Fading memories : the impact of stress hormones on the retrieval of emotional memories

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Chapter 3

Long-term outcomes of memory retrieval under stress

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Summary

Previous studies have found impairing effects of stress hormones on memory retrieval. So far, it is unknown whether these impairments are temporary, persistent throughout time, or whether the strength of the memory trace changes after retrieval because of the effects of stress hormones on memory processes during retrieval. In the present study, delayed cued recall (6 months after initial learning) was compared between male participants who had retrieved previously learned word pairs during stress or a control condition. Retrieval (with / without stress) had taken place either 1 day or 5 weeks after initial encoding. The group that had retrieved words under stress 5 weeks after encoding performed worse on long-term recall than the comparable control group. However, when words were retrieved under stress 1 day after encoding, no long-term effect was found, although performance at 6 months with relation to performance under stress was slightly increased compared to the control group. These results support previous findings in animals that stress may affect memory during reactivation. It further suggests that time intervals between encoding and reactivation may play an important role.

Introduction

Previous studies have found impairing effects of (stress related) elevated cortisol levels on memory retrieval in humans (de Quervain, Roozendaal et al., 2000; Kuhlmann, Piel et al., 2005; for a review see: Het et al., 2005). This impairing effect is mainly found for emotionally arousing memories or under arousing conditions (Buchanan, Tranel et al., 2006; Kuhlmann, Kirschbaum et al., 2005; Kuhlmann & Wolf, 2006b; Tollenaar et al, 2008a / Chapter 2). Two studies suggest that the effects of cortisol may be mediated by reduced medial temporal lobe (MTL) activation during retrieval (de Quervain, et al., 2003; Oei, et al., 2007). The impairing effects of cortisol on memory retrieval contrast with the enhancing effects of cortisol on memory consolidation (Andreano & Cahill, 2006; Buchanan & Lovallo, 2001; Cahill, et al., 2003; Kuhlmann & Wolf, 2006a).

The long-term consequences of memory impairments due to cortisol have never been studied before in humans. Therefore, it is unknown whether these impairments during retrieval are temporary or may lead to permanent changes in the memory trace. Longer lasting changes might be related to diminished rehearsal and hence re-encoding under the influence of cortisol, thereby weakening the strength of the memory traces that have not been retrieved. Another possibility is that memory traces are affected by stress during reactivation. Animal studies have shown that certain drugs can affect memory (i.e., a conditioned fear response in most studies) even after its reactivation. Previously consolidated memories seem to become labile again during reactivation and hence susceptible to impairment or facilitation for a distinct time period, a process often referred to as reconsolidation (e.g. Debiec et al., 2006; Nader et al., 2000; Przybyslawski & Sara, 1997). A study by Tronel and Alberini (2007) has recently shown that reconsolidation might de dependent on the glucocorticoid system, as they found that a glucocorticoid receptor antagonist can disrupt conditioned fear in rats after reactivation of an inhibitory avoidance memory. In line with that, Maroun and Akirav (2007) have found an impairing effect of stress on reconsolidation in rats, which was reversed by a glucocorticoid receptor antagonist. Both increases and decreases in basal cortisol levels thus seem to affect the process of reconsolidation. In the last years, several studies have shown that human procedural and declarative memories become labile after reactivation too (Forgato et al., 2007; Gallucio 2005; Hupbach et al., 2007; Walker et al., 2003). It is thus possible that increases in cortisol levels during reactivation of declarative memories might affect reconsolidation, and hence long-term recall, in humans.

If the strength of memories that have been encoded and consolidated long before can be influenced by stress hormones, this might have important clinical implications. The treatment of psychiatric disorders that are related to memory, like post-traumatic stress disorder (PTSD), could potentially be aided by drugs that can influence the strength of (traumatic) memories. Some clinical studies are consistent with the idea that stress hormones can affect the strength of traumatic memories after consolidation has taken place (Aerni et al., 2004; Weis et al., 2006). For example, in the study by Aerni et al., chronic PTSD patients who suffered from emotional flashbacks and nightmares were administered a low dose of cortisol for a month. All three patients in the study showed reduced symptoms of re-experiencing and intensity

of the traumatic memories compared to placebo. The authors argue that this effect could be due to the inhibiting effect of cortisol on excessive retrieval of traumatic memories. However, memory for the traumatic events itself was not explicitly assessed. Furthermore, in the study by Weis et al., memories for experienced traumatic events were not reduced after cortisol administration, despite reduced chronic stress symptoms in subjects. Hence, it remains to be investigated whether a reduction in PTSD symptoms is indeed mediated by a blocking effect of cortisol on emotional memory. Even though traumatic memories as present in PTSD patients don't compare with the (relatively mild) emotional stimuli used in many laboratory studies, understanding the basic mechanisms through which cortisol can affect the strength of emotional memories will be very helpful in directing further research on improving the treatment of these disorders.

To our knowledge, no study has yet reported whether increases in cortisol levels during reactivation of emotional memories have long-term effects on human memory. The present paper describes the 6 month follow-up to a study in which the effects of psychosocial stress exposure, and subsequent endogenous cortisol increases, on retrieval of previously encoded material was examined (see Tollenaar et al., 2008a / Chapter 2). Performance at follow-up was related both to initial encoding and to retrieval performance during stress to test whether impairments that were found on memory retrieval were not only temporary or permanent, but were potentially even further increased.

Methods

Participants

In the original study, which was approved by the ethics committee of the Leiden University Medical Center (LUMC), all 70 participants had agreed they could be contacted again for future research. For the follow-up, all participants were contacted again by the experimenter (M.S.T.) via a surprise telephone interview. In this interview, participants were first asked if they were willing to be questioned for 10 min. All subjects who were reached agreed. Sixty-five out of the 70 male students who had participated in the original study were included in the follow-up (five students could not be reached by phone or email). Thirty-one of them had the second session 1 day after initial learning (of whom 15 were in the control and 16 in the stress condition, missing four people in the stress condition) and 34 had the second session 5 weeks after learning (of whom 14 were in the control and 20 in the stress condition, missing one person in the control condition) (see Figure 3.1 for an overview of the test sessions). All participants were free of any medications and physical or psychological problems at the time of encoding and all sessions had taken place after 11.30 am to ensure low baseline cortisol levels in all participants.

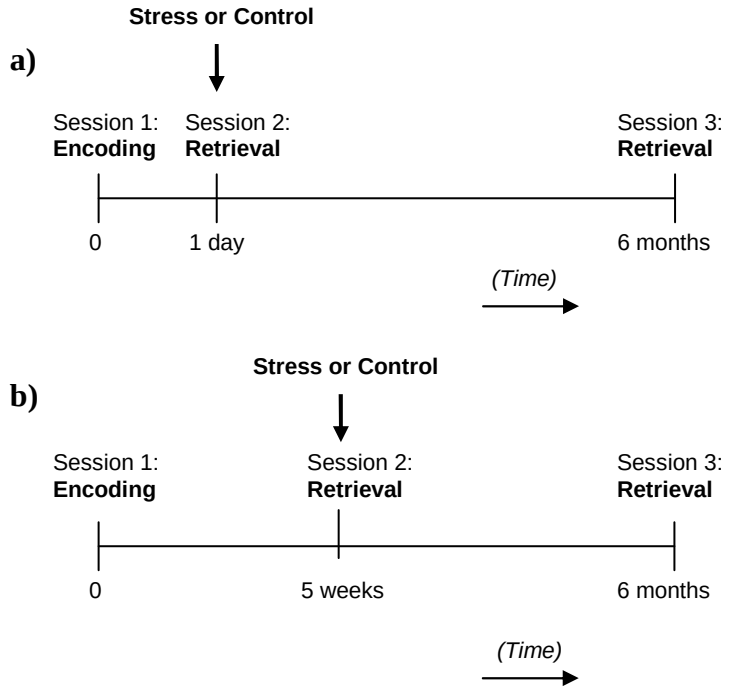

Figure 3.1. An overview of the testing sessions and retrieval tasks is presented (a) in the groups for whom the second session took place 1 day after encoding and (b) in the groups for whom the second session took place 5 weeks after encoding. On the first session, neutral and negative word pairs were encoded. On the second session, participants were exposed to either a stress or a control task after which retrieval of the word pairs was tested with a cued recall task. On the third session, retrieval was tested again with the cued recall task.

Memory task

A cued recall task was used, in which participants had to recall words that were coupled with cue words on the first day of the study, 6 months before the follow-up telephone interview. These words were the second, personal, associates to the cue words. On the first testing day participants were randomly given a list of 40 cue words, consisting of 20 neutral (e.g. “row”) and 20 negative (emotion) words (e.g. “cry”), similar in word length and frequency. Participants were asked to generate 2 associations to each word while having a clear image in mind of those associations (e.g. a participant named the words “sport” and then “water” in response to the cue word “row”). After this was done for all words, the experimenter coupled the cue words with the second association words that participants had generated, forming word pairs (i.e. “row” and “water”). The cue word was coupled to the second word association to reduce mere implicit associative recall. The word pairs were read aloud twice and recalled twice to complete initial learning. There was no mention that recall would be tested again on the subsequent session. Either 1 day or 5 weeks after initial encoding of the memorized material, cued recall was tested, as well as 6 months later. During the second session, retrieval was tested under either a stress or a control condition. No feedback was given on any of the retrieval occasions.

Psychological stress protocol

Psychosocial stress was induced using the Trier Social Stress Task, which is well known for inducing hypothalamic-pituitary-adrenal (HPA) axis responses, and hence cortisol increases (Kirschbaum et al., 1993). Cortisol was significantly elevated in the stress groups compared to the control groups after the start of the stress task (interaction of group by time; $F(2, 118) = 27.8$, $p < .001$). The cortisol responses between the groups that came back after 1 day or 5 weeks did not differ ($F(2, 54) = 1.76$, $p = .19$). The average increase from baseline ($M = 8.37$, $SE = 0.59$) until 25 min after onset of the stressor ($M = 13.86$, $SE = 0.98$) was 79 % (see Figure 3.2).

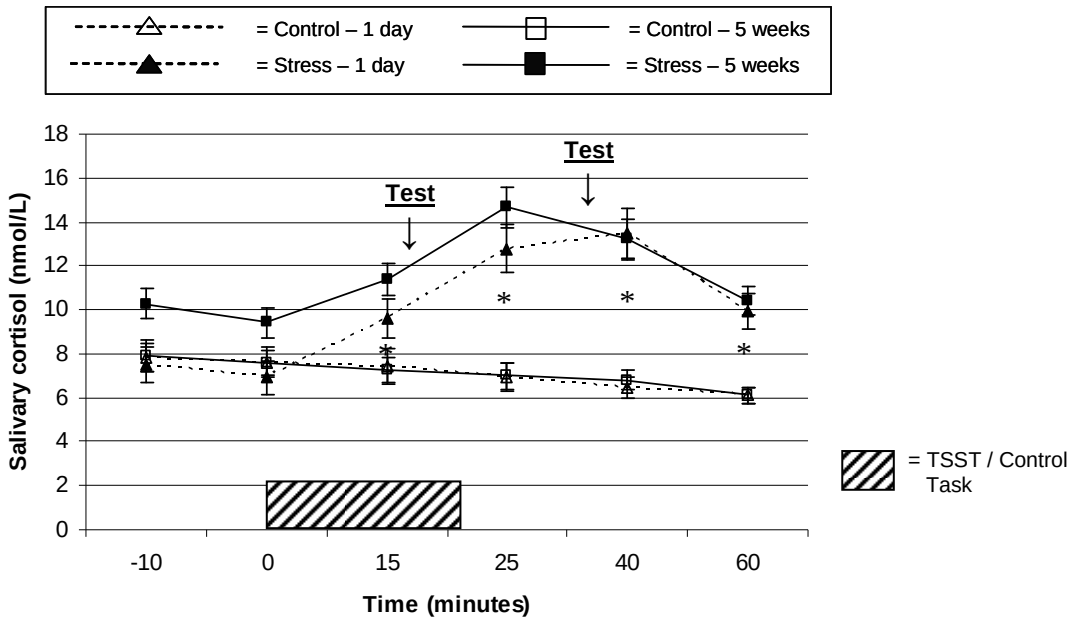

Figure 3.2. Mean (± SEM) free salivary cortisol (nmol/L) before, during, and after the stress or control task in the 2 stress groups and 2 control groups on the second session.

Notes: Test = *Retrieval testing during and after stress or control task; * = significant differences between control and stress conditions at p < 0.01.*

Statistical analyses

Delayed recall at 6 months follow-up (Session 3) was calculated as the percentage correct recall with respect to initial encoding (Session 1) and secondly with respect to retrieval performance 1 day or 5 weeks after encoding (Session 2). Valence of the words (neutral or negative) was treated as a within-subject variable and condition (stress or control) and the time intervals between the first and the second session (1 day or 5 weeks) were treated as between-subject variables in repeated measures ANOVA. In the original study a difference was made between memory retrieval tested *during* the actual stress task and memory retrieval tested *after* the stress task (when cortisol levels were still high), and we therefore added the factor "moment" as another within-subject variable in the above described analyses. Preliminary analyses revealed, however, that the moment factor did not have any significant main or interaction effects in the repeated measures ANOVAs (all *p*s > 0.05) and therefore all

data was collapsed on this factor and further analyses were performed in its absence. Areas under the curve (AUC) were calculated for the increases in cortisol between baseline and the end of the second session, and correlated to memory performance at 6 months in the two groups that received the stress task using Pearson's correlations. Analyses were performed with SPSS 14.0 (SPSS, Chicago, IL). The criterion for statistical significance was $p < 0.05$.

Results

Retrieval performance under stress versus control (on the second session) is described in detail in Tollenaar et al. (2008a) / Chapter 2. In short, retrieval performance 1 day after encoding was only slightly impaired by stress, on both neutral and negative memory. Retrieval performance after 5 weeks was affected by stress, but this effect was only seen in the recall of negative words. There were no effects of moment of testing (during or after the stress task) in the analyses in both groups.

Figure 3.3 shows memory performance at 6 months after encoding, with respect to initial learning, in the groups with the second session after 1 day and after 5 weeks (respectively, Figures 3.3a and b). The repeated measures ANOVA showed no significant main effects of condition ($F(1, 61) = 0.824$, $p = 0.37$) or time interval ($F(1, 61) = 3.09$, $p = 0.08$), but there was a significant condition by time interval interaction ($F(1, 61) = 6.57$, $p < 0.05$).

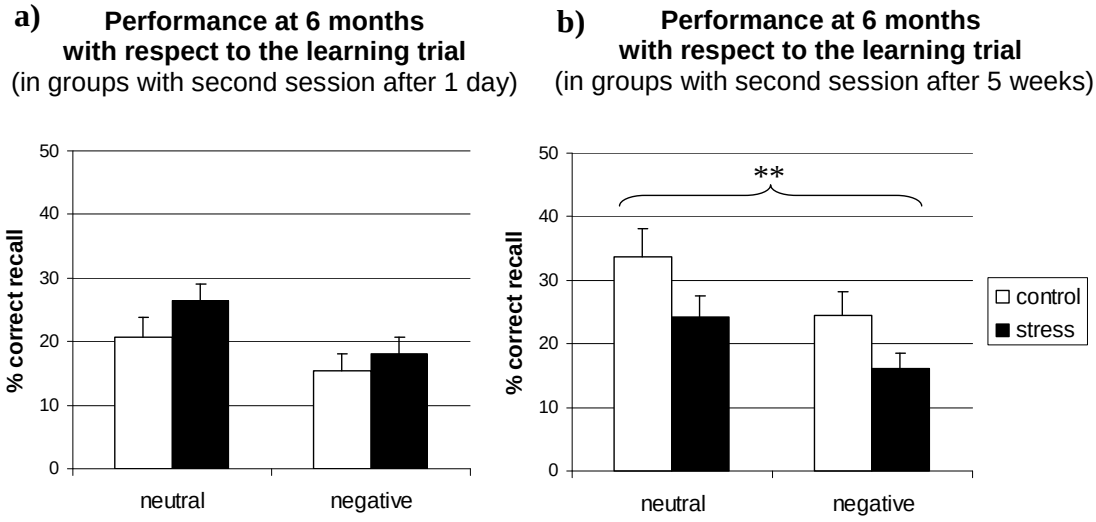

Figure 3.3. Recall of neutral and negative words at 6 months (Session 3), as a percentage of the last learning trial on the encoding day (Session 1) is presented (a) in the groups for whom the second session took place 1 day after encoding and (b) in the groups for whom the second session took place 5 weeks after encoding (for a description of the design, see Figure 3.1).

*Note: ** = significant difference between the stress and control group at p < 0.05.*

Post hoc analyses showed that the group that had recalled words under stress 5 weeks after learning retrieved significantly less of the words at 6 months than the comparable control group ($F(1, 32 = 4.82$, $p < 0.05$) (see Figure 3.3b), whereas the group that retrieved the words under stress 1 day after initial learning did not differ on 6 month recall from the comparable control group ($F(1, 29) = 1.96$, $p = 0.17$) (see Figure 3.3a). In addition, the control group that had its second session after 1 day performed worse at 6 months follow up than the control group that had its second session after 5 weeks ($F(1, 27) = 7.42$, $p < 0.05$), whereas the stress groups did not differ ($F(1, 34) = 041$, $p = 0.53$). Further, there was a main effect of valence ($F(1, 61) = 18.65$, $p < 0.01$), with more neutral words correctly recalled than negative words, but no interaction between condition and valence was found ($F(1, 61) = 0.08$, $p = 0.78$).

To investigate whether a *further* decline had occurred in memory performance after retrieval under stress, performance at 6 months was compared between the stress and control groups with respect to the second session, that is, performance at 6 months was calculated as a percentage of retrieval performance on session 2 (see Figure 3.4).

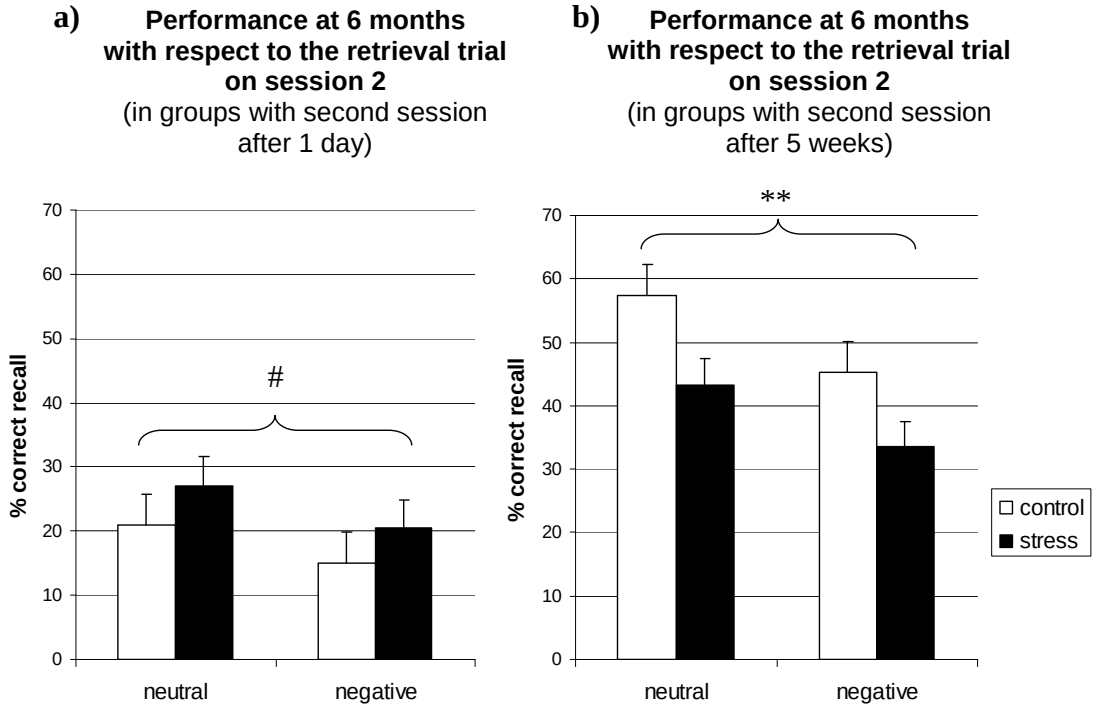

Figure 3.4. Recall of neutral and negative words at 6 months (session 3), as a percentage of the recall trial on the second session is presented (a) in the groups for whom the second session took place 1 day after encoding and (b) in the groups for whom the second session took place 5 weeks after encoding (for a description of the design, see Figure 3.1).

*Notes: The difference in recall percentages between Figure 3.4a and 3.4b is due to the differences in recall on session 2. ** = significant difference between the stress and control group at p < 0.05; # = difference between the stress and control group at p < 0.10.*

The repeated measures ANOVA showed no significant main effect of condition ($F(1, 61) = 1.10$, $p = 0.30$), but there was a significant main effect of time interval ($F(1, 61) = 46.75$, $p < 0.01$) and a significant condition by time interval interaction ($F(1, 61) = 7.07$, $p = 0.01$). Post hoc analyses showed that with the second session after 5 weeks, at 6 months the stress group also remembered significantly fewer words from the second session than the control group ($F(1, 32) = 4.47$, $p < 0.05$), see Figure 3.4b.

However, with the second session after 1 day, at 6 months the stress group tended to remember slightly more words from the second session than the control group ($F(1, 29) = 3.58$, $p = 0.07$), see Figure 3.4a. Since recall performance was calculated as a percentage of the second session, the main effect of time interval could not be interpreted clearly. That is, recall performance on the second session already differed significantly between the groups that came back after 1 day and after 5 weeks ($F(1, 66) = 328.68$, $p < 0.01$). Recall after 5 weeks was lower than recall after 1 day, leading to differences in recall performance at 6 months related to these baseline differences. Again, there was a main effect of valence ($F(1, 61) = 8.85$, $p < 0.01$), with more neutral words correctly recalled than negative words, but no interaction between condition and valence was found ($F(1, 61) = 0.02$, $p = 0.89$).

No significant correlations were found between total cortisol increase during the second session (with the stress task), and neutral or negative memory retrieval at 6 months, although correlations followed the trend with respect to group differences and even tended to be significant for the retrieval of negative words in the group with the second session after 1 day (1 day interval, neutral: $r = 0.28$, $p = 0.34$, negative: $r = 0.48$, $p = 0.08$; 5 week interval, neutral: $r = -0.06$, $p = 0.82$, negative: $r = -0.11$ $p = 0.65$). When performance at 6 months was related to performance on the second session, no significant correlations were found with cortisol increase either (1 day interval, neutral: $r = 0.24$, $p = 0.40$, negative: $r = 0.42$, $p = 0.14$; 5 week interval, neutral: $r = 0.02$, $p = 0.95$, negative: $r = -0.14$ $p = 0.58$).

Discussion

The present study found impairments in memory retrieval up to 6 months after initial encoding, when memories were recalled under stress 5 weeks after encoding. This effect was found for the retrieval of both neutral and negative words. Moreover, memory performance at 6 months was even further impaired with respect to performance under stress. These results thus show that retrieval during stress exposure does affect long-term memory.

The long-term memory impairments after retrieval under stress might partly be due to the fact that participants in the stress group retrieved less words under stress than the control group, leading to differences in amount of rehearsal and hence to differences in re-encoding of the learned material. However, besides impairments in the retrieval of emotional words (which was already present 5 weeks after learning under the influence of stress), after 6 months a further decrease was found in the retrieval of emotional words with respect to retrieval under stress compared to the control group, as well as a decrease in the retrieval of neutral words (which was not present 5 weeks after learning under the influence of stress). Taken together, this

suggests that stress affected memory also during or after reactivation and that more processes are involved than reduced rehearsal. These results are in line with the study by Maroun and Akirav (2007) who found an impairing effect of stress on reconsolidation in rats. A third process that may have been involved in the long-term memory impairments is enhanced extinction (Suzuki et al., 2004; Tronson & Taylor, 2007). Animal research has shown that cortisol can enhance extinction of learned associations after reactivation of the memory trace (Abrari et al., 2008; Cai et al., 2006; Yang et al., 2005). However, the word-pair learning paradigm that was used in the present study does not bear strong resemblance with fear conditioning or extinction, and hence extinction does not seem a very likely explanation for the present findings. Which processes are involved in the present findings can not be concluded from the current design.

No long-term impairing effects on retrieval were found for word pairs that were recalled under stress 1 day after encoding. In contrast, even a slight, borderline significant increase in memory was found for words retrieved under stress 1 day after encoding, associated with a moderate positive correlation between cortisol increase during the stress task and the retrieval of negative words at 6 months. The interval between encoding and reactivation thus seems to play a mediating role in the long-term outcomes of retrieval under stress. However, caution should be taken in interpreting differences between the 1 day and 5 week groups, because stress did not have an equally impairing effect on memory 1 day after learning as it did on memory 5 weeks after learning, potentially leading to the long-term differences. In addition, 1 day after learning, consolidation processes might still have played an important role. As cortisol has been found to increase memory consolidation in humans in some studies (Andreano & Cahill, 2006; Buchanan & Lovallo, 2001; Cahill et al., 2003; Kuhlmann & Wolf, 2006a) this may also partly explain the slightly enhanced long-term recall in the stress condition.

The effects of stress on long-term memory, when subjects were exposed to stress during retrieval 5 weeks after learning, are interesting in the light of two studies in rodents, showing that only recent memories can undergo reconsolidation at the time of memory reactivation (Milekic & Alberini, 2002; Suzuki et al. 2004). Our results suggest that in humans a greater time window for affecting consolidated memories may exist, even though the mechanisms through which these effects are mediated are still unclear. This is promising for clinical practice that would benefit from a long time span to affect well consolidated emotional memories. Furthermore, while Cai et al. (2006) only found effects of cortisol on long-term memory in mice when cortisol was administered during multiple retrieval trials, we found a long-term effect with only a single retrieval trial during stress.

Interestingly, the long-term effects of stress seemed to be equal for both neutral and negative memory. This is in contrast with studies showing that stress affects memory consolidation and retrieval mostly of emotional information (Cahill, et al., 2003; Kuhlmann, Piel, et al., 2005), but an animal study investigating the effects of a beta-blocker on reconsolidation also showed effects on both emotional and non-emotional material (Przybyslawski et al., 1999). It is to be noted that in this study, recall of negative material is lower than recall of neutral material. This contradicts common findings of enhanced recall of emotional material (Cahill, 1999),

and might be explained by the task that was used in this study (i.e., cued recall of negative versus neutral word pairs). Words associated with negative cue words may have been more difficult to keep apart because of a higher semantic cohesion between emotional words (Buchanan, Etzel et al., 2006; Dillon et al., 2006).

With regard to cortisol, we did not find clear results. Although the correlations between cortisol increase during stress and memory performance after 6 months did follow expected trends based on the group differences, the correlations themselves were not very strong (as the group sizes were rather small, power might be an issue). Future research will likely benefit from a greater focus on specific stress hormones through exogenous stress hormone administration in humans. Besides cortisol, (nor)adrenaline may play an important role in reconsolidation as well, as was found in animal studies (Debiec & Ledoux, 2004; Diergaarde et al., 2006; Przybyslawski et al., 1999) and in preliminary experimental studies in humans (e.g. Miller et al., 2004).

Another remarkable result from the present study is the fact that the control group that had its second session after 5 weeks performed significantly better on 6 month recall than the control group that had its second session after 1 day. An explanation could be that the time between the second and third session is shorter in the first group (21 vs. 26 weeks), but it is debatable whether this will have an impact on such a long time span. Another explanation could be that this group benefited from spaced learning (see Greene, 1989), with a longer time span of 5 weeks between the learning and first retrieval session compared to the group with only 1 day between these sessions. Interestingly, stress seems to have abolished the positive effect of delayed retrieval on long-term memory observed in the 5 week group.

Some limitations to the present study should be noted. In the present study, even though cortisol was still increased after the retrieval tasks, the effect of stress on memory retrieval confounds with the effects that stress hormones have *after* retrieval. Therefore, as was discussed above, we can not tell exactly whether the long-term memory effects are due to reconsolidation (or possibly extinction) mechanisms besides a rehearsal effect. To study whether stress hormones can affect memory *after* reactivation, treatments (or stress exposure) should be administered after the act of retrieval itself and should also be compared to a group that receives stress without retrieval to test whether reactivation of memory traces is necessary for the effects of stress hormones on long-term memory. Furthermore, since the group that retrieved words after 1 day responded differently to stress than the group that retrieved words after 5 weeks, comparison between these groups on the long-term is wary. Giving stress *after* memory retrieval could sort out these differences as well. In addition, even if effects of stress hormones are found on memory after reactivation, it still needs to be investigated whether these reconsolidation processes differ from consolidation processes (Walker et al., 2003).

To our knowledge, these results are the first to show that memory retrieval under stress has long-term effects on both neutral and emotional memory in humans. Further research is needed to elucidate the specific stress hormones and cognitive mechanisms that are involved in this process, as well as the specific time windows to affect memory. To this end, future research could benefit from adapting research designs from animal studies on extinction and reconsolidation. Such studies might be of importance to clinical practice, when more evidence indicates that cortisol or beta

blockers may moderate stress and excessive emotional memories (Aerni et al. 2004; Weis et al. 2006), or even reduce phobic fears (Soravia et al., 2006). However, the precise effects and timing of these interventions on memory should be discerned before deciding whether these therapies should become clinical practice.