Cortisol broadens memory of a non-stressful social interaction

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Abstract
Rationale Stress and its associated hormonal cascade are known to enhance long-term memory consolidation. Recently we have shown that central details of a stressful situation (Trier Social Stress Test; TSST) are remembered better than central details of a similar but non-stressful control condition (friendly Trier Social Stress Test; fTSST). We reasoned that since cortisol concentrations increase during stress (TSST) but remain low during the control condition (fTSST), a pharmacological increase in cortisol during the fTSST might be able to mimic the stress effects observed previously.

Objective The objective of the study was to assess the impact of a pharmacologically induced cortisol increase during the non-stressful friendly TSST on long-term memory for details presented during this event.

Methods In a double-blind between-group design, participants (final sample: 20 men and 13 women) either received hydrocortisone (20 mg) or a placebo and were then exposed to a non-stressful social interaction (fTSST). Affect, salivary cortisol, and salivary alpha-amylase (sAA) were assessed before and after the fTSST. Recognition memory for objects presented during this situation was assessed 1 day later.

Results Positive affect and sAA increased in response to the friendly TSST in both groups. Hydrocortisone enhanced memory for peripheral objects of the situation in men but not in women. Memory for central objects was not affected by the hormone.

Conclusions The results suggest that in a non-stressful positive social environment, cortisol induces a broadening rather than a narrowing of memory. In addition, the findings provide preliminary evidence that this effect might be more prominent in men.

Keywords Amygdala · Attention · Consolidation · Cortisol · Emotions · Healthy humans · Hippocampus · Memory · Sex differences · Stress

Introduction

Stress influences learning and memory processes through the activation of the sympathetic nervous system (SNS) and the hypothalamus-pituitary-adrenal (HPA) axis. Activity of these systems triggers several hormonal cascades and eventually releases noradrenaline and cortisol (Ulrich-Lai and Herman 2009). These stress hormones influence the hippocampus and the amygdala, areas involved in emotional memory processes (Joels et al. 2006). Stress can either enhance or reduce memory depending, among other things, on the timing of stress in relation to the learning event (Roozendaal et al. 2006a). Stress during learning and consolidation enhances memory performance, while stress during retrieval reduces memory performance (de Quervain et al. 2009; Roozendaal et al. 2006a; Wolf 2009). Importantly, rodent and human studies revealed that it is the interaction between the noradrenergic system and the glucocorticoid system which influences long-term memory in this phase-dependent fashion (de Quervain et al. 2007; Roozendaal et al. 2006b).

In humans, beneficial effects of post-learning stress have been demonstrated repeatedly (Cahill et al. 2003; Wolf 2009). Similarly, the administration of cortisol before acquisition was associated with enhanced memory consolidation, especially for an emotionally arousing material (Buchanan and Lovallo 2001; Wolf 2009). The effects of pre-acquisition stress in contrast have been more variable with enhancing, impairing, or absent effects reported (Wolf 2009; Zoladz et al. 2011).

Only few experimental studies in adult humans have tested memories of material presented during the stressful episode itself. Smeets et al. observed that words which were related to and used during the stressful task were remembered better (Smeets et al. 2007, 2009). In contrast, Schwabe and Wolf...
reported an impairment of words which were presented during the socially evaluated cold pressor task (Schwabe and Wolf 2010).

We recently provided further support that not only timing of stress is important for memory processes but also the relationship between the material to be learned and the stressor (Wiemers et al. 2014, 2013a). In an experimental study, we induced psychosocial stress in healthy participants by means of the Trier Social Stress Test (TSST; (Kirschbaum et al. 1993)) and assessed memory of this stressful episode 1 day later. Findings were compared to participants who went through a similarly arousing (as indexed by a similar increase in salivary alpha amylase) but non-stressful, in fact rather positive control condition (friendly TSST (fTSST); (Wiemers et al. 2013b)). We found that visual objects which are bound to the stress-inducing committee members and thus central to the stressful situation are remembered better than peripheral objects and also better than the same central objects encountered in a non-stressful situation fTSST (Wiemers et al. 2014)). These findings are in line with the emotional-binding hypothesis proposed by Mather (Mather 2007). This hypothesis postulates that memory for central details is enhanced during emotional arousal by within-object binding. We have ascribed the results from our previous study to the stress-induced noradrenergic activity within the amygdala, which in turn enhances memory storage in the hippocampus in interaction with the released glucocorticoids (Diamond et al. 2007; Joels et al. 2006; Roozenaal et al. 2009).

Since stress is associated with multiple neuroendocrine and affective alterations, the contribution of the stress hormone cortisol cannot be inferred from our previous findings. This was the aim of the current study. We explored the memory of healthy participants for central and peripheral visual details encountered during a non-stressful but arousing social interaction task (fTSST). One group of participants received hydrocortisone, while the other group received a placebo. We compared memory for stimuli perceived during this social interaction 1 day later. We hypothesized that a pharmacological cortisol increase during a non-stressful but arousing social interaction might be able to mimic the stress effects we had observed in our previous studies.

Methods

Participants

In this double-blind, placebo-controlled, between-subjects designed study, 36 participants (20 males) between the age of 20 and 30 years took part. Participants who had formerly taken part in the TSST, had a body mass index (BMI; weight in kg/height in m²) under 19 or over 30, were in medical treatment, or were taking medication influencing the HPA axis, as well as smokers, were excluded from participation. Additionally, pregnant or menstruating women and women taking hormonal contraception were excluded from participating in the study. Participants received a compensatory payment of 25€. The study was approved by the Local Ethical Committee of the Faculty of Medicine of the Ruhr-University Bochum, and the Declaration of Helsinki was followed.

Participants were randomly assigned to one of two groups. One group consisted of participants taking two pills of a placebo (18 people, 10 males), and the other group contained participants (18 people, 10 males) taking two pills of hydrocortisone (Jenapharm, 10 mg each pill, 20 mg in total). The selected dose was based on previous studies demonstrating memory-modulating effects of hydrocortisone in dosages between 10 and 30 mg (de Quervain et al. 2000; Wolf 2009).

Procedure

Testing took part on two consecutive testing days. Due to the circadian rhythm of cortisol, testing time was always in the afternoon. Participants came to the lab and first signed informed consent. Then they did a picture story exercise, irrelevant for the current report. Twenty-five minutes after arrival at the lab, participants provided the first saliva sample (baseline) and rated current affect by means of the “Positive and Negative Affect Schedule (PANAS)” (Watson et al. 1988). Afterwards, participants took two pills, either hydrocortisone or a placebo, and were then brought to another room where the friendly TSST (Wiemers et al. 2013b) took place. The friendly TSST lasts about 15 min and is a non-stressful social interaction (more details further below). After the friendly TSST, participants were brought back to the experimental room where they delivered three more saliva samples 1 min (+1), 15 min (+15), and 30 min (+30) after the end of the stressor. At time +1, the participants filled in the PANAS again. After the last saliva sample, participants were dismissed. The next day, participants came back to the lab, delivered a saliva sample (T2), and filled in the PANAS. Afterwards, participants did an object recognition task on a computer.

Material

Friendly TSST

The friendly TSST (fTSST) is a social interaction of the participant with a two-member committee (one male, one female). It has formerly been used as a control situation to the stress-inducing Trier Social Stress Test (TSST; (Kirschbaum et al. 1993)) because it consists of the same structure. It is arousing in the sense that it increases salivary alpha amylase but it does not activate the HPA axis (Wiemers et al. 2013b). It consists of a 5-min preparation time during
which participants make notes about their school and university time, career aspirations, hobbies, and favorite book or movie and afterwards have to hold a free speech lasting 10 min about their life and career aspirations. The committee reacts friendly by nodding and smiling to give participants a feeling of safety and appreciation. During the fTSST, 20 office objects were present in the room, some of which the committee interacts with at standardized points in time. These objects were the recognition objects to be remembered by the participants on the next day (see also (Wiemers et al. 2014, 2013a)).

Recognition objects

The recognition objects consisted of 20 objects. Ten of these were used by the committee and thus bound to the situation (central objects: pencil, pencil sharpener, stop watch, paper cup, water bottle, lozenge tin, stapler, paper tray, eraser, clipboard), while the other 10 were not used and thus designated as not bound to the situation (peripheral objects: puncher, book, file, scissors, handkerchiefs, coffee cup, dustbin, ruler, paper clips, and highlighter). Pictures of these objects served as target pictures in a recognition task. Pictures of 40 other objects served as distractor stimuli. Additionally, pictures of the committee’s faces served as recognition objects as well, along with four distractor face pictures (Wiemers et al. 2014, 2013a).

Object recognition task

Participants randomly saw pictures of objects on a computer screen for 2 s. After each picture, participants were asked if they had seen this object in the fTSST room. Preceded by a short blank screen and a fixation cross (1 s each), the next picture was presented.

Affect rating

Current affect was collected by the PANAS (Watson et al. 1988). Participants filled in on a 5-point scale the intensity of 20 feelings and emotions. Items can be subdivided into negative affect (NA) and positive affect (PA). Participants filled in the PANAS two times on the first (pre- and post fTSST) and once on the second testing day (T2).

Cortisol and alpha amylase measurements

Participants were asked to refrain from eating and drinking anything except water 1 h before testing. Saliva was sampled using Salivettes (Sarstedt, Nuernbrecht, Germany) four times on the first and once on the second testing day. Cortisol as a marker of HPA activity was analyzed by an immunoassay (IBL, Hamburg, Germany). Salivary alpha-amylase (sAA) as an indirect marker of noradrenergic activity was assessed using a quantitative enzyme kinetic method as described elsewhere (Rohleder and Nater 2009). Inter- and intra-assay variabilities were below 10 %.

Results

Study sample

Two female participants of the hydrocortisone group had to be excluded from analyses because one formerly took part in the TSST and the other one did not appear on the second testing day. One further female of the placebo group exhibited outlier values in cortisol above 2.5 SDs in the area under the curve with respect to increase (AUCi) measure (Pruessner et al. 2003), indicating that she showed a cortisol response to the fTSST, and was thus excluded from analyses. Datasets of 33 participants (20 males, 10 with hydrocortisone; 13 females, 6 with hydrocortisone) could be analyzed.

Cortisol

Cortisol data of one male participant was not analyzable and four more were unrealistic with values higher than 800 nmol/l and thus excluded from analyses of hormonal data. Since data for cortisol was not normally distributed, data was log-transformed. Data was analyzed with a within-subjects analysis of variance (ANOVA) with group affiliation (hydrocortisone vs. placebo) and sex (male vs. female) as between-subjects factors and time of measurement (baseline, +1, +15, +30) as within-subjects factor. Results reveal that the group affiliation made a difference in the cortisol concentration over time. This was reflected in a significant time × group interaction effect ($F(3,78)=85.89, p<.001$), a significant main effect of time ($F(3,78)=97.77, p<.001$), and a significant main effect of group ($F(1,26)=87.57, p<.001$). Post-hoc $t$ tests showed that cortisol concentration differed between groups at measurements +1, +15, and +30. The factor sex had no significant impact. The raw (untransformed) data of the two groups (measured in nmol/l) were the following: (placebo group: baseline, 10.83±1.34 (SE); +1, 12.35±1.44; +15, 12.54±1.89; +30, 10.55±1.63; cortisol group: baseline, 10.76±1.61; +1, 259.63±60.34: +15, 217.06±41.46; +30, 161.92±35.12).

Alpha amylase

SAA concentrations were not normally distributed and were thus log transformed (Rohleder and Nater 2009). Values from one male participant were missing due to an insufficient amount of available saliva. One female participant displayed outlier values at several time points and was removed from the
analysis. Data was analyzed with a within-subjects analysis of variance (ANOVA) with group affiliation (hydrocortisone vs. placebo) and sex (male vs. female) as between-subjects factors and time of measurement (baseline, +1, +15, +30) as within-subjects factor. Results revealed a main effect of time ($F(3,81)=18.01, p<.001$). No further significant main effects or interactions were observed. SAA concentrations (log U/l) increased in response to the fTSST from baseline, 1.82±0.06 (SE), to +1, 2.08±0.05. Afterwards, they decreased again to +15, 1.88±0.05, and +30, 1.83±0.05.

Affect

A within-subjects ANOVA with affect (positive affect, negative affect) and time of measurement (pre, post) as within-subjects factors and group (placebo vs. hydrocortisone) and sex (males vs. females) as between-subjects factors resulted in a significant time × affect interaction effect ($F(1,29)=11.41, p=.002$) and a significant main effect of affect ($F(1,29)=398.17, p<.001$). As displayed in Fig. 1, positive affect was higher after the fTSST than before the fTSST ($t(32)=-3.59, p=.001$). Negative affect did not change over time (mean NA (mNA) pre, 1.23±.04; mNA post, 1.19±.04). There were no interaction effects for affect with group affiliation or sex (neither for positive nor for negative affect).

Object recognition

In order to analyze the object recognition data, we calculated hit rates and false alarm rates and subtracted the false alarm rate from the hit rate to generate the discrimination index (Pr) as a measure of recognition accuracy (Snodgrass and Corwin 1988). This measure is derived from the two-high threshold model and is not influenced by response biases. Pr was calculated for central and peripheral objects as well as for pictures of the faces. A mixed model ANOVA with object type (central, peripheral) as within-subjects factor and group (hydrocortisone vs. placebo) and sex (male vs. female) as between-subjects factors was conducted. Results show a three-way interaction of object type × group × sex ($F(1,29)=5.78, p=.023$) and a significant main effect of object type ($F(1,29)=25.70, p<.001$). In order to follow up this interaction, the analysis was split based on object type. An ANOVA with group (hydrocortisone vs. placebo) and sex (male vs. female) as between-subjects factors was conducted. Results are displayed in Fig. 2. In addition, the underlying hit rates and false alarm rates are presented in Table 1.

For peripheral items, the ANOVA revealed a significant interaction between group and sex ($F(1,29)=8.17, p<.01$). Post-hoc t test show that men had a higher accuracy in recognizing peripheral objects if they had received hydrocortisone ($t(18)=3.52, p=.002$). This effect was driven by a higher hit rate while false alarms appeared not to be influenced (see Table 1).

For central items, the ANOVA revealed no main effect or interaction with the factor group. A trend toward a main effect of sex was observed ($F(1,29)=3.38, p=.08$), with women tending to show better recognition memory for central items compared to men.

A univariate ANOVA with Pr of the faces as dependent variable and condition and sex as fixed factors revealed no significant effects for the factor condition (main effect and interaction).

Discussion

In our previous studies (Wiemers et al. 2014, 2013a), we established that stress exposure is associated with enhanced long-term memory for central details (details which had been manipulated by the committee members). The goal of the current study was to characterize the role of the stress hormone cortisol in this process. We therefore explored the impact of cortisol on long-term recognition memory of an arousing but non-stressful, in fact rather pleasant social interaction. As expected, the pharmacological administration led to a substantial increase in salivary cortisol concentrations. Of note, the friendly TSST caused an overall increase in positive affect, which was influenced neither by cortisol nor by sex. Moreover, the fTSST induced an increase in sAA, indicative of increased noradrenergic arousal. The analysis of the memory data revealed that cortisol did not influence memory for central details, which were overall remembered better than peripheral details. In men, hydrocortisone induced a better recognition memory for peripheral details. In women, memory was not influenced significantly by hydrocortisone.

Previous work in the area of emotional memory has suggested that emotions might induce attentional narrowing (Easterbrook 1959), leading to a trade-off between enhanced memory for central but reduced memory for peripheral details (Christianson 1992). In contrast, the work of Martha suggests that details bound to the emotional stimulus are remembered better with no trade-off for unbound stimuli (Mather 2007). Our recent stress research was in line with this model by demonstrating a stress-induced enhancement of memory for central details without the parallel occurrence of a stress-induced decrease in memory for peripheral details (Wiemers et al. 2014, 2013a).

In the present experiment, we pharmacologically induced high cortisol concentrations in the absence of a stressful situation. It is of note that the friendly TSST has been shown to induce emotional arousal but no activation of the HPA axis (Wiemers et al. 2013b). In the current study, no cortisol increase occurred in the placebo group and a sAA increase
occurred in both groups, thus replicating these findings. Importantly, the friendly TSST was associated with an increase in positive affect. In contrast, the TSST is known to increase negative affect (Wiemers et al. 2013b). A previous study by Abercrombie et al. has reported that negative affect interacts with stress-induced cortisol concentrations in order to predict memory performance after stress (Abercrombie et al. 2005). Research on the emotional modulation of attention has suggested recently that threat but not emotional arousal per se is associated with attentional narrowing (van Steenbergen et al. 2011). Moreover, positive emotions have been linked to a broadening in perceptual and conceptual processes (Fredrickson 2004; Friedman and Forster 2010) especially if they are not associated with approach behavior (Gable and Harmon-Jones 2010).

Trying to integrate these distributed lines of evidence, one might suggest that social evaluative threat as induced with the TSST and its associated increase in negative affect causes attentional narrowing and/or enhanced binding, thereby boosting memory for central details of an episode (Wiemers et al. 2013a). Conceivably these effects might be mediated by a stress-induced activation of the amygdala (Roozendaal et al. 2009). Previous neuroimaging studies have revealed that endogenous cortisol concentrations are associated with enhanced amygdala activity to aversive stimuli (Wolf 2009). In contrast, pharmacologically administered glucocorticoids have been associated with amygdala desensitization (Henckens et al. 2010) and amygdala decoupling (Henckens et al. 2012). These neural alterations might underlie the observed enhancing effect of cortisol on memory for peripheral
details. In the absence of threat, cortisol may in contrast widen visual attention, thereby increasing memory consolidation for peripheral details. This explanation matches a previous study of ours in which post-learning stress was associated with an enhanced centrality bias (better memory for central details) under situations of high thematic arousal. In contrast, low thematic arousal (as in the fTSST) followed by stress caused a reduction in the centrality bias (better memory for peripheral details) (Echterhoff and Wolf 2012).

In the current study, cortisol enhanced memory for peripheral details in men only. It has to be noted that men in the placebo group showed poor recognition performance for the peripheral items ($P_r=-.02$). The recognition task we used is rather difficult since targets and distractors often only differ in a single feature (e.g., color). In our previous study (Wiemers et al. 2014), men in the friendly TSST condition also showed rather poor recognition accuracy for peripheral details ($P_r=.035$), while the performance of women was better ($P_r=.089$). It is conceivable that the poor recognition memory performance of men provided more room for an enhancing effect of cortisol to occur.

Previous research has observed sex differences in emotional memory (Cahill 2006) which might in part be caused by differences in brain lateralization (Cahill and van Stegeren 2003). Moreover, some studies have observed that the impact of stress on emotional memory and emotional learning differs between the sexes (see for review (Wolf 2013)). For example, stress-induced cortisol increases were associated with impaired immediate recall in men but not in women (Wolf 2013). Similarly, cortisol concentrations were associated with enhanced memory consolidation in men but not in women (Andreano and Cahill 2006). Moreover, effects in women might change during the course of the menstrual cycle (Andreano et al. 2008). The current study provides initial evidence that the enhancing effect of cortisol on memory for peripheral details might be restricted to or at least more prominent in males.

The present study has some limitations which need to be acknowledged. We did not assess overt attention, for example, by means of eye tracking, which would have given nice complementary results in how far attention processes can account for the effects of cortisol on memory processes observed here. The absent effects of cortisol on memory in women might be due to the sample size ($n=13$) and its associated lack of power. Moreover, sex steroid concentrations were not assessed.

Taken together, the present study illustrates similarities and differences between the impact of stress and the impact of hydrocortisone on memory. Both manipulations are associated with increased recognition memory of details of the specific episode. However, stress increases memory for central details, while hydrocortisone administered before a friendly social interaction increases memory for peripheral details. The comparison of the impact of stress- and pharmacologically induced cortisol elevations on long-term memory enhances our mechanistic understanding of the processes underlying memories of stressful episodes.

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**Conflict of interest** The authors declare that they do not have a conflict of interest.

**References**

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### Table 1 Hit rates (HR) and false alarm rates (FA) for male and female participants

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