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Abstract

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Performance on a declarative memory task is better in high than low cortisol responders to psychosocial stress

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Summary

Increased levels of circulating glucocorticoids (GCs) due to stress have been shown to result in enhanced consolidation and impaired retrieval of memory in humans. Several studies have shown that participants may be categorized as high and low responders with regard to GC levels elicited by stress. In the current study, we studied the differential effects of acute psychosocial stress on declarative memory processes in high and low responders. Twenty male participants were exposed to the Trier Social Stress Test (TSST) and a rest condition, and they completed the Rey Auditory Verbal Learning Test (RAVLT). Results show that there was no general effect of psychosocial stress on declarative memory processes. However, high cortisol responders displayed better immediate free recall after being exposed to stress. Findings are discussed in the context of possible positive relations of stress and declarative memory performance.

Key words: HPA axis, cortisol, psychosocial stress, memory, learning

Acknowledgments

We would like to thank all participants of the study. UMN and MK acknowledge the financial support of the Swiss National Science Foundation.
Stress has been proposed to interfere with cognitive capacity (de Kloet et al., 1999) and the hypothalamic-pituitary-adrenal (HPA) axis has been shown to interact with brain structures involved in memory. Glucocorticoids (GCs), the main output substance of the HPA axis, are hormones that can easily pass the blood-brain barrier, thus affecting a variety of memory-related brain areas via specific intracellular receptors or via the interaction of the hormone with neurotransmitter receptors on the cell surface (Sauro et al., 2003; Het et al., 2005). Several studies have confirmed the effect of increased levels of GCs on different memory processes (Roozendaal, 2002). Among these studies, most have employed exogenous administration of GCs. Results from these studies were predominantly showing enhanced memory consolidation, whereas studies focusing on memory retrieval processes found impaired retrieval due to increased GC levels (Kirschbaum et al., 1996; de Quervain et al., 2000; Buchanan and Lovallo, 2001; Wolf et al., 2001a; Lupien et al., 2002; Monk and Nelson, 2002; de Quervain et al., 2003; Tops et al., 2003; Maheu et al., 2005b; Buchanan et al., 2006). Although pharmacological challenge studies reveal important mechanisms about memory processes, the mostly non-physiological doses cannot simulate real-life stress situations (Lupien and Schramek, 2006). Thus, generalizability of previous research to real-life situations might be somewhat limited by the focus on exogenous hormone application.

More realistic paradigms, such as the Trier Social Stress Test (TSST; Kirschbaum et al., 1993), combine tasks known to elicit HPA axis changes due to incontrollable and social-evaluative characteristics of the situation (Dickerson and Kemeny, 2004). In studies using the TSST or similar paradigms, psychosocial stress mostly resulted in impaired memory retrieval (Kirschbaum et al., 1996; Lupien et al., 1997; Wolf et al., 2001b; Kuhlmann et al., 2005b), with some studies showing enhanced consolidation (Abercrombie et al., 2006; Beckner et al., 2006). Importantly though, individual cortisol responses due to stress may vary greatly (Kirschbaum et al., 1995). As a consequence, recent studies have explored memory performance in groups with high versus low cortisol responses to a psychosocial stress
paradigm revealing inconsistent results. In one study, high responders were shown to display better declarative memory (Domes et al., 2002), whereas high responders showed impaired memory performance in other studies (Wolf et al., 2001b; Takahashi et al., 2004; Elzinga and Roelofs, 2005).

The present study follows up on this inconsistency and explores possible positive relations of high GC stress responses and declarative memory performance extending the literature in two aspects. First, we address some methodological limitations of Domes et al. (2002) who compared high and low ‘responders’ collapsed across both the stress and the control conditions (Domes et al., 2002). Second, while previous studies mostly applied one free recall task, the present study tests declarative memory using a standardized declarative memory test that provides a number of indicators such as immediate and delayed free recall and recognition.

Methods

Design and participants

The study applied a within-person manipulation of stress (versus non-stress) with randomized and counterbalanced order of condition (interval: 2 weeks). Twenty male participants (age: \( M = 23.75 \) years, \( SD = 2.15 \); range: 20-27 years) were recruited from the local student populations. Only male participants were included in the study to avoid confounding of our dependent variables by sex-related factors (e.g. Kirschbaum et al., 1999). All participants were medication-free and non-smokers with normal BMI (BMI: \( M = 22.13 \), \( SD = 1.97 \), range: 18.94-26.37). Exclusion criteria were acute or chronic somatic or psychiatric disorders. Subjects with high chronic stress and dispositional stress reactivity as measured by the Trier Inventory for the Assessment of Chronic Stress (TICS) (Schulz et al., 2004) and the Stress Reactivity Scales (SRS) (Schulz et al., 2005), respectively, were excluded. Participants had to abstain from excessive physical activity within 48 hours, any sporting
activities within 24 hours, intake of alcohol and caffeine within 18 hours and eating within 60 minutes before the study.

The study was conducted in accordance with the Declaration of Helsinki and all procedures were carried out with the adequate understanding and written consent of the participants.

Materials and procedure

Stress protocol: The Trier Social Stress Test (TSST) was applied (Kirschbaum et al., 1993). The testing took place between 1400h and 1800h. Stress condition: After providing a basal saliva sample (−30 pre-TSST; see Figure 1) and filling out some questionnaires (regarding exclusion criteria, see above), participants were introduced to the TSST. Then participants were given 15 minutes to prepare their free speech. Following this, participants were exposed to a simulated job interview (5 minutes) followed by a mental arithmetic task (5 minutes) in front of an audience. Further samples of saliva were taken 5 minutes after baseline (−25 pre-TSST), immediately before the TSST, immediately after completion of the TSST, and 15, 30, 45, as well as 60 minutes after completion of the TSST. Between minute 15 and 30 post-TSST participants were completing the main part of the memory procedure (trials 1-7; see below). The delayed recall part (trial 8) together with the recognition memory part (trial 9) of the memory procedure was administered with an additional 20 minutes delay (i.e., 50 minutes after the TSST; between saliva samples 45 and 60 post-TSST). Non-stress condition: Each participant was free to choose a quiet activity with magazines made available. Physiological and psychological variables were assessed at the same intervals as in the stress condition.

Psychological measures: Manipulation check measures. Short-term fluctuations of mood and anxiety were assessed by a German multidimensional mood questionnaire (MDBF; Steyer et al., 1997) and the German version of the State and Trait Anxiety Inventory (STAI;
Spielberger et al., 1970; Laux et al., 1981) immediately before and after the stress/rest induction.

Memory and learning procedure. The Rey Auditory Verbal Learning Test (RAVLT; Helmstaedter et al., 2001) was used to assess declarative memory. Here, the interviewer reads aloud 15 words to the participant in 5 subsequent trials and participants have to recall those words after each trial (immediate recall). After the 5th trial an interference list of 15 different words is read to the participants and tested (trial 6; interference). Then, participants have to recall the 15 words from trial 1 to 5 right after the interference list (trial 7 in relation to trial 5; immediate forgetting) and about 20 minutes thereafter (trial 8; delayed recall). After trial 8, participants have to recognize the 15 words from trial 1 to 5 from an orally presented word list also containing the 15 words from the interference list and 20 phonetically or semantically similar distractor words in order to examine participants’ recognition performance (trial 9; recognition). The RAVLT provides two parallel versions that were assessed in a randomized counterbalanced order in relation to the stress condition.

Saliva sampling methods and biochemical analyses

Salivary cortisol was collected 8 times using Salivette (Sarstedt, Sevelen, Switzerland) collection devices and stored at –20°C after completion of the session until biochemical analysis took place. After thawing, saliva samples were centrifuged at 3000 rpm for 5 minutes. Salivary free cortisol was analyzed by using a commercial chemiluminescence immunoassay (LIA) (IBL Hamburg, Germany). Inter- and intraassay coefficients of variation were below 10%. To reduce error variance caused by imprecision of the intraassay, all samples of one participant were analyzed in the same run.

Statistical analysis

Cortisol data were analyzed by repeated measures analyses of variance (ANOVA). Data were tested for normal distribution and homogeneity of variance using a Kolmogorov-Smirnov and Levene’s test. Where appropriate, planned comparisons were performed and (the
df and) \( p \)-values were adjusted according to Bonferroni, or Greenhouse-Geisser (in the repeated measures data). Effect size is given in \( \eta^2 \) indicating proportion of explained variance. \( p \)-values are two-tailed and a \( p \)-value of < 0.05 is considered significant. Unless indicated otherwise, results shown are means ± standard error of means (SEM).

Results

**Manipulation check of the stress paradigm**

*Psychological stress responses:* In the stress condition after the introduction to the stress test, the participants’ mood (MDBF) was significantly worse than in the non-stress condition (\( t_{19} = 4.12; p < 0.01 \)) and they displayed more restlessness (MDBF) (\( t_{19} = 8.81; p < 0.001 \)). Immediately after the stress condition, the same results were found (mood: \( t_{19} = 2.49; p < 0.05 \); restlessness: \( t_{19} = 3.78; p < 0.01 \)). Anxiety levels also differed significantly between the two conditions (STAI-state). In the stress condition, the introduction to the stress test (\( t_{19} = -4.23; p < 0.001 \)), as well as the actual test (\( t_{18} = -3.7; p < 0.05 \)) resulted in higher anxiety ratings than at the respective time points in the non-stress condition.

*Salivary cortisol responses:* The stress test resulted in a significant increase in salivary cortisol across the complete sample (\( F(1.84,34.0) = 13.53; p < 0.001 \), Figure 1). In the rest condition, a significant time effect could be observed (\( F(1.75,33.32) = 12.04; p < 0.001 \), Figure 1), however, the decreasing slope indicates the natural afternoon course of cortisol. The salivary cortisol concentrations differed significantly between the stress and rest conditions (\( F(1.99,75.46) = 15.98; p < 0.001 \)), with a major peak after the psychosocial stress test.

*Heart rate parameters:* The TSST resulted in a significant increase in heart rate (\( F(4.92,93.5) = 15.15; p < 0.0001 \)), whereas the rest condition did not (\( F(4.23,76.07) = 1.81; p = 0.13 \)). Heart rate changes over time were significantly different in the two conditions (\( F(6.52,241.14) = 11.73; p < 0.0001 \)).
Memory performance: Complete sample. In a first step, we analyzed stress effects on the memory measures provided by the RAVLT across the complete sample. A 2 (Stress condition) x 5 (RAVLT trials 1-5) repeated-measurement ANOVA on immediate recall revealed a significant main effect of learning in RAVLT trials, $F(2.29,43.54) = 84.55, p < .001; \eta^2 = .82$. The ANOVA did not reveal a significant main effect of stress condition, $F(1,19) = .25, p > .6; \eta^2 = .01$, nor a significant interaction, $F(2.98,56.64) = 1.06, p > .3; \eta^2 = .05$.

Conducting one factorial (Stress condition) repeated-measurement ANOVAs on interference (trial 6; $p > .4$), delayed recall (trial 8; $p > .3$) and recognition (trial 9; $p > .3$) did not reveal any significant differences. A 2 (Stress condition) x 5 (RAVLT trials 5 versus 7) repeated-measurement ANOVA on immediate forgetting revealed significant forgetting ($p < .01$), but no stress effect ($p > .16$) nor an interaction ($p > .7$).

High versus low responders. In a second step, we split the sample in high and low responders (median split) according to their cortisol level at the time RAVLT testing started in the stress-condition (cortisol level for low responders 13.96 nmol/l versus 32.90 nmol/l for high responders; $t_{18} = -5.74; p < .001$). Considering the within-person design of the study, importantly, order of TSST administration did not affect grouping of participants into high and low responders, $\text{Chi}^2 (1) = .8; p > .37$.

A mixed 2 (GC Responder: high versus low; between-subjects) x 5 (RAVLT stress session trials 1-5, repeated within-subjects measurement) ANOVA on immediate recall revealed a significant main effect of learning in RAVLT trials, $F(2.57,46.20) = 61.20, p < .001; \eta^2 = .77$ (see Figure 2). In addition, the ANOVA also revealed a significant main effect of responder, $F(1,18) = 8.55, p < .01; \eta^2 = .32$, indicating superior overall performance in high GC responders. Finally, the ANOVA also revealed a significant interaction, $F(2.57,46.20) = 4.06, p < .05; \eta^2 = .18$. Post-hoc planned comparisons indicated that the interaction was due to superior performance of the high responders in the first RAVLT trial ($p < .01$), in the middle (trial 3; $p < .05$) and the last trial (trial 5; $p < .05$) of the immediate recall sequence.
Conducting one factorial (Responder condition) between-person ANOVAs on interference (trial 6; \( p > .16 \)), delayed recall (trial 8; \( p > .19 \)) and recognition (trial 9; \( p > .15 \)) did not reveal any significant differences. A mixed 2 (Responder condition, between-person) x 5 (RAVLT trials 5 versus 7; repeated-measurement) ANOVA on immediate forgetting revealed significant forgetting (\( p < .05 \)), overall superior recall performance of high-responders (\( p < .05 \)) but no interaction (\( p > .8 \)) indicating no group difference in forgetting.

Parallel ANOVAs on RAVLT performance in the rest session did only show corresponding effects of RAVLT trials, but no superior performance of those participants that had been high responders in the stress session.²

Discussion

While there was no general effect of psychosocial stress on declarative memory processes, high cortisol responders displayed better memory performance after being exposed to stress. This supports initial findings reported by Domes et al. (2002) by testing this effect under more rigorous experimental constraints, such as excluding menstrual cycle influences (in Domes et al.’s study only women – mostly postmenopausal – were examined) and confounding effects by smoking by examining non-smoking men only. Moreover, applying a within-subjects design, the present study was able to compare high GC-responders and low responders to the TSST. While this corroborates findings of possible positive correlations between stress-induced GC changes and declarative memory, our results appear to be in contrast to results reported by others who demonstrated a deterioration of memory performance in TSST responders (Kirschbaum et al., 1996; Wolf et al., 2001b; Takahashi et al., 2004; Elzinga and Roelofs, 2005). This different finding may be explained by the different memory functions tested or by the time of testing (morning vs. afternoon). A recent meta-analysis by Het, Ramlow and Wolf (2005) has shown that studies which administered cortisol in the morning found significant memory impairment, while studies conducted in the afternoon observed a memory enhancement. As an alternative route of further exploring
possible mechanisms underlying our findings the valence of the material to-be-remembered might be varied. Previous research on stress and emotional stimuli has shown no effects for neutral material, but positive effects of stress on encoding and consolidation of emotional material (Maheu et al., 2005a; Payne et al., 2006; Smeets et al., 2006), and negative effects of stress on retrieval of negative material (Kuhlmann et al., 2005a). Thus, future research will have to corroborate our results by systematically varying the emotionality of the task material.

Importantly, our findings underline the relevance of considering the amount of stress-related cortisol changes in psychosocial stress research. Although median split analyses do not allow for causal conclusions and we did not directly manipulate cortisol concentrations, our data suggest that the issue of high versus low responders has to be considered in future studies on stress and memory. In fact, comparing experimental stress versus rest conditions alone may blur stress effects on memory performance. Finally, the present results reveal initial evidence that the effects on declarative memory may be strongest in immediate free recall performance while delayed recall, recognition and rate of forgetting (missing interaction in comparing trials 5 versus 7) seem to be less affected. Future studies using an experimental design that directly manipulates cortisol changes, however, will have to further explore these potentially differential effects.

Some limitations have to be addressed. First, the stressor was applied prior to stimulus presentation, thus cortisol was elevated during encoding, consolidation, and retrieval. Second, our study primarily focuses on memory performance in men. No generalization can be made with regard to women. Third, pre-TSST preparation interval was longer than reported in the literature. Fourth, subjects with higher cortisol responses to the TSST might generally respond with greater central nervous arousal to stimuli, which could non-specifically enhance encoding. These hypotheses warrant further investigation.
In this context, we also tested for order effects in psychological stress responses (MDBF, STAI), cortisol reactivity, and memory performance. Again, importantly, there were no order effects in any of those measures.

Combining analyses into one overall three-factorial mixed 2(stress, within-subjects) x 2 (responder, between-subjects) x 5 (RAVLT trials 1-5, within-subjects) ANOVA, the stress x responder interaction did not reach significance ($p = .16$), presumably because of the limited power of such an analysis in the present sample (power = .28). However, when restricting the analyzed data points of the overall analyses to the critical first and last trials of the immediate recall sequence, even the stress x responder interaction in the combined analysis turned out to be significant ($p < .05$).

However, when comparing the present data with prior studies closely following the traditional TSST design we did not obtain any differences (all $F$’s < 1). This underlines the robustness of the TSST against procedural changes.
Figure legends

Figure 1: Salivary cortisol concentrations in the non-stress and in the stress condition across the complete sample. The grey bar represents the time of stress exposure. Error bars represent Standard Error of the Mean (SEM). Between minute 15 and 30 as well as 45 and 60 after the stress test, participants were completing the memory and learning task.

Figure 2: Memory and learning performance in the Rey Auditory Verbal Learning Test (RAVLT) in the stress session comparing high and low GC responders. Error bars represent Standard Error of the Mean (SEM).
Figure 1

Salivary cortisol in nmol/l

Non-Stress
Stress

Time in min

Trial 1-7
Trial 8&9
Figure 2

[Graph showing RAVLT Score across trials for High Responder and Low Responder groups.]

- Trial 1, Trial 2, Trial 3, Trial 4, Trial 5, Trial 6 (Interference), Trial 7, Trial 8 (Delayed Recall), Trial 9 (Recognition)
Abercrombie, H.C., Speck, N.S., Monticelli, R.M., 2006. Endogenous cortisol elevations are related to memory facilitation only in individuals who are emotionally aroused. Psychoneuroendocrinology 31, 187-196.


