table 1). The neuroanatomical underpinning of this phenomenon is an interaction between the BLA and the hippocampus.

Whereas GCs exert positive effects on consolidation, the effects on memory retrieval are negative. de Quervain and colleagues were the first to report that in rodents stress or GC treatment impaired memory retrieval (de Quervain, Roozendaal, & McGaugh, 1998). Rats were trained on the first day and retrieval was tested the next day. Foot shock stress prior to retrieval testing impaired it. Additional experiments demonstrated that corticosterone was the mediator of these effects (de Quervain et al., 1998). These findings have been replicated by others (Diamond et al., 2006). Follow-up studies by Roozendaal et al. reported that similar to the effects on consolidation, the effects on retrieval require noradrenergic activation in the

BLA (and the hippocampus) and can be prevented by BLA lesions or by beta blocker injections (Roozendaal, de Quervain, Schelling, & McGaugh, 2004; Roozendaal, Griffith, Buranday, de Quervain, & McGaugh, 2003; Roozendaal, Hahn, et al., 2004).

Studies on humans have replicated the GC-induced retrieval deficits. Findings appear to be similar for studies using word lists, paired associates or autobiographical cues as test material (Buss, Wolf, Witt, & Hellhammer, 2004; de Quervain, Roozendaal, Nitsch, McGaugh, & Hock, 2000; Kuhlmann, Kirschbaum, & Wolf, 2005; Kuhlmann & Wolf, 2005; Wolf et al., 2001). Moreover, psychosocial stress-induced cortisol elevations also lead to poorer memory retrieval (Buchanan, Tranel, & Adolphs, 2006; Domes, Heinrichs, Rimmele, Reichwald, & Hautzinger, 2004; Kuhlmann, Piel, & Wolf, 2005). Interestingly the negative effects of GCs on memory retrieval are also more prominent for emotional arousing material (Buchanan et al., 2006; Kuhlmann, Kirschbaum, et al., 2005; Kuhlmann, Piel, et al., 2005). Again it seems that arousal is more important than valence (Buchanan et al., 2006; Kuhlmann, Piel, et al., 2005). The specific effects on arousing material suggest a critical role of noradrenergic activation in the amygdala for the occurrence of the GC effects in humans. This has recently been demonstrated with pharmacological manipulations (beta blockade; de Quervain, Aerni, & Roozendaal, 2007). Propranolol treatment blocked the negative effects of cortisone on the retrieval of arousing words. In line with this pharmacological study is another experiment observing that a relaxed non-arousing retrieval test situation abolishes the effects of GCs on memory retrieval (Kuhlmann & Wolf, 2006a). Moreover, the study of Tollenaar, Elzinga, Spinhoven, and Everaerd, 2008, found that the stress-induced cortisal increase is associated with impaired memory retrieval tested during stress exposure.

Table 1
Summary of acute GC effects on different memory forms in rodents and humans

Memory type	Rodents	Humans
Declarative long-term memory acquisition and immediate recall	No strong effects reported	Impairing effects *Effects stronger for neutral material, effects stronger in the morning (higher basal cortisol levels)*
Declarative long-term memory consolidation	Enhancing effects *Effects depend on test-induced arousal*	Enhancing effects *Effects stronger for arousing material independent of valence*
Declarative long-term memory retrieval	Impairing effects	Impairing effects *Effects stronger for arousing material independent of valence*
Working (short-term) memory	Impairing effects	Impairing effects *Influence of emotionality of the learning material not yet investigated*
Fear conditioning acquisition	Enhancing, impairing or absent effects	Enhancing as well as impairing effects *Discrepancies are in part due to sex differences*
Fear conditioning consolidation	Enhancing effects *Controversy about the specificity of the effects for contextual fear conditioning*	Possibly enhancing effects, not sufficiently investigated
Fear conditioning extinction	Enhancing effects	Not sufficiently investigated

Modulatory influences are described in *italics*; please refer to the text of each memory domain for selected references.

Twenty minutes after termination of the stressor no such association was observed. This finding thus also suggests that arousal is necessary for cortisol-related memory impairments to occur.

Till now, the localization of the GC effects on memory retrieval with functional imaging techniques has received little attention. The first study using PET observed a reduced blood flow in the medial temporal lobe after cortisone treatment which was associated with poorer retrieval performance (de Quervain et al., 2003). An event related fMRI study reported reduced activation in the hippocampus and the superior frontal gyrus during successful memory retrieval when subjects had received cortisol (Oei et al., 2007). Thus both imaging studies suggest that the effects of cortisol on retrieval are at least in part mediated by the medial temporal lobe.

All in all, cortisol enhances emotional memory consolidation but impairs emotional memory retrieval (see Table 1). Animal and human studies indicate that emotional arousal is an important prerequisite for the occurrence of these effects. Similar to the effects on consolidation, the BLA and the hippocampus are the neuroanatomical sites for the negative effects on retrieval. Thus, although a stressful learning episode is consolidated well, the retrieval of previously learned material is less efficient under stress.

A number of previous studies have investigated the effects of stress or GC treatment on immediate or only slightly delayed (10–30 min) retrieval. In these studies phase specific effects cannot be established, since all memory phases (encoding, consolidation and retrieval) are influenced simultaneously. Findings with this approach have been inconsistent. Here the effects of stress or GCs appear to be influenced by the circadian cortisol rhythm with studies in the morning, when the endogenous cortisol levels are high, being more likely of finding negative effects (Het, Ramlow, & Wolf, 2005; Lupien et al., 2002; Maheu, Collicutt, Kornik, Moszkowski, & Lupien, 2005). This has been interpreted in the framework of an inverted U-shaped dose response curve between cortisol and memory. In addition, the arousal or valence of the learning material seems to influence the results. For stress studies with short delays neutral information seems to be more impaired by GC treatment or stress (Maheu et al., 2005; Payne et al., 2006; Smeets, Jelicic, & Merckelbach, 2006; Tops et al., 2003). This is in contrast to the effects on consolidation and retrieval of long-term episodic memory (see above and Table 1). It is likely that the effects are mediated by different brain regions (PFC versus amygdala and hippocampus).

4.2. Acute stress and working memory in animals and humans

The short-term active 'on-line' storage of information in memory is referred to as working memory (LaBar & Cabeza, 2006). Here, prefrontal brain regions like the dorsolateral prefrontal cortex and the anterior cingulate gyrus

are crucial. The effects of stress and stress hormones have also been investigated for this memory domain, even though less data exist (Lupien & Lepage, 2001).

Brief stress in monkeys leads to working memory impairments which are mediated by adrenergic and dopaminergic mechanisms (Arnsten, 2000). In rats stress or GC treatment impairs working memory (Roozendaal, McReynolds, & McGaugh, 2004; Shansky, Rubinow, Brennan, & Arnsten, 2006). Again the effects of GCs occur only in the context of noradrenergic activation in the BLA (Roozendaal, McReynolds, et al., 2004; Roozendaal, Okuda, et al., 2006).

In humans pharmacological studies observed that GC treatment was accompanied by poorer WM performance (Lupien, Gillin, & Hauger, 1999; Lupien & Lepage, 2001; Wolf et al., 2001), while other studies failed to find the effects (Kuhlmann, Kirschbaum, et al., 2005). At least one pharmacological study (Lupien et al., 1999) and one stress study (Oei, Everaerd, Elzinga, van Well, & Bermond, 2006) indicate that impairing effects of GCs occur only when task load is high. This might explain some of the non-significant findings. A recent psychosocial stress study observed that cortisol stress responders exhibited impaired WM only when performance was tested during the stress paradigm itself, while the difference disappeared shortly after stress exposure (Elzinga & Roelofs, 2005). This finding provides further evidence for an interaction between GCs and adrenergic arousal (Roozendaal, Okuda, et al., 2006). The influence of emotional arousal or emotional valence of the learning material in working memory tasks has received little attention as of today. Previous animal studies have used relatively neutral learning paradigms (Arnsten, 2000; Roozendaal, McReynolds, et al., 2004; Shansky et al., 2006). Similarly, all human studies cited above have used emotional neutral learning material (digits or numbers, Elzinga & Roelofs, 2005; Lupien et al., 1999; Oei et al., 2006; Wolf et al., 2001). Thus even though mounting evidence suggests that stress or GC treatment impairs working memory, the role of the emotional content of the learning material remains to be further characterized (see Table 1).

4.3. Acute stress and fear conditioning in animals and humans

An overwhelming literature exists on the effects of GCs on emotional learning in rodents, which dates back to several decades. Various tasks have been used ranging from active or passive avoidance tasks (e.g. Bohus & Lissak, 1968; Flood et al., 1978; Kovacs, Telegdy, & Lissak, 1977) to eye-lid conditioning (Shors, 2004) and to fear conditioning. For the present review, only aspects of the fear conditioning literature will be highlighted.

During simple cue fear conditioning, the subject learns an association between a previously neutral stimulus (a tone or a visual signal) and an aversive event which is most often realized with an electric shock (see also Mineka &

Oehlberg, 2008; Baas, van Ooijen, Goudriaan, & Kenemans, 2008; Iberico et al., 2008). For this form of conditioning the amygdala together with thalamic regions is crucial (LaBar & Cabeza, 2006). The more complex form of contextual fear conditioning requires the subjects to learn that only in a certain environment (e.g. a specific cage) does the tone signal the occurrence of a shock. Here the hippocampus has a pivotal role (LaBar & Cabeza, 2006).

Multiple studies have implied the noradrenergic system in fear conditioning. Noradrenergic signals from the locus coeruleus increase noradrenergic activity in the BLA, which leads to enhanced acquisition and also to enhanced reconsolidation of fear conditioning (Debiec & LeDoux, 2004; O'Donnell, Hegadoren, & Coupland, 2004; Schulz, Fendt, & Schnitzler, 2002). At the same time extinction appears to be reduced by enhanced noradrenergic activity (O'Donnell et al., 2004).

Central or peripheral injections of GCs lead to an enhanced consolidation of an acquired fear conditioning response. This has been shown using cue conditioning (Hui et al., 2004; Roozendaal, Hui, et al., 2006; Zorawski & Killcross, 2002) and contextual conditioning (Cordero, Kruyt, Merino, & Sandi, 2002; Cordero & Sandi, 1998). Again, evidence exists that noradrenergic activation in the BLA is a prerequisite for some of these effects (Roozendaal, Hui, et al., 2006). Several reports describe a selective role for GCs in the consolidation of contextual fear (Cordero et al., 2002; Cordero, Merino, & Sandi, 1998; Cordero & Sandi, 1998; Pugh, Tremblay, Fleshner, & Rudy, 1997). Removal of corticosterone led to an impaired consolidation of contextual fear but had no effects on cue conditioning (Pugh et al., 1997). This would suggest that GCs orchestrate specifically the interaction between the amygdala and the hippocampus. In sum, a number of animal studies highlight the relevance of GCs for the consolidation of a conditioned fear response. While some studies suggest that this effect is specific for contextual fear conditioning, several recent studies suggest that GCs also enhance cue fear conditioning (Hui et al., 2004; Roozendaal, Hui, et al., 2006; Zorawski & Killcross, 2002). Discrepancies might be attributable to differences in the procedures used (e.g. shock intensity, GC dosage, etc. Cordero & Sandi, 1998).

In addition to their effects on fear memory consolidation, GCs also influence extinction. GC treatment enhanced extinction while blockade of endogenous corticosterone production with metyrapone led to reduced extinction (Barrett & Gonzalez-Lima, 2004; Cai, Blundell, Han, Greene, & Powell, 2006; Yang, Chao, & Lu, 2006). This observation is of clinical relevance since it might underlie some of the beneficial effects of cortisol treatment in patients with anxiety disorders (see below).

Only recently the effects of stress hormones on fear conditioning have been investigated in humans. In three studies, basal or psychosocial stress-induced cortisol levels were associated with enhanced acquisition of fear conditioning (Jackson, Payne, Nadel, & Jacobs, 2006; Zorawski, Blanding, Kuhn, & LaBar, 2006; Zorawski, Cook, Kuhn, & LaBar, 2005). This effect occurred in male subjects only. In one study, stress induced cortisol levels were also associated with enhanced consolidation of fear memory (Zorawski et al., 2006), which would be in line with the rodent studies mentioned above. The first fMRI study investigating the effects of acute cortisol treatment on fear conditioning also observed sex specific effects albeit in the opposite direction. Here cortisol impaired the acquisition of the fear response in men, but enhanced it in women (Stark et al., 2006). This was evident at the peripheral level (effects on skin conductance) but also in the brain (effects in several prefrontal regions). The discrepancies between this study and the previous stress studies could be due to the different cortisol levels induced and/or from the fact that stress is associated with multiple endocrine alterations (e.g. increased CRH secretion), while pharmacological GC treatment leads to a selective cortisol increase (and reduced CRH secretion; Stark et al., 2006). Even though more research is needed, it is remarkable that all human studies on this topic observed sex differences. In contrast, studies investigating cortisol effects on episodic memory rarely observed sex differences.

All in all, GCs influence fear conditioning. Comparable to their effects on declarative memory, they enhance fear consolidation. Selective effects on fear retrieval have not been well studied. The potential of GCs to facilitate extinction has potential clinical relevance since it could enhance the therapeutic process. In humans, the impact of stress hormones on fear conditioning has only recently received attention and additional research is warranted (refer to Table 1 for a summary).

5. Chronic stress

The previous sections have revealed a complex picture on how acute stress can enhance but also impair memory in a phase and domain specific manner. A different scenario emerges for conditions of chronic stress or constantly elevated stress hormones. Chronic stress has mostly a negative impact on the body (e.g. the cardiovascular system, the immune system, the skeleton) and on the brain (e.g. on the hippocampus and on prefrontal regions, Belanoff, Gross, Yager, & Schatzberg, 2001; De Kloet et al., 1998; Herbert et al., 2006; McEwen, 1998). Animal research has provided insight into the neurochemical and neurostructural alterations induced by chronic stress. A few examples most relevant to the topic of this review are given below.

5.1. Chronic stress and memory in animals

In rodent models, experimentally induced chronic stress leads to poor performance in spatial memory tasks known to depend on the hippocampus (Bodnoff, Humphreys, Lehman, Diamond, & Rose, 1995; Conrad, Galea, Kuroda, &

McEwen, 1996; Herbert et al., 2006). Similar results have been observed in tree shrews (Ohl & Fuchs, 1999). It had been suggested that chronic stress leads to neuronal death in the hippocampus (Sapolsky, 1999), but newer research suggests a slightly different picture reporting maintained neuronal numbers after chronic stress (Leverenz et al., 1999; Sousa, Almeida, Holsboer, Paula-Barbosa, & Madeira, 1998; Vollmann-Honsdorf, Flugge, & Fuchs, 1997). Chronic stress however results in a retraction of dendrites in the CA 3 region of the hippocampus, which has been referred to as 'dendritic atrophy' or 'dendritic remodeling' (Herbert et al., 2006; McEwen, 2003). Dendritic atrophy occurs transiently in chronically stressed animals and a recovery has been observed after stress termination (McEwen, 2003; Radley, Rocher, Janssen, et al., 2005). A similar stress-induced dendritic retraction occurs in the PFC (Radley & Morrison, 2005). The effect appears to be specific to the medial PFC, and it did not occur in the orbital frontal cortex (Liston et al., 2006). The dendritic atrophy in the mPFC was associated with compromised set shifting capabilities (Liston et al., 2006).

In contrast to the hippocampus and the PFC, the amygdala becomes hypertrophic in conditions of chronic stress (McEwen, 2003; Radley & Morrison, 2005; Sapolsky, 2003). Increases in dendritic arborization (Vyas, Mitra, Shankaranarayana Rao, & Chattarji, 2002) and spine density (Mitra, Jadhav, McEwen, Vyas, & Chattarji, 2005) in the BLA have been observed. Moreover the CRF system of the amygdala, which is involved in anxiety (Landgraf, 2005; Mitchell, 1998), becomes hyperactive in response to chronic stress (Schulkin, Gold, & McEwen, 1998). Thus the balance between these brain regions is altered. While hippocampal and PFC functioning becomes impaired, amygdala functioning is enhanced.

Even though stress-induced dendritic atrophy in the CA3 region has been reported to be associated with spatial memory impairments, the functional significance of the dendritic retractions is less well understood. Conrad proposed that the effects are indirectly mediated via an enhanced HPA reactivity which then impairs spatial memory (Conrad, 2006). Support for this comes from another laboratory which reported that CA3 lesion-induced spatial memory impairments could be reversed when the increase in corticosterone was prevented (Roozendaal et al., 2001).

The effects of chronic stress on the brain are, of course, not restricted to the dendritic retractions discussed above. Especially interesting is that chronic stress (as well as acute stress in some studies) reduces adult neurogenesis in the dentate gyrus (Gould, Tanapat, Rydel, & Hastings, 2000; Herbert et al., 2006; Joels et al., 2004; McEwen, 2003). The dentate gyrus is one of the few regions of the brain where new neurons are produced during adulthood (Gould et al., 2000). While the function of these newborn neurons is disputed, an involvement in the aspects of memory and learning appears likely (Leuner, Gould, & Shors, 2006).

In addition to these structural alterations, chronic stress also influences several monoaminergic systems (dopamine,

serotonin, and noradrenalin) in the hippocampus as well as in other brain areas of relevance for memory like the prefrontal cortex (De Kloet et al., 2005; Luine, Spencer, & McEwen, 1993).

Interesting from a psychopharmacological perspective is that dendritic atrophy in the CA3 region as well as reduced neurogenesis in the dentate gyrus can be prevented with antidepressants and anticonvulsants (Conrad et al., 1996; Czeh et al., 2001; Magarinos, Deslandes, & McEwen, 1999; Magarinos, McEwen, Flugge, & Fuchs, 1996). Also, treatment with a glucocorticoid receptor antagonist was able to reverse a stress-induced reduction in neurogenesis (Mayer et al., 2006). Similarly, the memory impairments can be prevented with antidepressants and anticonvulsants (Conrad et al., 1996; Czeh et al., 2001; Magarinos et al., 1996). In addition, a pharmacological reduction of active GC concentrations in the hippocampus (11 beta HSD synthesis inhibition) was able to prevent memory decline associated with HPA hyperactivity (Seckl, Yau, & Holmes, 2002; Yau et al., 2001).

Given the broad neuroanatomical and neurochemical alterations induced by chronic stress, it might come as no surprise that other memory domains are also influenced. As stated, studies in animals have reported that chronic stress leads to impaired spatial memory (mediated by the hippocampus) but also to impaired working memory (mediated by the PFC; Bodnoff et al., 1995; Conrad et al., 1996; Herbert et al., 2006; Liston et al., 2006; Lyons, Lopez, Yang, & Schatzberg, 2000). A different picture emerges for fear conditioning where chronic stress enhances performance (Conrad, LeDoux, Magarinos, & McEwen, 1999). This is in line with the idea that amygdala functioning is enhanced during chronic stress (Sapolsky, 2003). This behavioral observation is in keeping with the structural alterations in the amygdala (Mitra et al., 2005; Vyas et al., 2002). Thus, under conditions of chronic stress, cognitive and explicit forms of memory mediated by the hippocampus and parts of the PFC are impaired, while basic emotional learning mediated by the amygdala is facilitated.

5.2. Chronic stress and memory in humans

There are of course no experimental studies on the topic of chronic stress in humans due to ethical constraints. Some human pharmacological studies treated subjects for several days with GCs and observed episodic memory impairments, sometimes in combination with impairments in prefrontal mediated tasks (McAllister-Williams & Rugg, 2002; Newcomer, Craft, Hershey, Askins, & Bardgett, 1994; Schmidt, Fox, Goldberg, Smith, & Schulkin, 1999; Young, Sahakian, Robbins, & Cowen, 1999). Similar observations stem from clinical investigations on the effects of a pharmacologically indicated GC treatment (e.g. in the context of arthritis or other autoimmune disorders). Here patients also showed memory impairments (Brunner et al., 2005; Wolkowitz, Reus, Canick, Levin, & Lupien, 1997), which were in one study associated with smaller hip-

pocampal volumes (Brown et al., 2004). In addition, prednisone treatment in patients with Alzheimer's dementia led to a stronger decline in memory (Aisen et al., 2000).

An informative example of chronically elevated endogenous cortisol levels are Cushing patients. Due to tumors they show markedly increased cortisol levels. These patients report psychological symptoms such as depression, irritability as well as cognitive failures (Whelan, Schteingart, Starkman, & Smith, 1980). Cognitive deficits are apparent in neuropsychological tests. Moreover, the patients have smaller hippocampal volumes as demonstrated with structural MRI (Starkman, Gebarski, Berent, & Schteingart, 1992). This hippocampal atrophy appears to be, at least in part, reversible after successful treatment of the hypercortisolemia (Bourdeau et al., 2002; Starkman, Giordani, Gebarski, Berent, & Schork, 1999). The latter observation would go along well with the substantial plasticity of the hippocampus observed in rodents.

6. Stress hormones, emotional memories and psychiatric disorders

A role of HPA axis alterations has been proposed for several psychiatric disorders and there is no dearth of literature on this topic. For the present review, the role of alterations in the (nor)adrenergic and the glucocorticoid system for the development and treatment of psychiatric disorders will be discussed for depression, PTSD and phobias. Emphasis will be given to the question as to whether stress hormone-induced modulations of emotional memory and learning processes might be of relevance (see Table 2). An important modulatory role of the HPA axis for age-associated cognitive decline and dementia has received considerable attention. The interested reader is referred to recent reviews (Herbert et al., 2006; Lupien et al., 2005; Wolf, 2006).

6.1. Depression

A major depressive episode is characterized by depressed mood and a loss of interest (anhedonia; American Psychiatric Association, 1994). In addition, sleep disturbances and changes in psychomotor activity are common. Recurrent circular negative thoughts are also typical. Besides, the ability to think and concentrate is diminished and the entire information processing including attention, memory encoding and retrieval is characterized

by a negative bias (Leppanen, 2006; see also Hertel & Mahan, 2008); see Table 2.

Neuroimaging studies have reported amygdala hyperactivity in the face of inconclusive volumetric findings (Campbell & MacQueen, 2006; Nestler & Carlezon, 2006). Reductions in hippocampal volumes have been reported reliably (Campbell & MacQueen, 2006; Campbell, Marriott, Nahmias, & MacQueen, 2004). In addition, hypoactivity in prefrontal brain regions and volume reductions in some of these regions have been suggested (e.g. in the subgenual prefrontal cortex, the anterior cingulate gyrus, the obitofrontal gyrus and the dorsolateral prefrontal cortex; Drevets, 2000; Hasler, Drevets, Manji, & Charney, 2004; Mayberg, 1997). Of relevance for anhedonia hypofunction in the mesolimbic reward system has been observed (Nestler & Carlezon, 2006).

Alterations of monoaminergic systems are thought to be crucially involved in depressive disorders. Most antidepressant drugs influence the serotonergic and/or the noradrenergic system (Holtzheimer & Nemeroff, 2006; Tremblay & Blier, 2006). Having said this hyperactivity of the HPA axis is one of the most consistent findings in patients with depression and a role of the HPA axis in this disorder has been hypothesized. Evidence comes from studies reporting elevated CRH levels in the cerebrospinal fluid (Nemeroff et al., 1984) or from studies detecting elevated basal levels of ACTH and cortisol in plasma (Deuschle et al., 1997). Moreover a deficient negative feedback of the HPA axis could be demonstrated with the dexamethasone (Dex) suppression test or with the combined Dex/CRH challenge test (Heuser, Yassouridis, & Holsboer, 1994). Several models try to explain the occurrence of HPA hyperactivity in depression. Nemeroff and colleagues have provided evidence that an increased central CRH drive is at the core of clinical depression. Other authors, in contrast, suggest that deficient glucocorticoid receptors are responsible for the HPA axis hyperactivity (Holsboer, 2000). Pariante and colleagues have demonstrated that GR signaling is reduced in depression, suggesting that the brain is in a state of glucocorticoid resistance (Pariante, 2006; Pariante, Thomas, Lovestone, Makoff, & Kerwin, 2004). Thus, despite having high cortisol levels, patients with depression might not receive an adequate (feedback) signal from the hormone.

Important to note is that HPA hyperactivity is not present in all patients. Distinct subtypes of depression might be characterized by HPA hyper- versus hypo-activity

Table 2
Examples of emotional memory and emotional learning disturbances in psychiatric disorders

Psychiatric disorder	Learning and memory dysfunction of relevance for psychopathology
Depression	Negative attentional bias; Enhanced consolidation and retrieval of negative information; Unspecific retrieval from autobiographical memory
PTSD	Involuntary retrieval (flashbacks, intrusions), Failure to integrate the trauma as a coherent episode into autobiographical memory; Exaggerated conditioned fear which is context independent; impaired fear memory extinction
Phobias	Exaggerated conditioned fear; Impaired fear memory extinction

(Gold & Chrousos, 2002). Hyperactivity might be frequent in patients with melancholic depression or psychotic depression (Belanoff, Kalehzan, Sund, Fleming Ficek, & Schatzberg, 2001; Gold & Chrousos, 2002). In other subgroups a hypoactive HPA axis is observed, which resembles observations made in burn-out or chronic fatigue syndrome (Gold & Chrousos, 2002).

Elevated cortisol levels in depression could impact on the function and structure of the brain and might thus be linked to the affective and cognitive disturbances of the patients (Herbert et al., 2006). The memory of depressed patients is characterized by a negative bias with a preferred storage and retrieval of negative information (Leppanen, 2006). Several studies have linked increased cortisol levels to impaired cognitive functions in depressed patients (Belanoff, Kalehzan, et al., 2001; Rubinow, Post, Savard, & Gold, 1984). When focusing more on specific relationships between cortisol and emotional memory in depressed patients, laboratory studies in healthy subjects suggest that a shift towards a negative memory bias (Tops et al., 2003) or a fearful hypervigilant response style (Roelofs, Bakvis, Hermans, van Pelt, & Van Honk, 2007) could be the result of elevated cortisol levels. The negative bias might reflect changes in brain lateralization (decreased activity of the left prefrontal cortex associated with approach behavior and/ or increased activity of the right prefrontal cortex associated with withdrawal (Davidson, 2004; Davidson, Pizzagalli, Nitschke, & Putnam, 2002)). Interestingly recent basic science evidence has been presented which states that stress or cortisol treatment influences cerebral lateralization (Czeh et al., 2007; Tops et al., 2005).

Another aspect of memory distortions in depression, the lack of specificity when recalling autobiographical information (Williams et al., 2007), might also be related to cortisol. Young subjects treated with cortisol showed a reduced specificity in an autobiographical memory test (Buss et al., 2004). However, a first study trying to relate basal cortisol levels in depressed patients to their autobiographical memory failed to observe strong associations (Barnhofer, Kuehn, & Jong-Meyer, 2005).

It has been speculated that HPA hyperactivity is responsible for the hippocampal atrophy observed in depressed patients (Sapolsky, 1996, 2000). Some studies have found that disease duration is associated with the severity of hippocampal atrophy, which would support the idea of a negative impact of disease-associated HPA hyperactivity on this structure (MacQueen et al., 2003; Sheline, Sanghavi, Mintun, & Gado, 1999; Videbech & Ravnkilde, 2004). However this issue remains controversial. In addition, the attempt to link HPA activity to hippocampal volumes in patients with depression has led to mixed results (O'Brien, Lloyd, McKeith, Gholkar, & Ferrier, 2004). One study observed that hippocampal volume reductions were specific to those patients who had experienced a trauma during childhood (Vythilingam et al., 2002). This suggests that a developmental perspective might be indicated. In line with these clinical findings, animal studies have demonstrated that early life stress can lead to HPA hyperactivity and to a reduction in hippocampal volumes (Coe et al., 2003).

With respect to the amygdala, structural MRI studies have been mixed (Campbell & MacQueen, 2006; Davidson et al., 2002). Functionally imaging studies reported increased amygdala activity or reactivity (Drevets, 2003; Whalen, Shin, Somerville, McLean, & Kim, 2002). In one study cortisol levels were associated with increased amygdala activity (Drevets et al., 2002), which would be in line with the excitatory effects of cortisol on this structure observed in rodents.

In addition to changes in limbic regions, prefrontal alterations have been observed in depression most notably in the subgenual prefrontal cortex (Drevets et al., 1997). Moreover, a shift towards right prefrontal activation occurs (Davidson, 2004; Davidson et al., 2002). In this context it is interesting to repeat that prefrontal regions like the medial prefrontal and the anterior cingulate gyrus are influenced by glucocorticoids, but are also crucially involved in HPA axis feedback (Ahs et al., 2006; Diorio, Viau, & Meaney, 1993; Radley, Rocher, Miller, et al., 2005; Radley et al., 2004; Wolf, Convit, de Leon, Caraos, & Quadri, 2002). Moreover, these regions are part of a network involved in attention and working memory (Smith & Jonides, 1999).

Thus current models of depression appear to converge on the idea that dysfunction in a limbic cortical network, which includes the amygdala, the hippocampus, the anterior cingulate and several parts of the PFC, is underlying the disorder (Drevets, 2000; Hasler et al., 2004; Mayberg, 1997). While there is substantial evidence for HPA hyperactivity in certain patients with depression, the relationship of this phenomenon to alterations in hippocampal, amygdala and PFC integrity needs further investigation. More longitudinal studies (O'Brien et al., 2004) and intervention studies (Vythilingam et al., 2004) are needed in order to disentangle the temporal and causal aspects of the associations between alterations in the HPA axis and the memory dysfunctions and memory biases observed in depression.

With respect to the treatment of depression, pharmacological approaches aimed at reducing HPA activity in hypercortisolemic patients appears promising. Possible options are CRF- and GR antagonists (Berton & Nestler, 2006). In addition, most other antidepressants influence HPA activity (Ising et al., 2005). Information about the HPA axis status of a certain patient will in the future allow the selection of more targeted drugs. In addition, it might allow to predict the likelihood of a treatment response (Berton & Nestler, 2006; Ising et al., 2005).

6.2. PTSD

Post traumatic stress disorder is characterized by re-experiencing (intrusions, flashbacks and nightmares), avoidance and hyperarousal (American Psychiatric Association, 1994; see also Holmes & Bourne, 2008), see Table 2.

Current models of the disorder have suggested an enhanced amygdala reactivity resulting in an exaggerated fear memory trace and a missing context sensitivity of the conditioned fear response due to hippocampal dysfunction (Rauch et al., 2006). In addition, prefrontal deficits could be involved in the failure to extinct the traumatic memory (Rauch et al., 2006). An additional role of a dysfunctional hippocampus has been suggested for the distorted explicit memory of the trauma and the often missing integration of the trauma into autobiographical memory (Brewin, 2001; Buckley, Blanchard, & Neill, 2000; Ehlers & Clark, 2000; Ehlers, Hackmann, & Michael, 2004).

The brain regions thought to be involved in PTSD overlap with the regions associated with depression. This might come as no surprise, since both disorders are characterized by anxiety and affective disturbances and have substantial comorbidity (Nemeroff et al., 2006). Differences between the disorders might be the result of different neuroendocrine profiles, different triggers (chronic stress versus a traumatic event) or neurochemical alterations in the brain not typically picked up with current neuroimaging technologies.

Hyperactivity of the noradrenergic system has been proposed as one key pathological mechanism in PTSD. In electrophysiological studies an increased startle response in these patients is frequently observed (O'Donnell et al., 2004). Neuroendocrine studies indicate increased (nor)adrenergic arousal originating from the locus coeruleus (O'Donnell et al., 2004). Evidence comes from noradrenalin measurements out of plasma, urine or CSF. It is suggested that noradrenergic hyperactivity leads to an over consolidation of the traumatic memory trace. In this model, trauma reminders lead to repeated noradrenergic arousal and a further strengthening of the traumatic memory trace resulting in a positive feedback cycle (O'Donnell et al., 2004; Pitman & Delahanty, 2005). A role of noradrenergic hyperactivity in PTSD is supported by pilot studies showing that treatment with a beta blocker shortly after trauma exposure reduces the risk of developing PTSD (O'Donnell et al., 2004; Pitman & Delahanty, 2005).

With respect to cortisol the majority of studies investigating basal levels found lower cortisol levels in PTSD patients. However, the findings are not universal and missing differences as well as higher cortisol levels in PTSD patients have been reported (Yehuda, 2003, 2006). Discrepancies might be in part attributable to the adequate control of concurrent depression in the studied populations. After the low-dose Dexamethasone feedback test, several studies detected that PTSD patients show a super-suppression indicative of an enhanced negative feedback (Yehuda, 2002, 2006). In line with these findings, an enhanced GC sensitivity could be demonstrated in the periphery (Rohleder, Joksimovic, Wolf, & Kirschbaum, 2004). Three studies looked at 'central' GC sensitivity by investigating the effects of glucocorticoid treatment on learning and memory tasks in patients with PTSD. One study reported stronger negative effects of cortisol on hippocampal dependent

declarative memory in patients with PTSD. In addition, only in PTSD patients did the glucocorticoid lead to impairments in working memory (Grossman et al., 2006). In another experiment a more pronounced effect of cortisol on hippocampal dependent trace conditioning was found (Vythilingam et al., 2006). In this study PTSD patients, but not healthy controls, showed impairment after cortisol treatment. Thus both studies suggested exaggerated effects of GCs on memory in PTSD. Discrepant to these studies, a third study reported blunted effects of dexamethasone on declarative memory in PTSD (Bremner et al., 2004). It remains to be investigated whether this discrepancy is related to the use of dexamethasone or to the different treatment regime, which in the Bremner et al.'s study lasted for three days.

In contrast to the evidence for reduced basal cortisol the cortisol response to psychological stressors (either trauma scripts or trauma non-specific laboratory stressors) appears to be exaggerated in PTSD patients (De Kloet et al., 2006; Elzinga, Schmahl, Vermetten, Van Dyck, & Bremner, 2003; Heim et al., 2000). Few prospective studies have investigated the relationship between low cortisol levels and trauma development. The studies available suggest that lower cortisol levels shortly after trauma exposure are a risk factor for the future development of PTSD (Delahanty, Raimonde, & Spoonster, 2000; McFarlane, Atchison, & Yehuda, 1997).

Structural imaging studies have detected reduced hippocampal volumes in PTSD patients when compared to trauma-exposed subjects without PTSD (Karl et al., 2006). Initially it had been hypothesized that a massive trauma-induced HPA response might have resulted in hippocampal atrophy in those patients (Sapolsky, 1996). However, a recent twin study has pinpointed to an alternative interpretation. This unique study suggests that a smaller hippocampus is a risk factor for PTSD rather than the result of PTSD (Gilbertson et al., 2002).

Thus lower basal cortisol levels as well as smaller hippocampal volumes might be risk factors for rather than direct causes of PTSD. Nevertheless, both biological markers could reflect early adversity or early trauma (Nemeroff et al., 2006; Yehuda, 2006). In this context, epigenetic processes might also be of relevance (Yehuda, 2006).

With respect to possible mechanisms, lower cortisol levels might lead to a less well integrated memory trace of the trauma into autobiographical memory. Cortisol is critical for the interaction between the amygdala and the hippocampus during emotional memory encoding. Similarly, corticosterone is important for contextual fear conditioning (Cordero et al., 2002; Cordero et al., 1998; Cordero & Sandi, 1998; Pugh et al., 1997). Thus having a blunted cortisol response to the trauma in combination with the presence of a smaller hippocampus might lead to an amygdala mediated fear memory trace of the trauma, which does not integrate well into the autobiographical (hippocampally driven) memory context. In addition lower cortisol levels, especially in combination with an

enhanced noradrenergic drive, might enhance the risk for memory intrusions, flashbacks and nightmares, since cortisol has been shown to reduce emotional memory retrieval (Buchanan et al., 2006; Kuhlmann, Kirschbaum, et al., 2005; Kuhlmann, Piel, et al., 2005; Wagner, Degirmenci, Drosopoulos, Perras, & Born, 2005). However, those studies which found an exaggerated (rather than a blunted) HPA response of PTSD patients to trauma exposure or stress exposure appear to contradict this model (De Kloet et al., 2006), so that more empirical evidence is needed.

The idea that cortisol is beneficial for patients with PTSD has gained support from small pharmacological trials. In placebo controlled studies, Schelling and colleagues could show that cortisol treatment in intensive care unit patients reduced the risk for PTSD (Schelling et al., 2006). Similarly a placebo controlled double blind pilot study with three patients with chronic PTSD found a reduction in PTSD symptoms in response to low-dose cortisol treatment (Aerni et al., 2004). A combination of reduced emotional memory retrieval and enhanced fear extinction might underlie these beneficial effects.

In sum, treatment with beta receptor blockers and/or with cortisol appears to have promising potentials for the secondary prevention and probably also for the treatment of PTSD. These beneficial effects most likely reflect the modulatory role of the two neuroendocrine stress systems on emotional memory retrieval, fear extinction or fear reconsolidation (O'Donnell et al., 2004; Pitman & Delahanty, 2005). Clearly, additional evidence is needed before recommendations for clinicians can be given.

6.3. Phobia

Phobias are characterized by an irrational fear of specific situations (e.g. a social interaction) or objects (e.g. snakes, spiders, planes). It has been suggested that these strong fear responses are the result of a conditioned fear response (see also Table 2) which has been conceptualized in the context of biological preparedness and vulnerability factors (Armfield, 2006; Field, 2006; Ohman, 2005; Ohman & Mineka, 2001; see also Mineka & Oehlberg, 2008). Again, a crucial involvement of the amygdala has been postulated, since it responds rapidly and automatically to threat cues (Lang, Davis, & Ohman, 2000; Mineka & Ohman, 2002). The amygdala of phobic patients reportedly responds stronger or faster to phobiogenic stimuli (Larson et al., 2006; Straube, Mentzel, & Miltner, 2006).

Given the evidence that stress hormones influence emotional learning, the investigation of the stress hormones in phobias is of interest. With respect to the HPA axis, changes in basal activity have been observed seldom even though few studies on this topic exist (e.g. Martel et al., 1999; Potts, Davidson, Krishnan, Doraiswamy, & Ritchie, 1991). However, an enhanced response to phobia specific threats has been reported in several studies (Alpers, Abelson, Wilhelm, & Roth, 2003; Condren, O'Neill, Ryan, Bar-

rett, & Thakore, 2002; Furlan, DeMartinis, Schweizer, Rickels, & Lucki, 2001).

Since cortisol has beneficial effects on emotional memory in PTSD, the group from de Quervain has explored the therapeutic potential of cortisol for social phobia and spider phobia. In social phobia pretreatment with cortisol leads to a reduced anxiety response to a psychosocial stressor (Soravia et al., 2006). Similar effects have recently been observed in a study with healthy non-phobic subjects. Again, cortisol pretreatment resulted in a reduced impact of the stressor on mood (Het & Wolf, 2007). In spider phobics, cortisol administration resulted in decreased fear ratings in response to repeated exposition to a spider picture, which was maintained after treatment was discontinued (Soravia et al., 2006). These studies suggest that, similar to the effects in PTSD, cortisol might also be able to beneficially modulate emotional memory in phobias.

Taken together, while HPA alterations appear not to be central to most phobias, cortisol could nevertheless have interesting pharmacological properties for the treatment of phobias. Impaired phobia associated memory retrieval in combination with enhanced extinction of the phobic response could be potential mechanisms underlying these positive effects (Soravia et al., 2006).

7. Future perspectives

In the next paragraph a few venues for future research are outlined. The focus will be on sex differences, susceptibility genes and a lifespan developmental approach.

7.1. Sex differences

There is a higher prevalence of women in most of the psychiatric disorders discussed in this review (unipolar depression, PTSD, specific phobias but not social phobia (Nemeroff et al., 2006; Yehuda, 2002)). In contrast, the prevalence of women is lower in conduct disorders, psychopathy, substance abuse and autism. In several of the basic science studies reviewed, sex differences have been observed, as for instance the difference in lateralization between men and women when it comes to amygdala involvement in emotional memory consolidation (Cahill, 2006). Also with respect to the effects of stress on memory, sex differences have been repeatedly observed, especially in animal studies. However, the direction of these effects appears to be different depending on the used paradigms. For example, acute stress enhances eye-lid conditioning in male rats, but impairs it in female rats (Shors, 2004). Similarly, stress has a stronger negative impact on working memory in female rats, an effect attributable to their estradiol levels (Shansky et al., 2004; Shansky et al., 2006). While these studies suggest that females are more susceptible to acute stress, work by others indicates the opposite. In a spatial memory task, stress impaired memory in male rats, but enhanced it in female rats (Conrad et al., 2004).

Similarly chronic restraint stress led to spatial memory impairments in male rats only, while performance of female rats was enhanced (Luine, 2002). In humans, sex differences have been reported for the effects of stress or cortisol treatment on fear conditioning (Jackson et al., 2006; Stark et al., 2006; Zorawski et al., 2006). In contrast, the impairing effects of stress or cortisol on declarative memory retrieval appear to occur reliably in both sexes (de Quervain et al., 2000; Kuhlmann, Kirschbaum, et al., 2005; Kuhlmann, Piel, et al., 2005; Wolf et al., 2001).

Taken together, while there is a clear need to pay attention to the subject's sex when conducting research on the topic of stress and emotional memory, the results obtained so far do not allow a clear conclusion with respect to which sex is more susceptible. Moreover, a conceptual framework is needed which is able to integrate the current knowledge about sex differences into testable hypotheses on sex specific susceptibilities to stress-associated disorders.

7.2. Susceptibility genes

Not all subjects exposed to a trauma or exposed to situations of chronic stress develop psychiatric symptoms. Thus people differ in their vulnerability to adverse events. Progress has been made in the characterization of genes that render their carrier to be more vulnerable to stress (Charney & Manji, 2004; De Kloet et al., 2005; Wurtman, 2005). One example is the functional polymorphism in the serotonin transporter gene (5HTT). Carriers of one or two short alleles have an increased risk of a major depression in response to stressful life events (Caspi et al., 2003). Neuroimaging studies reported enhanced amygdala activity of carriers of the short allele (Hariri et al., 2002). Also this allele was associated with higher cortisol levels and smaller hippocampal volume in older adults (O'hara et al., 2007). Another example is the observation that common polymorphisms of the glucocorticoid and mineralocorticoid receptor gene (DeRijk et al., 2006) are associated with differences in the HPA response to stress (Wust et al., 2004). The clinical relevance of these polymorphisms has recently been reviewed elsewhere (DeRijk & De Kloet, 2005). Thus future studies investigating the impact of stress hormones on emotional memory should try to benefit from advances made in the field of molecular and behavioral genetics.

7.3. Life span perspective

Related to the issue of vulnerability genes is the topic of early programming of the stress system and the need to develop a lifespan perspective when relating the influence of stress on emotional memory in the context of psychopathology. Animal studies have established that pre- and postnatal stress can have long-lasting effects on the neuroendocrine system and on the functional integrity of prefrontal and limbic regions (Seckl & Meaney, 2006). For example, while neonatal handling leads to reduced HPA

reactivity throughout life, maternal separation has the opposite effect (De Kloet et al., 2005; Meaney et al., 1991). Besides, prenatal stress has been associated with enhanced HPA activity, smaller hippocampal volumes and a reduced neurogenesis in adulthood in rhesus monkeys (Coe et al., 2003). Similar evidence has commenced to accumulate in human studies. For example, early trauma has been associated with increased risk for depression, an exaggerated response to stress and reduced volumes of the hippocampus (Heim et al., 2000; Nemeroff et al., 2006; Vythilingam et al., 2002). Stress during pregnancy or low birth weight is associated with HPA hyperactivity of the child, which appears to last into adulthood (Wadhwa, 2005; Wust, Entringer, Federenko, Schlotz, & Hellhammer, 2005). In this context a long-lasting role of maternal care on HPA responsivity as well as on hippocampal volumes has been suggested (Buss et al., 2007; Pruessner, Champagne, Meaney, & Dagher, 2004). Thus a lifespan perspective will help to explain some of the variance observed in studies with adult subjects or adult patients.

8. Summary

The review has highlighted some of the recent advances in the field of stress hormone induced memory modulation. For acute stress the effects of stress depend on the memory domain and on the memory phase studied (encoding, consolidation, and retrieval). In addition, the effects are modulated by specifics of the learning material (e.g. the emotional arousal induced by it). Also important to note is that for some memory domains sex differences have been detected.

For chronic stress effects the findings indicate structural alterations in the hippocampus and PFC, which are associated with impaired memory. However, in the amygdala, hypertrophy occurs and amygdala mediated forms of learning are enhanced, suggesting that a shift from PFC and hippocampal-based 'cognitive' learning towards an amygdala-based 'affective' learning occurs. Since these observations are mostly based on data obtained in animals, more human studies combining structural and functional neuroimaging with neuroendocrine measures are warranted.

In the last part of the review, it was illustrated how these basic science findings might help to enhance our understanding of several psychiatric disorders. A modulation of emotional memory and emotional learning by stress hormones appears to be of relevance for the aetiology and/or for the treatment of depression, PTSD and phobias.

Thus the last decade has seen substantial progress in this exciting area and the future looks even more promising. A more thorough neuroendocrine diagnostic work-up in combination with new drugs or specific psychotherapies targeted at specific neuroendocrine circuits in the brain should lead to an enhanced treatment success for several psychiatric disorders.

Acknowledgement

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