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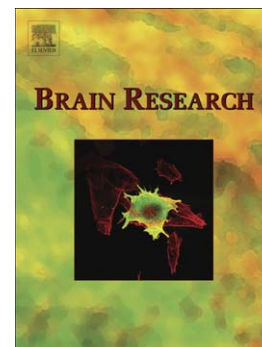
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PII: S0006-8993(09)00768-9
DOI: doi:[10.1016/j.brainres.2009.04.013](https://doi.org/10.1016/j.brainres.2009.04.013)
Reference: BRES 39149

To appear in: *Brain Research*

Received date: 23 December 2008
Revised date: 8 April 2009
Accepted date: 9 April 2009



Please cite this article as: Oliver T. Wolf, Stress and memory in humans: Twelve years of progress?, *Brain Research* (2009), doi:[10.1016/j.brainres.2009.04.013](https://doi.org/10.1016/j.brainres.2009.04.013)

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Stress and memory in humans: Twelve years of progress?

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Running title: Stress and memory in humans

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Acknowledgement: The work of the author was supported by several grants from the German Research Foundation (DFG). I wish to thank all my colleagues and co-workers who contributed to the studies discussed in this manuscript. Without their enthusiasm and support none of the studies could have been conducted.

Abstract

Stress leads to an enhanced activity of the hypothalamus-pituitary adrenal (HPA) axis resulting in an increased release of glucocorticoids from the adrenal cortex. These hormones influence target systems in the periphery as well as in the brain. The present review paper describes the impact of the human stress hormone cortisol on episodic long-term memory. Starting out with our early observation that stress as well as cortisol treatment impaired declarative memory, experiments by the author are described, which result in an enhanced understanding of how cortisol influences memory. The main conclusions are that stress or cortisol treatment temporarily blocks memory retrieval. The effect is stronger for emotional arousing material independent of its valence. In addition cortisol only influences memory when a certain amount of testing induced arousal occurs. A functional magnetic resonance imaging (fMRI) study suggests that the neuronal correlate of the cortisol induced retrieval blockade is a reduced activity of the hippocampus. In contrast to the effects on retrieval cortisol enhances memory consolidation. Again this effect is often stronger for emotionally arousing material and sometimes occurs at the cost of memory for neutral material. A fMRI study revealed that higher cortisol levels were associated with a stronger amygdala response to emotional stimuli. Thus stimulatory effects of cortisol on this structure might underlie the cortisol induced enhancement of emotional memory consolidation. The findings presented are in line with models derived from experiments in rodents and are of relevance for our understanding of stress associated psychiatric disorders.

Key words: stress; cortisol; memory; hippocampus; amygdala; humans

Introduction

Most people would intuitively agree with the statement that stress influences memory. However when asked about the direction of the effect different opinions might exist. For example one person might recall that he forgot a dentist appointment because he was under heavy work load at his company. This would suggest that stress impairs memory. Another person might tell a story about a fearful event during her childhood years (e.g. being attacked by a large dog) which she still remembers vividly decades later. This person might conclude that stress enhances our memory.

Researchers in the field of psychoneuroendocrinology have made substantial progress over the last decades in trying to disentangle conditions and mechanisms underlying the impact of stress on memory. It has become evident that glucocorticoids from the adrenal cortex, secreted in response to an increased activation of the hypothalamus-pituitary adrenal (HPA) axis are crucial in this context. By reviewing experiments in which I have been involved over the last twelve years the present manuscript describes advances made in studies with human participants. The focus will be on effects of the stress hormone cortisol on declarative/episodic memory.

The notion that stress influences memory has a long history in clinical psychology. The Freudian hypothesis of trauma associated memory suppression would be one example. In the area of neurology/psychiatry cases of dementia had been reported in response to high dose glucocorticoid treatment (for a recent review see (Wolkowitz et al., 2004)). The research on the impact of stress on memory received an important early boost by the discovery that glucocorticoids (GCs) bind to specific receptors in the hippocampus (McEwen et al., 1968). It thus appeared highly likely that this key region for declarative/episodic memory (Nadel and Moscovitch, 1997; Squire and Bayley, 2007) is influenced in its function by stress.

Studies in laboratory animals dating back to the 70s of the last century observed that GCs (primarily corticosterone in rats and mice) modulate memory (e.g. (Flood et al., 1978; Kovacs et al., 1977)). Repeatedly beneficial effects of GCs were found when animals were treated with the hormone after the initial memory training. In contrast at a different level of analysis stress and stress hormones reduced neuronal plasticity in the hippocampus as indicated by reduced long-term potentiation (Diamond et al., 1992; Diamond and Rose, 1994; Pavlides et al., 1993). The latter observation would predict a disturbing influence of stress on hippocampal based memory.

While clinical observations and basic neuroscience studies indicated that stress and the associated neuroendocrine stress response of the sympathetic nervous system and the HPA axis influences memory, experimental studies in humans on this topic had been scarce.

Moreover the few exceptions were not designed to test some of the hypothesis evolved from basic neuroscience studies cited above (Beckwith et al., 1986; Fehm-Wolfsdorf et al., 1993; Wolkowitz et al., 1990).

Stress, cortisol and memory in humans

First evidence

In a first approach to this topic we conducted a correlative study on the relationship between the stress induced cortisol increase and declarative memory. Stress was induced using the Trier Social Stress Test (TSST; (Kirschbaum et al., 1993)). Declarative memory was tested using a word list with recall being tested after a brief delay. Thus encoding and retrieval took place after stress exposure. A strong correlation was detected illustrating that a more pronounced cortisol response was associated with poorer memory (Kirschbaum et al., 1996). Results are shown in Figure 1a. This initial finding obviously did not allow us to postulate a causal involvement of cortisol. Therefore a placebo controlled study was conducted testing the hypothesis that a single cortisol administration would impair memory. In addition the hypothesis was explored that this effect would be specific for hippocampus mediated declarative/episodic memory (verbal and spatial), but would not occur for procedural (implicit) memory (Kirschbaum et al., 1996). To this aim healthy participants received either cortisol (Hydrocortisone) or a placebo. Verbal memory was tested using a word list. Between the encoding of the list and its retrieval two spatial memory tasks had to be conducted by the subjects. Implicit memory was assessed using a word stem completion priming paradigm, while explicit memory was tested with a cued recall task. Results revealed that cortisol lead to impairments in verbal and spatial declarative memory, while having no effect on procedural (implicit) memory (see Figure 1b).

Insert Figure 1a and 1b about here

In line with studies conducted by others which had used Dexamethasone instead of hydrocortisone and a prolonged (multiple day) treatment (Newcomer et al., 1994) we concluded at this time that cortisol treatment, similarly to stress exposure impaired hippocampal mediated memory in humans (Kirschbaum et al., 1996). However these findings were at odds with rodent studies observing beneficial effects of GC treatment on memory (e.g. (Flood et al., 1978; Kovacs et al., 1977)).

These two early studies lead to several new questions. Two important ones were the following: Do the effects of stress or cortisol treatment differ according to the specific memory phase involved (encoding, consolidation, retrieval)? Are the effects of stress on memory

influenced by the emotional arousal of the learning material? Since the combination of pharmacological and stress studies had been very informative this combined approach was used in future studies whenever feasible.

Stress, cortisol, and memory retrieval

Long-term memory can be separated in distinct memory phases. The initial encoding of the material is followed by a consolidation process. If those two processes are successful a memory trace can be retrieved hours to days to years later. It is well established that the hippocampus is crucially important for episodic memory encoding/consolidation but also for episodic memory retrieval, even though the latter point is debated (Nadel et al., 2000; Squire and Bayley, 2007). In order to experimentally separate these different memory phases a long retrieval interval (hours to days) has to be chosen so that the experimental manipulations can target a specific memory phase. In our initial studies (see above) encoding, consolidation and retrieval all took part after stress or cortisol treatment, thus preventing us to draw conclusions about a possible phase dependent effect of the stress hormone.

Stress and memory retrieval: Initial preliminary evidence

Two stress studies conducted in older healthy subjects suggested that a stress induced cortisol increase was associated with poorer memory retrieval of items learned before stress exposure (Lupien et al., 1997; Wolf et al., 1999). However in both studies the experimental design (the timing of the tests) did not allow to clearly separate effects on consolidation from effects on retrieval. At this time the findings were interpreted as indicating that the stress induced cortisol release lead to a retrograde amnesia (Wolf et al., 1999), which was in line with studies in rodents (Diamond et al., 1996). Looking back at this finding a temporarily impairing effect of stress on memory retrieval would have been a plausible alternative explanation.

Cortisol and memory retrieval

Using a 24 hour delay de Quervain and colleagues demonstrated that stress prior to testing impaired memory retrieval in rats tested in the water maze (de Quervain et al., 1998). Pharmacological follow up studies confirmed that the stress induced release of corticosterone was causing this retrieval deficit (de Quervain et al., 1998). Additional experiments illustrated that this effect was mediated by activation of glucocorticoid receptors (GRs) in the hippocampus. Moreover effects depended on an intact basolateral amygdala (Roosendaal et al., 2003). Two years after their initial experiments with rodents (de Quervain et al., 1998) the authors were able to show similar effects in humans. Cortisone impaired

delayed memory retrieval, while having no strong effect on encoding or consolidation (de Quervain et al., 2000).

In our own research we initially conducted a study with young and older subjects, which was designed to separate effects of cortisol on memory retrieval versus memory encoding (Wolf et al., 2001). We observed that a single intravenous injection of hydrocortisone impaired delayed (75 min.) retrieval of items from a shopping list. Results are depicted in Figure 2. These findings illustrated that cortisol can impair retrieval of material, which has been learned rather recently (a little more than one hour ago). In addition this effect occurs in young and older subjects to a similar degree.

Insert Figure 2 about here

Cortisol and retrieval: A case for state dependent learning?

A rather general explanation of these retrieval deficits relied on the concept of state dependent learning (e.g. (Clark et al., 1983; Schramke and Bauer, 1997)). Thus when learning took place without stress (or cortisol treatment) retrieval of this material is impaired in response to stress or cortisol treatment because cortisol induces a different 'state'. Even though this theory would not be able to explain the beneficial effects of cortisol on memory consolidation (see below as well as (Diamond et al., 2007; Joels et al., 2006; Roozendaal et al., 2006b; Wolf, 2008)), which also induce a change in the state of the subject, the negative effects on retrieval could theoretically reflect a state dependent effect (Wolf et al., 2001).

To empirically address this explanation we tested possible state dependent influences of stress on memory (Wolf et al., 2002c). Participants were stressed with the TSST before the initial learning and/or before delayed retrieval, which was tested four weeks later. Results provided no evidence for a state dependent effect, but the findings were limited by the habituation to the repeated exposure to the stressor (the TSST) and the relatively poor memory after the long delay (Wolf et al., 2002c).

More efficiently the state dependent hypothesis of the cortisol induced retrieval deficits was addressed in a recent collaborative study (Coluccia et al., 2008). Here patients with rheumatoid arthritis were treated with the synthetic glucocorticoid prednisone or a placebo one hour before delayed retrieval testing in a double blind crossover design. One day prior subjects had learned a word list as described previously (de Quervain et al., 2000). On this day all patients received prednisone, either as part of their daily medication schedule or as part of the aim to standardize the hormonal condition during initial encoding (Coluccia et al., 2008). Prednisone treatment before retrieval impaired retrieval in the patients despite the fact that they had learned the words on the previous day under prednisone (Coluccia et al., 2008). This finding clearly does not support the state dependent hypothesis and indicates

that GCs block memory retrieval independent of the hormonal state during the initial encoding of the learning material.

At the time the last experiment was published several alternative explanations had been put forward to explain why stress sometimes impaired and sometimes enhanced memory. The model from Roozendaal suggested that GCs enhance memory consolidation but impair memory retrieval (Roozendaal, 2002). An alternative although not exclusive model from Lupien and colleagues argued that GCs influence memory in an inverted U shaped manner and that GCs enhance memory at times of low cortisol levels (in the afternoon) and impair memory at times of high cortisol levels (in the morning; (Lupien and McEwen, 1997).

Additional recent models by others, which focused on the temporal and/or spatial association between stress hormone release and memory formation (Diamond et al., 2007; Joels et al., 2006; Sandi and Pinelo-Nava, 2007) were not available at the time the next analysis was conducted.

Cortisol and memory: A quantitative summary of the published evidence

In order to test those two hypotheses (phase dependent or circadian dependent effects of cortisol on memory) and in order to better summarize and integrate previous research in humans we conducted a meta- analysis (Het et al., 2005). Of interest were studies which had tested the effects of cortisol administration on memory in healthy subjects using a placebo controlled design. In total 16 studies fulfilled the stringent inclusion criteria. In a first step we compared those studies which administered cortisol before the initial encoding with those studies which administered cortisol before retrieval testing. Results revealed that on average cortisol significantly impaired memory retrieval with the size of the effect being medium ($d = -.49$). In contrast cortisol treatment before encoding on average had no significant effect. In order to test possible additional moderating factors the remaining studies were grouped according to the time of day (morning or afternoon) when they were performed. This analysis revealed that cortisol treatment in the morning was associated with a significant impairment in memory, while cortisol treatment in the afternoon was associated with enhanced memory (Het et al., 2005). Thus the Roozendaal model (Roozendaal, 2002) of a cortisol induced retrieval impairment as well as the Lupien model of a circadian cortisol effect (Lupien and McEwen, 1997) could both be supported with this meta- analysis.

Due to the small number of studies several additional interesting questions could not be answered. For example the studies which gave cortisol before encoding differed substantially in the used retention delay (ranging from minutes to days). Corresponding to the delay cortisol levels in some studies were still elevated at times of retrieval (e.g. (Kirschbaum et al., 1996)), while they were not elevated anymore in studies using a delay of hours to days (e.g. (Buchanan and Lovallo, 2001)). At a descriptive level those studies in which cortisol was not

elevated anymore at the time of retrieval testing reported on average beneficial effects on memory, which would be in support of the Roozendaal model.

Stress and memory retrieval

So far it can be concluded that pharmacologically induced cortisol elevations, often in the upper physiological range impairs memory retrieval in humans. What had not been successfully demonstrated was a stress induced retrieval deficit in humans. In some previous studies (see above) the delay between encoding and retrieval was not long enough to exclude possible effects of post encoding stress on consolidation (Lupien et al., 1997; Wolf et al., 1999). Two additional studies on this topic were plagued by poor retrieval performance (possible floor effect (Domes et al., 2004; Wolf et al., 2002c)).

In our stress and retrieval experiment (Kuhlmann et al., 2005b) subjects learned a word list on the first day. At the second day they were either stressed or exposed to a control condition a few minutes prior to delayed free retrieval testing. After stress exposure subjects were significantly less able to retrieve words from the previously learned list (Kuhlmann et al., 2005b). Thus in line with stress experiments in rodents and pharmacological experiments the data supported the notion that psychosocial stress induced cortisol elevations block memory retrieval. Since our original publication the finding of a stress reduced retrieval deficit has been replicated by several groups (Buchanan et al., 2006; Buchanan and Tranel, 2008; Smeets et al., 2008; Tollenaar et al., 2008), even though not unequivocally (Beckner et al., 2006).

Stress, cortisol and memory retrieval: Are the effects modulated by the arousal or valence of the learning material?

The previous studies had shown that cortisol or stress treatment in humans leads to poorer memory retrieval. This is the case for studies employing traditional declarative memory tasks (de Quervain et al., 2000; Wolf et al., 2001) as well as for studies using autobiographical memory tasks (Buss et al., 2004). What had not been addressed systematically was the question of a potential influence of arousal or valence of the learning material on this effect. This issue can be easily studied in humans by varying the emotionality of the used stimuli (words, pictures, movies etc.). Previous word list studies either had used neutral material (e.g. items from a shopping list (Wolf et al., 2001)) or had used words which were not further analyzed with respect to this issue (de Quervain et al., 2000).

Given that emotional arousal enhances memory consolidation and that emotional arousal appears to interact with some effects of stress or cortisol on memory (e.g. (Buchanan and Lovullo, 2001; Cahill et al., 2003; Jelicic et al., 2004; Smeets et al., 2006)) this was the logical next question to be addressed.

In an initial experiment we tested the effects of cortisol on the retrieval of neutral and negative words. Similar to the previous cortisol retrieval studies mentioned above we again were able to show that cortisol impaired delayed free memory retrieval. Most interestingly cortisol significantly impaired retrieval of negative words; while in contrast it had only a minor effect on neutral words (see Figure 3a). Thus the effects of cortisol on memory retrieval were stronger for negative material. This finding was in line with the idea of a critical involvement of the amygdala and its interaction with the hippocampus in mediating the impairing effect of cortisol on retrieval (Roosendaal et al., 2003;Roosendaal et al., 2004). It argued against the interpretation of a mood congruent effect of the cortisol manipulation and also against the idea that the better consolidated emotional words are less susceptible to effects of cortisol on their retrieval.

In our second study on this topic we wanted to test whether similar effects would occur after exposure to psychosocial stress. In addition we wanted to find out if the emotional arousal (low or high) or the emotional valence (positive to negative) is the crucial factor influencing the effects of stress on retrieval (Kuhlmann et al., 2005b). To this aim participants were exposed to stress and afterwards had to retrieve a previously learned word list. This time the list contained negative, neutral and positive words. Negative and positive words are both emotional arousing, but of course are substantially different in their valence. The results indicated that stress impaired retrieval and that the effect occurred for positive as well as for negative words (Kuhlmann et al., 2005b). Results are displayed in Figure 3b. Thus emotional arousal rather than valence seems to be important in determining which items are influenced by stress.

Insert Figure 3a and 3b about here

In sum stress (Kuhlmann et al., 2005b) as well as cortisol treatment (Kuhlmann et al., 2005a) impaired memory retrieval and this effect was especially pronounced for emotional arousing material independent of its valence. Since the original publication of these findings three years ago several studies from other laboratories have replicated this finding. In at least three stress studies (Buchanan et al., 2006;Smeets et al., 2008;Tollenaar et al., 2008) and one cortisol study (de Quervain et al., 2007) the impairing effects on retrieval were more pronounced for emotional arousing material compared to neutral material.

The testing situation as another source of arousal

In addition to the influence of the arousal induced by different learning stimuli the specifics of the test situation might also vary in the amount of arousal it induces. This potentially important issue has been largely neglected in animal and human research alike and it is

plausible that substantial differences between the labs exist. In rodents the used tasks are often arousing/stressful (e.g. the water maze) and even in less stressful tasks (e.g. regular maze tasks) the situation is initially novel to the animal, which also induces arousal. In humans in contrast during pharmacological studies it is often attempted to relax the subjects as much as possible, however the impact of different test situations is rarely investigated and most often the specific test situation is not described. Okuda and coworkers had demonstrated in rats, that a habituation to the testing environment abolished the effects of glucocorticoids on several aspects of object recognition (Okuda et al., 2004). Thus while rats for whom the testing environment was novel and arousing showed the expected effects of GC injections, memory of the habituated rats was not influenced by the steroid. In order to investigate the influence of the testing environment on the effects of glucocorticoids on memory retrieval in humans we performed an experiment in which the design was identical to two previous studies from our laboratory (Kuhlmann et al., 2005a; Kuhlmann and Wolf, 2005). Again subjects learned a word list in the morning and retrieval was tested in the afternoon. In a double blind crossover design participants received cortisol or placebo orally. In this study however we modified the testing condition in order to assure a relaxed testing situation (Kuhlmann and Wolf, 2006a). Subjects spend waiting period between cortisol or placebo ingestion and delayed retrieval testing in the office of the experimenter, who at times chatted with the participants. The upcoming retrieval testing was not announced in advance and the participants had not to change their positions for the upcoming retrieval test. In contrast during the typical more formal procedure participants had to wait in a different room or in the hallway and were called upon for the retrieval testing, which took place in a testing room to whom the tester and the participants walked together. Analysis of the data revealed that under the relaxed testing condition no effect of cortisol on memory retrieval was apparent. This was in contrast to the two previous studies which had observed effects of cortisol on retrieval. Thus in line with the data obtained in rats our study illustrated that the effects of cortisol on memory retrieval require at least a moderate amount of testing induced arousal (Kuhlmann and Wolf, 2006a). This observation is of relevance for all scientists working in this field since it shows that a too relaxed testing atmosphere will prevent the detection of cortisol effects on memory in humans. A possible lack of testing induced arousal might also underlie some of the non-significant effects of cortisol on memory reported in the past (see (Het et al., 2005).

Cortisol and memory retrieval: A look in the human brain

As summarized above stress or cortisol treatment leads to impaired (free) memory retrieval. While this has been shown repeatedly at the behavioral level the neuronal correlates of this effect had not been studied sufficiently. A previous resting glucose positron emission tomography (PET) study had reported that cortisol reduced glucose uptake in the

hippocampus (de Leon et al., 1997). Another study investigated the effects of cortisone treatment on retrieval associated activations using $H_2^{15}O$ PET (a method allowing characterizing regional cerebral blood flow). Cortisone led to a reduction in cued recall, an effect associated with blood flow reduction in the posterior right medial temporal lobe (de Quervain et al., 2003).

At that time functional magnetic resonance imaging (fMRI) studies on this topic were missing. fMRI has the advantage of a superior temporal and spatial resolution compared to PET. In collaboration with colleagues from the Netherland we conducted a study in which the effects of cortisol on memory retrieval were tested (Oei et al., 2007). Participants learned a word list outside the scanner and recognition was tested inside the scanner, once after placebo and once after cortisol treatment (double blind crossover design). The experimental protocol was highly similar to a previous study of mine, which had shown negative effects of cortisol on memory retrieval (Wolf et al., 2001). Cortisol treatment led to a reduced activation in both hippocampi during memory retrieval (see Figure 4). In addition decreased activations were observed in the prefrontal cortex. This first fMRI study on cortisol and memory retrieval was in line with previous PET studies (de Leon et al., 1997; de Quervain, 2006) and rodent studies using site specific injections (Roozendaal et al., 2003). Together these experiments strongly suggest that cortisol influences the hippocampus in a way which leads to a less successful retrieval of previously learned information.

Insert Figure 4 about here

Stress, cortisol and retrieval: An interim summary

So far it can be concluded that studies by us and others have established that a stress or pharmaco- induced cortisol increase causes a memory retrieval deficit. This is often especially pronounced for arousing material, independent of its valence. Moreover at least in pharmacological studies a certain testing induced arousal appears to be a pre-requisite for the occurrence of cortisol effects on memory. A neuronal correlate of the cortisol induced retrieval impairment is a reduced activity of the hippocampus.

Effects of cortisol and memory retrieval: What for?

As mentioned previously it might appear surprising that the stress response, which has been evolved to facilitate successful coping is associated with impaired memory retrieval. And this issue has been debated ever since the first publication of this phenomenon (De Kloet et al., 1999). Several explanations appear plausible.

For example it could be beneficial when in the case of an acute threat negative memories of previous threat related events are blocked in order to prevent a negative emotional overshoot

(Het and Wolf, 2007; Soravia et al., 2006). This might allow a focused analysis of the current situation without distracting emotional intrusions.

Alternatively it has been suggested that a temporary retrieval blockade allows the brain to encode or consolidate the important aspects of the stressful situation more efficiently (Roosendaal, 2002), and see below). There is evidence that retrieval interferes with encoding (e.g. (Allan and Allen, 2005)). Thus a stress induced retrieval blockade might provide the background for an enhanced encoding and consolidation of the stressful episode itself. This beneficial effect of stress hormones on memory consolidation is addressed in the next part of this paper.

Stress, cortisol and memory consolidation

So far this review has focused mostly on disruptive effects of stress on memory. However as already stated repeatedly stress of course does not always impair memory. In fact the acute stress response has evolved in order to facilitate adaptation (De Kloet et al., 2005; McEwen, 1998) and thus it would make little sense from an evolutionary standpoint if stress would impair memory. In line with these theoretical arguments a vast literature primarily based on rodent studies has illustrated that glucocorticoids enhance memory consolidation, especially when they are released in response to a stressful learning episode (see for current reviews (Diamond et al., 2007; Joels et al., 2006; Roosendaal, 2000)).

Despite the impressive amount of animal studies documenting a facilitating effect of glucocorticoids on memory (consolidation) evidence in humans had been scarce.

Buchanan and Lovallo were the first to report that cortisol treatment before the (incidental) encoding of pictures of different emotionality resulted in an enhanced memory for emotional arousing pictures independent of their valence (Buchanan and Lovallo, 2001). In a related study post learning stress enhanced memory for arousing slides but not for neutral slides (Cahill et al., 2003). The use of a post learning manipulation in the latter study excluded the possibility that the observed effects were caused by an influence of stress on the initial encoding of the learning material. Together both studies suggested that cortisol enhanced emotional memory consolidation while having little effect on neutral memory consolidation. However in some studies glucocorticoids were associated with enhanced memory consolidation independent of the arousal of the learning material (Abercrombie et al., 2003; Maheu et al., 2004) or were associated with poorer consolidation (Rimmele et al., 2003).

In our own experiment in the area of cortisol and memory encoding/ memory consolidation (Kuhlmann and Wolf, 2006b) we administered cortisol prior to the encoding of emotional

(positive, neutral and negative) pictures. Free recall was tested twice, once immediately after encoding and once 24 hours later. Using this design we could differentiate effects of the hormone on initial encoding or short term storage from the effects of cortisol on memory consolidation. Results showed as expected that arousing pictures (independent of their valence) were better remembered than neutral ones. The cortisol and placebo groups did not differ in the immediate recall test. However when memory retrieval was tested again 24 hours later a different picture emerged. Participants from the cortisol group remembered more emotional pictures but fewer neutral pictures than participants from the placebo treated control group (Kuhlmann and Wolf, 2006b). Results are shown in Figure 5. Thus cortisol enhanced the facilitating effect of emotional arousal on memory consolidation. This observation fitted well to findings obtained in rodents indicating that glucocorticoids interact with arousal induced noradrenergic activation in the basolateral amygdala leading to an enhanced memory consolidation in the hippocampus (Roosendaal et al., 2006a). Several recent stress studies are also in agreement with our findings. Here stress lead to an enhancement of memory for emotional items while impairing memory for neutral items (Payne et al., 2006; Payne et al., 2007; Smeets et al., 2006). Together these studies suggest that the stress associated release of GCs leads to a prioritized storage of emotional information into long term memory.

Insert Figure 5 about here

The situation might be different if stress is administered post learning. In line with earlier studies (Cahill et al., 2003) we recently were able to show that stress immediately after learning selectively enhanced the consolidation of emotional material, while having no effects on neutral material (Smeets et al., 2008). However in other studies post learning stress also had beneficial effects on rather neutral material (Andreano and Cahill, 2006; Beckner et al., 2006), which would fit to the pharmacological studies from Lupien and coworkers (Maheu et al., 2004).

Taken together, while most human studies support the notion that stress or cortisol enhances memory consolidation, the specificity of the effects for arousing material is less consistent. It appears likely that additional modulators (e.g. the arousal induced by the test situation, the specifics of the memory test, and the intensity of the stressor) are responsible for this still somewhat heterogeneous picture.

Cortisol and emotional memory consolidation: A look in the brain

Similarly to our efforts to localize the effects of cortisol on retrieval (see above) we were also interested in localizing the effects on memory encoding/consolidation by using fMRI during

memory encoding. In collaborations with colleagues from the Netherland salivary cortisol levels were collected from subjects participating in a study on the effects of emotional arousal on memory (van Stegeren et al., 2006). Participants viewed pictures belonging to four different arousal categories (low to extreme). Before and after image acquisition participants collected saliva and the mean cortisol level was used for future analysis. Using a median split participants were post hoc divided into a low and a high endogenous cortisol group. A hypothesis driven region of interest analysis revealed that the group with higher cortisol levels reacted with a more pronounced amygdala response to the emotional pictures (see Figure 6; (van Stegeren et al., 2006;van Stegeren et al., 2007)). This study demonstrated for the first time in vivo in the human that emotional arousal and cortisol interact in modulating activity of the amygdala. Again the findings were well in line with previous experimental work in rodents (Roozendaal et al., 2006a).

Insert Figure 6 about here

Stress, cortisol and memory consolidation: An Interim summary

In contrast to the studies reviewed at the beginning, which illustrated that stress or cortisol treatment lead to poorer memory retrieval the last paragraphs have shown that the same neuroendocrine messenger enhances memory consolidation. This effect is again often stronger for emotional arousing material and sometimes occurs at the cost of neutral material. The neuronal correlates of these behavioral effects are a cortisol associated enhancement of amygdala activity during the encoding of emotional material.

Are these experimental findings of relevance for conditions of chronic GC treatment, aging or psychiatric disorders?

The reader might wonder whether the acute effects of cortisol on declarative memory are of relevance for the understanding of more chronic conditions like glucocorticoid therapy, age associated HPA hyperactivity or psychiatric disorders. It is suggested that this is the case and brief examples are outlined below.

First it has to be emphasized that a clear separation between acute and chronic effects is often difficult. For example patients receiving GC therapy often show signs of memory impairments (Brown et al., 2004;Wolkowitz et al., 2004). It appears intuitively plausible to suspect that these deficits are the result of the chronic GC exposure, which in laboratory animals causes neuronal atrophy and reduced neurogenesis in the hippocampus (Fuchs et al., 2006;McEwen, 2005). However in a collaborative study (Coluccia et al., 2008) with

colleagues from Switzerland it could be shown that a single day without the daily GC dose leads to memory retrieval comparable to those of a well matched control group. No evidence for a chronic impairment was found in this study and also no signs of structural alterations (atrophy) of the hippocampus. Thus some of the memory impairing effects in those patients reflect acute and not of chronic effects (Coluccia et al., 2008).

This recent finding might also be of relevance for understanding the relationship between cortisol levels and memory in older subjects. In the past the observed associations between higher cortisol levels and poorer memory (Lee et al., 2007; Li et al., 2006; Lupien et al., 1998; Seeman et al., 1997; Wolf et al., 2002b) have been often interpreted as reflecting chronic effects of the hormone on the brain, possibly reflecting structural alterations in the hippocampus due to chronic GC overexposure. In line with these findings were studies observing associations between cortisol levels and hippocampal volumes in older subjects (Lupien et al., 1998; Wolf et al., 2002a), but those findings could not always be replicated (MacLulich et al., 2005). The recent results with GC therapy patients (Coluccia et al., 2008) suggest that some of the associations observed in older subjects might 'just' reflect acute effects of cortisol on memory retrieval. In fact in some studies GC levels were assessed around the time of the cognitive testing (Lee et al., 2007) thus making a separation between acute and chronic effects impossible. A memory test in a university setting might be more stressful for older participants, and therefore older subjects might be acutely more affected by elevated cortisol levels at the time of testing (see for a more elaborated review on this topic: Lupien et al., 2007). Thus future research in this area faces the challenge to separate acute from chronic effects more carefully.

Finally the results on acute effects on declarative memory are also of relevance for psychiatric disorders (see for a longer review on this topic: (Wolf, 2008). For example in patients with post traumatic stress disorders (PTSD) flashbacks are one of the key symptoms (Wolf, 2008). The frequent observation that these patients have lower basal cortisol levels (Yehuda, 2002) might be one factor responsible for this involuntarily retrieval of highly emotional memories, since cortisol blocks emotional memory retrieval in healthy subjects. In fact a first pilot study reported that low dose cortisol treatment improved PTSD symptoms (Aerni et al., 2004). In addition initial evidence exists that cortisol treatment might also be able to prevent the occurrence of PTSD symptoms in intensive care unit patients (Schelling et al., 2004). This example illustrates that the experimental findings outlined in this review can lead to a better understanding and a more targeted treatment of psychiatric disorders characterized by emotional memory disturbances.

Summary and outlook

To summarize, the present overview has summarized our advanced understanding on how stress hormones acutely influence declarative/episodic memory in humans. In a series of experiments it could be demonstrated that stress or cortisol treatment acutely leads to reduced memory retrieval efficiency. This might constitute a problem during exams (Schoofs et al., 2008a) or during testimonies. The cortisol induced retrieval blockade is especially strong for emotional laden information apparently independent of its valence. A neuronal correlate of this is a reduced activity of the hippocampus during memory retrieval. In contrast stress or cortisol beneficially impacts on emotional memory consolidation, possibly at the cost of the storage of neutral information. Here an enhanced amygdala response during the encoding of emotional material could be the underlying mechanism. While these effects have been obtained in laboratory studies with young subjects the findings are of relevance for our understanding of chronic conditions, the aging process and psychiatric disorders (Wolf, 2006; Wolf, 2007; Wolf, 2008).

The current review has exclusively focused on the effects of stress on long-term episodic memory. By doing so important effects of stress on other types of learning and memory have been neglected. For example a growing literature suggests that stress influences working memory, which relies on the prefrontal cortex (Lupien et al., 1999; Oei et al., 2006; Schoofs et al., 2008b). How these effects interact with stress effects in the medial temporal lobe is poorly understood. In addition it is unknown if the effects of stress on the PFC are also mediated by emotional arousal of the learning material.

Another exciting line of recent research indicates that stress not only influences memory in a quantitative fashion (better or worse) but also in a qualitative fashion (involvement of different memory systems). In humans and rodents stress was associated with a decrease use of cognitive (hippocampal based) strategies but an increase use of caudate based stimulus response strategies (Kim et al., 2001; Schwabe et al., 2007; Schwabe et al., 2008).

Other topics for future research include a stronger focus on interindividual differences and sex differences (Wolf, 2008) as well as an increased effort to investigate and conceptualize dose response relationships of cortisol on human memory similar to recent advances in this area in rodents (Conrad, 2005; Sandi and Pinelo-Nava, 2007). Thus a lot of work is still ahead of the scientific community but given the dynamic of this highly interdisciplinary field a continuous rapid progress can be expected.

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Figure Legends

Figure 1a : Association between stress induced cortisol levels and memory. Figure 1b Effects of cortisol treatment on declarative and non-declarative memory. Reprinted from Kirschbaum et al. (1996) with permission from Elsevier.

Figure 2: Effects of cortisol on delayed memory retrieval. Retrieval was impaired in young as well as old subjects. Reprinted from Wolf et al. (2001) with permission from the American Psychological Association (APA).

Figure 3a. Effects of cortisol administration on retrieval of negative and neutral words. Cortisol only significantly impaired retrieval of negative words. Reprinted from Kuhlmann et al. (2005a) with permission from Elsevier.

Figure 3b. Effects of stress on retrieval of positive, neutral, and negative words. Stress impaired the retrieval of positive as well as negative words (combined into arousing words) but had no effect on neutral words. Reprinted from Kuhlmann et al. (2005b) with permission from the Society for Neurosciences.

Figure 4. Coronal slices showing the effects of cortisol on hippocampal activity during memory retrieval. Cortisol reduced activation as compared to placebo in the left and right hippocampus.

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Figure 5. Effects of cortisol on immediate and 24 hour delayed memory of neutral and arousing slides. While cortisol had no influence on immediate recall it influenced memory consolidation leading to an enhanced memory for emotionally arousing slides, at the cost of memory for neutral slides. Reprinted from Kuhlmann and Wolf (2006) with permission from the American Psychological Association (APA).

Figure 6. Interaction between endogenous cortisol levels and amygdala response to emotional pictures. The emotional slides varied according to their emotional arousal between 1 (low) and 4 (extreme). Coronal (top panels) and axial (bottom panels) sections at the level of the amygdala for contrasts of CAT2, 3 and 4 with the neutral CAT1 pictures.

Participants with higher cortisol levels (Cort_High) showed for all three contrasts stronger amygdala activation in response to the emotional slides as compared to participants with low cortisol levels (Cort_Low).

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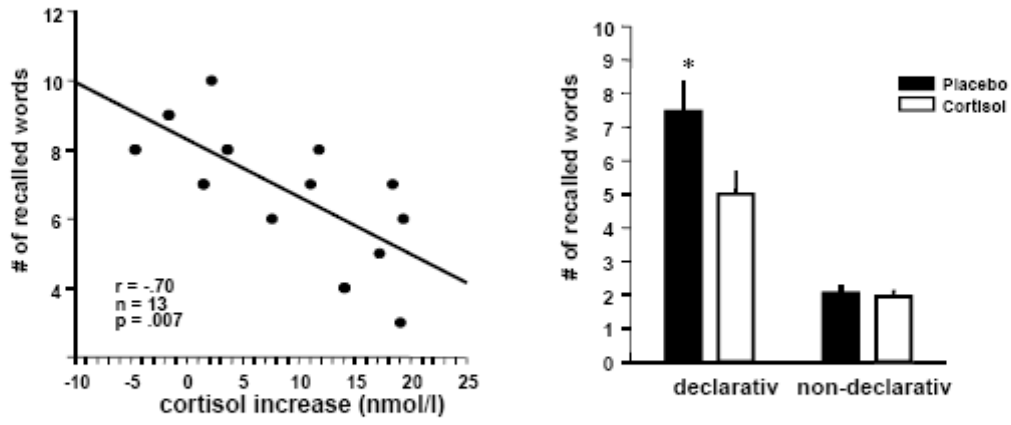


Figure 1a & 1b

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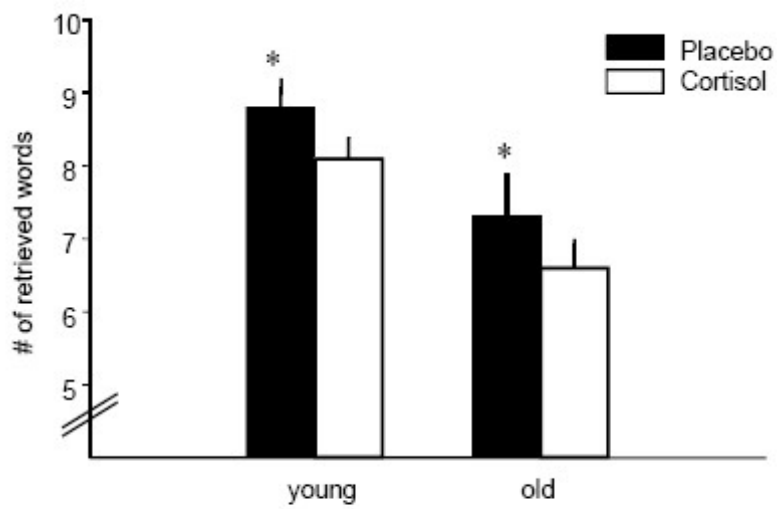


Figure 2

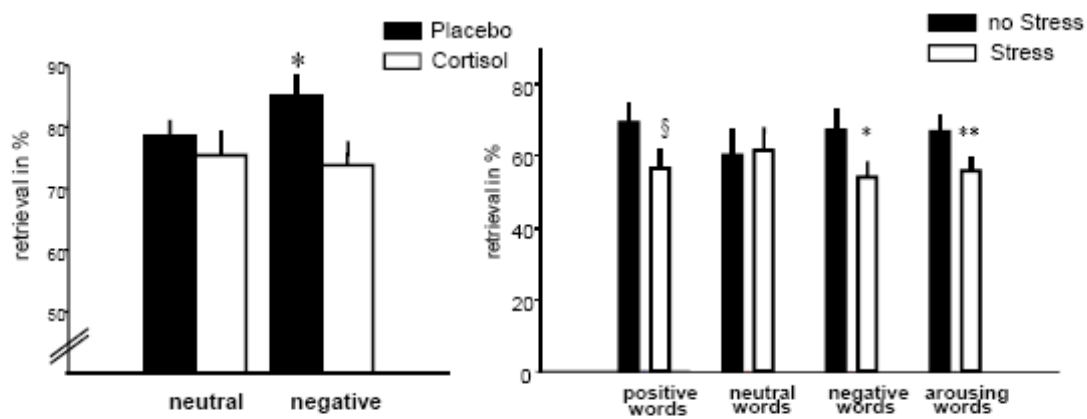
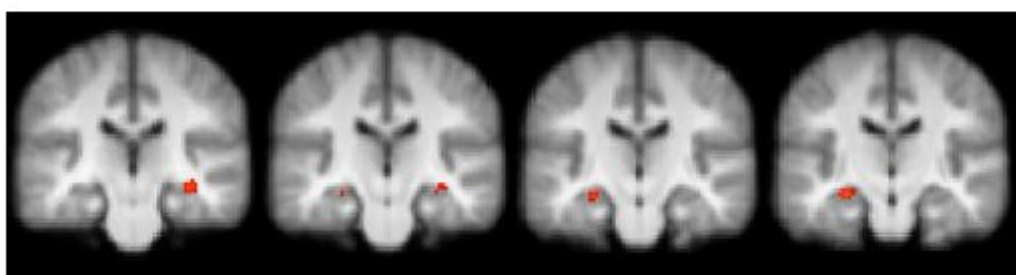


Figure 3a & 3b

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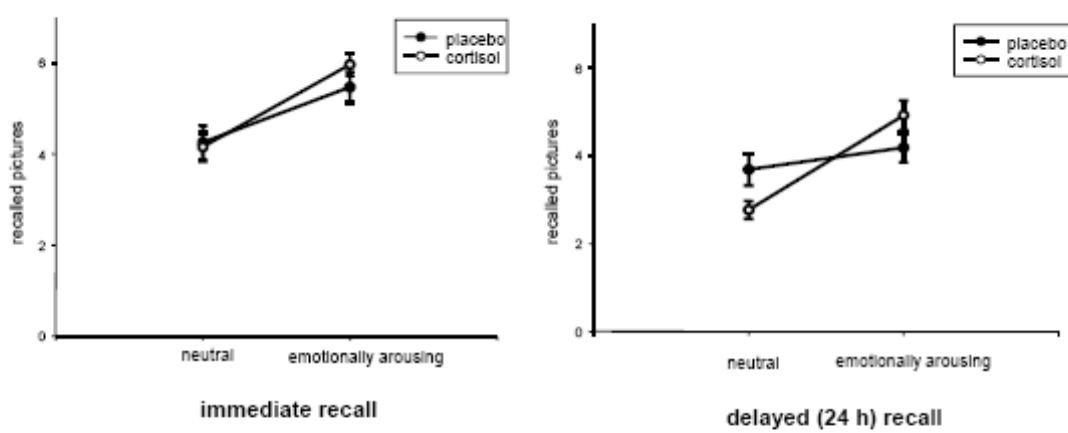
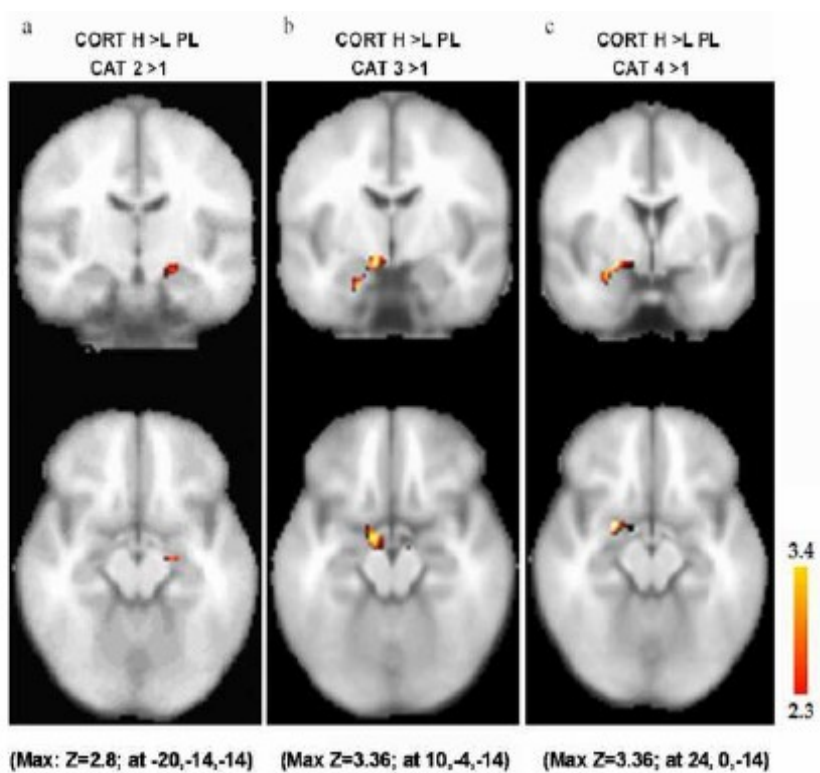


Figure 5



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