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The relationship between stress induced cortisol levels and memory differs between men and women

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Abstract

Epidemiological as well as experimental studies in elderly subjects have suggested that postmenopausal women are more susceptible to the memory impairing effects of elevated cortisol levels than elderly men. Little is known however about gender differences in the susceptibility to acute stress in young subjects. In the present study a total of 58 healthy young subjects learned a word list, with recall being tested after a brief distraction task. Twenty-two subjects had to learn the list after exposure to a psychosocial stressor (Trier Social Stress Test: TSST), while the remaining subjects served as controls. Free cortisol was determined via saliva samples taken before and 10 minutes after stress. Subjects exposed to the stressor, did not show impaired memory performance per se when compared to the control group. However the cortisol increase in response to the stressor was negatively correlated ($r=-0.43$, $P<0.05$) with the memory performance within the stressed group (i.e., subjects showing a larger cortisol response recalling less words than subjects showing only a small cortisol increase). Additional analysis revealed, that this correlation was solely caused by the strong association observed in men ($r=-0.82$, $P<0.05$), while no association was observed in women ($r=-0.05$, P=ns). Our data suggests, that gender modulates the association between cortisol and memory after stress. Whether these differences reflect activational effects of sex steroids or developmentally-

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programmed sex differences awaits to be determined.

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1. Introduction

Epidemiological studies suggest that women have a higher incidence of several psychiatric disorders in which hypothalamus pituitary adrenal (HPA) axis dysregulations might be involved as causal or modulatory factors (e.g. post-traumatic stress disorder, major depression and Alzheimer's disease (Jorm et al., 1987; Breslau et al., 1997; Desai and Jann, 2000). Beside other research strategies, the investigation of gender differences in the response to stress might help to elucidate some of the underlying mechanisms responsible for these findings.

Exposure to stress influences cognition in animals and humans and it has been demonstrated that the stress-induced release of glucocorticoids (GCs; corticosterone in rats, cortisol in humans) is among other factors like epinephrine or CRH responsible for these effects. Studies in rodents have revealed that GCs enhance or impair performance dependent on the specific memory type tested and on the timing of the stress exposure, respectively (Diamond et al., 1996; Lupien and McEwen, 1997; de Quervain et al., 1998; De Kloet et al., 1999; Roozendaal, 2000). Experimental studies in humans have repeatedly shown, that GC administration can interfere with performance in working memory as well as declarative memory tasks, (Wolkowitz et al., 1990; Kirschbaum et al., 1996; Newcomer et al., 1999; Lupien et al., 1999; de Quervain et al., 2000; Wolf et al., 2001). Even though the data are not entirely consistent it appears that acute GC treatment impairs working memory (Lupien et al., 1999; Wolf et al., 2001) and delayed recall of declarative material (de Quervain et al., 2000; Wolf et al., 2001). Prolonged treatment (several days) seems to be needed in order for declarative learning deficits to occur (Newcomer et al. 1994, 1999; Schmidt et al., 1999; Young et al., 1999). In line with these pharmacological studies, memory impairing effects have been observed in young and elderly subjects after exposure to psychosocial laboratory stressors (Kirschbaum et al., 1996; Lupien et al., 1997; Wolf et al., 1999).

Only a few studies have tried to investigate whether memory processes of women and men might differ in their susceptibility to acute stress. A recent animal study strongly suggests that gender plays an important role in the effects of stress on cognition. Woods and Shors reported that stress enhanced classical conditioning in male rats, whereas it impaired it in female rats (Wood and Shors, 1998). In humans, an epidemiological study observed that higher basal cortisol levels were associated with poorer memory in elderly women, but not men (Seeman et al., 1997), suggesting, that elderly women are more susceptible to the effects of glucocorticoids. Similarly an experimental study in elderly humans found that exposure to a laboratory stressor impaired the recall of previously learned material more strongly in elderly women when compared to elderly men (Wolf et al., 1999). Most of the prior human

studies investigating young subjects only studied men or the investigated populations were too small to detect gender differences (Kirschbaum et al., 1996; Lupien et al. 1997, 1999). Moreover studies which included women did not control for phase of the menstrual cycle and/or the use of oral contraceptives (Newcomer et al., 1999; de Quervain et al., 2000).

In a previous study from this laboratory, it was observed that the stress-induced cortisol increase was negatively correlated with the memory performance after cessation of the stressor (Kirschbaum et al., 1996). Those subjects, who reacted with a strong cortisol increase performed more poorly in the memory task, than those subjects showing only a mild cortisol response. This pilot study did not include an unstressed control group and also did not consist of enough female subjects in order to address the issue of possible gender differences. The study reported here was therefore designed to *first* test the hypothesis, that subjects exposed to psychosocial stress perform poorer in a memory test than subjects from a control group, *secondly* to investigate whether the stress-induced cortisol increase is a predictor of memory performance after the stressor, and *thirdly* to explore the possibility that the relationship between the stress-induced cortisol increase and memory might differ between women and men.

2. Methods

2.1. Subjects

Participants of a larger study, which investigated endocrine response patterns to psychosocial stress exposure were also tested for memory performance. Smokers, subjects suffering from acute or chronic hormonal dysregulations, atopic-, psychosomatic-, or psychiatric diseases were excluded. All subjects reported to be free of medication. Before entering the study all participants received oral as well as written information about the study, provided written consent and underwent a comprehensive medical examination. The study protocol was approved by the ethics committee of the University of Trier.

Fifty-eight young healthy university students (25 women and 33 men) participated in the memory testing part reported here. None of the women used oral contraceptives and all women were tested in the late luteal phase (days 21–25) of their menstrual cycle according to self report. Menstrual cycle phase was validated post hoc by measurements of estradiol and progesterone levels. Indeed the women had estradiol and progesterone levels similar to those reported in previous studies from this laboratory (progesterone 7.3±1.0 ng/ml; estradiol 146.6±15.2 pg/ml) indicative for the luteal phase of the menstrual cycle. The luteal phase was chosen since during this phase, stress-induced free cortisol levels do not differ between men and women (see Kirschbaum et al., 1999).

After waking up at 0700 h, testing took place in the late morning hours (between 1000 h and 1200 h). Out of the total of 58 subjects, 22 participants were exposed to a psychosocial stressor before memory testing (14 women and 8 men), while the

others served as a control group. The latter group was exposed to the laboratory stressor one hour after memory testing. The two groups did not differ significantly with respect to age (stress group 24.9±1.2 years (mean±SE); control group 23.6±0.5 years) and body mass index (stress group 22.3±0.4 kg/m^2; control group 22.0±0.3 kg/m^2; $P>0.10$, Student's *t*-tests).

2.2. Memory testing

A word list containing 25 words was presented to the subjects on a piece of paper with the instruction to learn the words by reading them aloud at a speed of one word every three seconds. The words were taken from a pool of German words (Heubst and Hager, 1994) all of which were of high concreteness (e.g. typewriter, rainbow) and 10–15 letters in length. After the learning phase a 25 second distractor task was presented (reading aloud colour words from a piece of paper, without further instructions) in order to abolish the possibility, that the subject could use silent rehearsal strategies. Immediately after the distractor task free recall of the word list was tested.

2.3. Psychosocial stress

Subjects were recruited into the study with the understanding that the reactivity of the HPA-axis after psychosocial stress would be tested. As psychosocial stress protocol, the Trier Social Stress Test (TSST) was employed (Kirschbaum et al., 1993). This laboratory stressor mainly consists of a free speech and a mental arithmetic task in front of an audience. Including introduction to the free speech and a preparation phase the total procedure takes approximately 15 minutes. The TSST has been repeatedly shown to substantially increase free as well as total cortisol levels. Saliva samples for the assessment of free salivary cortisol were collected immediately before onset of the stress sessions as well as 10 minutes after cessation of stress, when cortisol levels peak and memory testing started. No saliva samples were collected from the control group at the time of their memory testing.

2.4. Saliva sampling and free cortisol analysis

Saliva was collected by the subjects using Salivette (Sarstedt, Rommelsdorf, Germany) collection devices. The devices were stored at −20 degrees Celsius until biochemical analysis. Before assaying the saliva samples for cortisol, they were thawed and spun at 3000 rpm for 10 minutes, which results in low viscosity saliva. Cortisol in saliva was determined by a time-resolved immunoassay with time-resolved fluorometric detection as described in details elsewhere (Dressendorfer et al., 1992)

2.5. Statistical analysis

Differences between the stress and the control group were analysed by ANOVA with the independent factors "group" and "gender". The cortisol response to the

stressor within the stressed group was analysed by ANOVA with the independent factor "gender" and the within factor "time" (pre- and post stress). The relationship between cortisol (delta increase (absolute levels) pre- and post stress levels) and memory performance was computed using Pearson's correlation.

3. Results

3.1. Cortisol reaction to the stressor

Free cortisol levels doubled in response to the TSST from 10.4±1.1 nmol/l to 20.9±2.3 nmol/l. The net cortisol increase was 10.3±2.3 nmol/l in women (baseline: 8.6±1.1 nmol/l; post-stress: 18.9±2.5 nmol/l) and 11.0±4.2 nmol/l in men (baseline: 13.5±2.2 nmol/l; post-stress: 24.5±4.7 nmol/l). ANOVA indicated a significant main effect of "stress" ($F(1,20)=23.84$, $P<0.001$), in the absence of a gender main effect or a gender by stress interaction (both P values>0.10).

3.2. Memory performance: comparison between the stressed group and the control group

As a group, subjects exposed to the psychosocial stressor did not show poorer memory performance than subjects from the control group (stress group, men: 9.9±1.2 words; stress group women: 9.6±0.7 words; control group men: 8.9±0.6 words; control group, women: 11.0±0.8 words). ANOVA indicated neither a significant group or gender main effect nor a significant interaction (all P values>0.10).

3.3. Memory performance: within stress group analysis

Based on previous data from this laboratory (Kirschbaum et al., 1996), the relationship between the stress-induced cortisol increase and memory was further evaluated using correlations. Within the stress group ($n=22$), the cortisol increase was negatively correlated with memory performance ($r=-0.43$, $P<0.05$), i.e., subjects showing a larger cortisol response recalled less words than subjects with smaller cortisol increases. Additional analysis revealed that this effect was solely caused by the strong negative correlation observed in men ($r=-0.82$, $P<0.05$), while no significant association was observed in women ($r=-0.05$, $P=0.87$; see Figs. 1 and 2). In addition to the association with the net increases (deltas) the association with the post stress cortisol levels were also investigated. However, the correlations were much smaller and did not reach significance (total group: $r=-0.26$, $P=0.26$, men only: $r=-0.56$, $P=0.15$; women only: $r=0.01$, $P=0.96$). The correlations with the pre-stress cortisol levels were also not significant (total group: $r=0.24$, $P=0.28$, men only: $r=0.34$, $P=0.40$; women only: $r=0.13$, $P=0.67$).

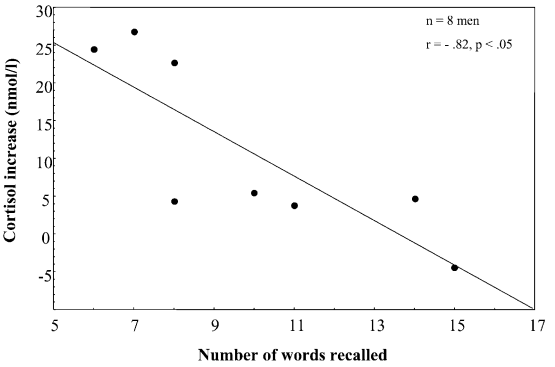

Fig. 1. Correlation between the psychosocial stress induced free salivary cortisol increase (10 min post stress level minus pre stress level) and recall of a word list (containing 25 words) in 8 young healthy men.

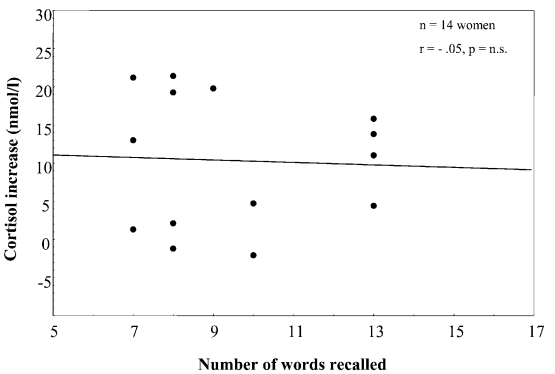

Fig. 2. Correlation between the psychosocial stress induced free salivary cortisol increase (10 min post stress level minus pre stress level) and recall of a word list (containing 25 words) in 14 young healthy women. All women were in the luteal phase of their cycle.

4. Discussion

In the present experiment, exposure to psychosocial stress in the laboratory did not impair recall of a word-list when the stress group was compared to a non-stressed control group. Even though the stressor lead to a two-fold cortisol increase, peak cortisol levels were still much lower than those observed in previous pharmacological studies (e.g. (Kirschbaum et al., 1996 (experiment II); de Quervain et al., 2000). It could be speculated that more pronounced stress-induced cortisol increases are required for detection of significant group differences between stressed and non-stressed subjects. Another possible explanation for the finding is the memory test employed (recall of a word list after a brief delay), which might be less sensitive to cortisol-induced effects than previously used working or declarative memory tests (Wolkowitz et al., 1990; Kirschbaum et al., 1996; Lupien et al., 1999; de Quervain et al., 2000; Wolf et al., 2001). Stress exposure between the learning and the recall

phase in contrast to stress exposure before learning could also have lead to different results (Lupien et al., 1997; Wolf et al., 1999).

While the between group comparison did not reveal any significant stress effects, interesting relationships were revealed when memory performance was related to the individual stress response pattern. Here a negative association between the cortisol increase and memory was observed, replicating our previous results (Kirschbaum et al., 1996). Extending these findings, we here report that the relationship between stress-induced cortisol release and memory performance shows a clear-cut sex dimorphism. While a strong relationship was observed in men ($r=-0.82$, explaining 67% of the total variance), no such association was observed in women. Since the women were in the luteal phase a time of high estradiol and progesterone levels they did not differ in their stress induced free cortisol increase from the men group, which is in line with previous studies from this laboratory (Kirschbaum et al., 1999). Differences in cortisol levels therefore can not account for the observed gender differences. The current data could suggest that recall of words is less sensitive to the disruptive effects of a stress induced cortisol increase in women compared to men. However because of the correlative nature of the findings other explanations for the observed gender differences in the association between stress induced cortisol levels and memory can not be ruled out. Future studies should give cortisol orally in order to address this question more directly. All women participating in the present experiment were in the luteal phase of their cycle, therefore it also awaits to be determined, whether the relationship between the stress-induced cortisol increase and memory performance changes over the course of the menstrual cycle.

A previous study in elderly humans found that basal cortisol levels (cross-sectional) as well as their development over time (longitudinal) were associated with poorer declarative memory in women but not in men (Seeman et al., 1997). In line with these data a second study reported that psychosocial stress had stronger negative effects on recall of previously learned declarative material in elderly women when compared to elderly men (Wolf et al., 1999). In the current study an opposite picture emerged with young men showing a stronger association between stress, cortisol, and memory than young women. Possible reasons for these discrepancies are the age of the subjects and the age-associated changes in the hormonal status. In the current study young women with high estradiol and progesterone levels were tested, while in the two latter studies postmenopausal women with low estradiol levels were investigated.

The idea that estradiol modulates the relationship between cortisol and memory is supported by a recent study in elderly women in which basal cortisol levels were associated with poorer memory (digit span test) in female hormone replacement therapy (HRT) non-users but not in female HRT users (Carlson and Sherwin, 1999). Evidence that estradiol, in addition to its multiple demonstrated activities within the brain (McEwen and Alves, 1999), might also show stress protective potencies has also been provided by a study in rodents (Galea et al., 1997). Female rats exposed to repeated stress failed to show the reorganization and shrinkage of dendrites of hippocampal pyramidal neurons that has been repeatedly demonstrated in male rats. Besides circulating gonadal hormone levels, developmentally-programmed sex dif-

ferences in the hippocampus (Juraska, 1991) may also be involved in these sex differences in stress induced memory impairment. However effects mediated via different brain structures (e.g. the prefrontal cortex) could also account for the observed effects (see for discussion (Wolf et al., 2001).

Other explanations for the differences between the current data and previous human studies are of course possible. For example the delayed memory testing employed in previous studies (Seeman et al., 1997; Wolf et al., 1999) might assess hippocampally-mediated declarative memory functions, while the recall test used in the present experiment might at least partially assess prefrontal cortex mediated working memory functions (Arnsten and Goldman-Rakic, 1998; Lupien et al., 1999). The present study only used a single memory test, which also did not allow us to address the issue of effects on learning versus effects on recall. Moreover the possibility exists that the findings reflect changes in attention. More elaborated cognitive testing would not have been feasible due to time and man-power constraints. Clearly, additional experiments are needed to evaluate the possibility that gender and stress might interact in a memory domain-specific manner.

In sum, the current study provides first evidence for human gender differences in the association between stress induced cortisol elevations and memory performance after cessation of the stressor. In this small study young men with a strong stress induced cortisol increase showed reduced memory performance after stress, while no such association was observed in young women. Whether these differences are related to female sex steroids or rather reflect developmentally-programmed gender differences awaits to be determined in future studies.

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