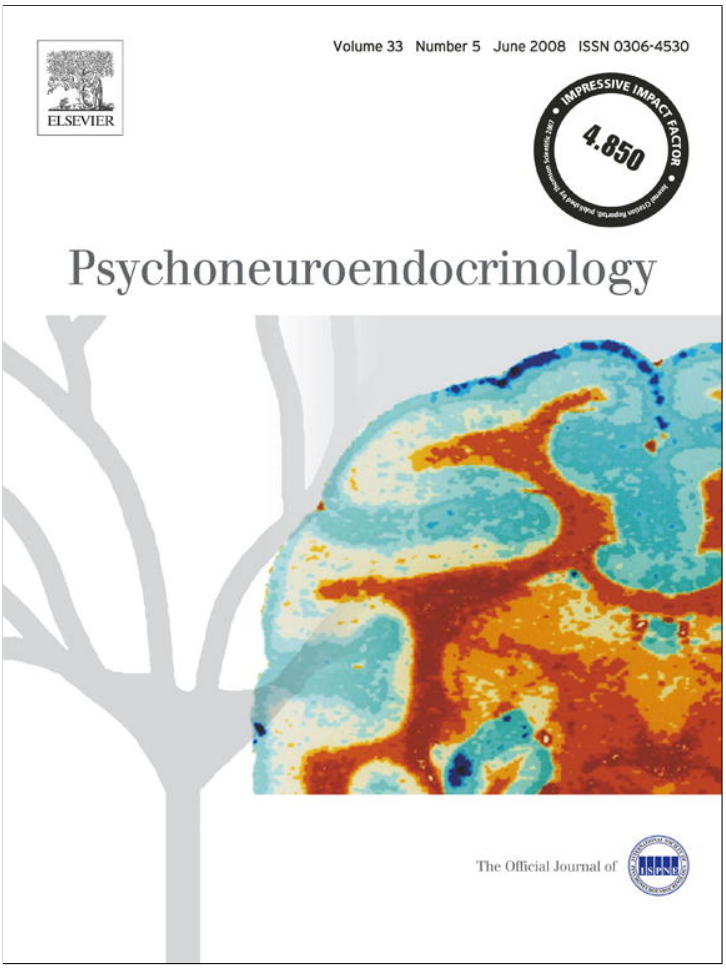

Psychoneuroendocrinology (2008) 33, 643–653

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Psychosocial stress induces working memory impairments in an *n*-back paradigm

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Received 24 October 2007; received in revised form 11 February 2008; accepted 12 February 2008

KEYWORDS
Working memory;
n-Back paradigm;
Psychosocial stress;
HPA;
SNS;
Prefrontal cortex

Summary
In contrast to the substantial number of studies investigating the effects of stress on declarative memory, effects of stress on working memory have received less attention. We compared working memory (numerical *n*-back task with single digits) in 40 men exposed either to psychosocial stress (Trier Social Stress Test (TSST)) or a control condition. Task difficulty was varied using two conditions (2-back vs. 3-back). Salivary cortisol (as a marker of hypothalamus–pituitary–adrenal (HPA) activity) and salivary alpha-amylase (sAA as a marker of sympathetic nervous system (SNS) activity) were assessed immediately before and three times after the stress or control condition. As expected stress resulted in an increase in cortisol, sAA, and negative affect. Subjects exposed to stress showed significant working memory impairments in both workload conditions. The analysis of variance indicated a main effect of stress for reaction time as well as accuracy. In addition, for reaction time a stress × block interaction occurred. Follow up tests revealed that only during the first block at each level of difficulty performance was significantly impaired by stress. Thus, the effects of stress became smaller the longer the task was performed. Results provide further evidence for impaired working memory after acute stress and illustrate the time course of this phenomenon.

1. Introduction

Stress leads to activation of the sympathetic nervous system (SNS) and an increased activity of the hypothalamic–pituitary–adrenal axis (HPAA; de Kloet et al., 2005). The first rapid response of the SNS is mediated via the catecholamines adrenaline and noradrenaline. The second somewhat slower stress response consists of activation of the HPAA and leads to the release of glucocorticoids from the adrenal cortex (GCs; cortisol in humans; corticosterone in rodents).

Numerous studies have demonstrated that acute stress or elevated SNS and/or GC concentrations affect learning and memory in animals and humans (LaBar and Cabeza, 2006; Wolf, 2006; Roozendaal et al., 2006). Stress can result in enhancing as well as impairing effects on declarative long-term memory (Wolf, 2006; Roozendaal et al., 2006; Joels et al., 2006; Lupien et al., 2007). The direction of the effect appears to depend primarily on the phase of

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0306-4530/$ - see front matter © 2008 Published by Elsevier Ltd.
doi:10.1016/j.psyneuen.2008.02.004

declarative memory affected. While the consolidation of emotional material is enhanced by stress, delayed retrieval of previously learned material is impaired (Wolf, 2006, 2008; Roozendaal et al., 2006; Lupien et al., 2007). Those effects appear to be caused by the action of glucocorticoids on GC sensitive receptors in the amygdala and hippocampus (Roozendaal, 2002; Joels et al., 2006; Diamond et al., 2007). However, findings suggested that the modulation of memory functions through GCs require concurrent SNS activity. Animal and human studies observed a dependence of the level of arousal and/or adrenergic activity during testing on the GC effects on declarative memory (Abercrombie et al., 2006; Kuhlmann and Wolf, 2006a, b; de Quervain et al., 2007).

While the effects of stress on declarative memory have received considerable attention fewer studies tested its influence on working memory (WM). The concept of WM refers to the structures and processes used for temporarily maintaining, updating, and manipulating information (Baddeley, 2003). Multiple studies indicate that these processes mainly rely on the integrity of the prefrontal cortex (PFC) (Fuster, 2000; Petrides, 2000; Muller and Knight, 2006) and parietal structures (Baldo and Dronkers, 2006), although this view is not without controversy (Andres, 2003).

Evidences from histopathological studies in rodents, monkeys, and humans indicate a large number of glucocorticoid receptors within the PFC and thus suggest that the PFC might be a target for GCs in the brain (Meaney and Aitken, 1985; Patel et al., 2000; Webster et al., 2002; Perlman et al., 2007). Moreover, the PFC is influenced by stress-sensitive noradrenergic projections from the locus coeruleus. Animal studies observed an enhancing effect of moderate noradrenaline concentrations on WM and an impairment under high concentrations (Arnsten, 1997, 2000; Arnsten and Li, 2005). It is suggested that within a normal range noradrenaline increases the prefrontal control of behaviour, whereas high levels induced a decreased behavioural PFC control (Chamberlain et al., 2006). For WM, comparable to declarative memory processes, human and animal studies revealed a tight interaction between the HPAA and the SNS. GCs did not unfold their modulating influence on WM in the absence of concurrent (nor)adrenergic activity (Arnsten, 2000; Elzinga and Roelofs, 2005; Roozendaal et al., 2006).

Even though a few previous studies in humans observed negative effects of cortisol- or stress-treatment on WM (Lupien et al., 1999; Wolf et al., 2001a; Elzinga and Roelofs, 2005; Oei et al., 2006) the empirical situation is rather heterogeneous. Several previous studies have used the digit span task to assess WM. Here participants are asked to repeat a series of digits either in the same order (forward condition) or in the reversed order (backwards condition). The length of the digit series typically increases up to a maximum of nine digits (eight for backwards). There are most often two trials for each series length and the task is stopped if a subject fails to correctly repeat both digit series of a particular length (Wechsler, 1987).

While some studies using the digit span test observed an impairing effect of cortisol administration (Wolf et al., 2001a) or psychosocial stress exposure (Elzinga and Roelofs, 2005) other studies failed to find effects using the same task (Hoffman and al'Absi, 2004; Kuhlmann and Wolf, 2005; Kuhlmann et al., 2005; Smeets et al., 2006). However, it is questionable whether the digit span task is a sensitive measure for small changes induced by experimental manipulations in young, healthy subjects (Reynolds, 1997; D'Esposito and Postle, 1999; Unsworth and Engle, 2007).

Besides the digit span task some previous studies used the immediate recall of wordlists to test the effects of stress on memory. These tasks rely at least in part on WM functions but also reflect declarative memory processes (Tops et al., 2004; Lezak et al., 2004). Again inconsistent results are reported. Some studies found an impaired immediate recall for neutral (Jelici et al., 2004) and pleasant words (Tops et al., 2004) after acute cortisol administration or psychosocial stress. Other studies in contrast only observed effects for the delayed, but not the immediate recall (de Quervain et al., 2000; Wolf et al., 2001a; Smeets et al., 2006). One contributing factor for the heterogeneous results might be related to the higher susceptibility of simple WM tasks for influencing experimental variables (e.g. phonological similarity or word length) compared to more complex tasks (Unsworth and Engle, 2007). In addition, immediate recall not only depends on WM but also on declarative memory processes and therefore a theoretical interpretation of the findings mentioned above remains difficult (but see Tops et al., 2004).

For more complex WM tasks results seem to be more consistent and impairments were repeatedly found after stress or GC administration (Lupien et al., 1999; Young et al., 1999; Oei et al., 2006). Two well-employed paradigms in WM research are the Sternberg- and the *n*-back-paradigm (Sternberg, 1966; Owen et al., 2005). In the Sternberg paradigm (Sternberg, 1966) a memory set containing one to four digits or letters is presented. Subsequently, a series of recognition sets are displayed and subjects have to decide as quickly and as accurately as possible whether or not one of the target stimuli is present. Target as well as recognition set size can vary in the number of letters/digits they contain (see Lupien et al., 1999; Oei et al., 2006). The WM load is manipulated by the number of required comparisons. This task thus focuses especially on the processes of maintenance and controlled search (Unsworth and Engle, 2007).

Using the Sternberg paradigm studies showed that both, the acute administration of high doses of hydrocortisone (Lupien et al., 1999) and the induction of psychosocial stress (Oei et al., 2006) impaired WM. These effects were in both studies restricted to trials with high task difficulty (a high comparison load; Lupien et al., 1999; Oei et al., 2006).

Another WM task is the *n*-back paradigm. Here subjects are asked to monitor series of briefly presented stimuli and have to decide in each trial if the currently presented stimuli is the same as the one presented two or three trials before (a more detailed description can be found in the method section). The main emphasis of this task is thus on monitoring and constant updating in WM (see Unsworth and Engle, 2007). Imaging studies demonstrated that frontal and parietal regions are continuously involved when subjects attend to various forms of the *n*-back paradigm (Fletcher and Henson, 2001). For the *n*-back task only the effect of pharmacological GC manipulation on WM was tested in healthy subjects or patients (Monk and Nelson, 2002;

Brunner et al., 2005). In addition, the influence of self-reported daily stress or cognitive interference was investigated using this task (Sliwinski et al., 2006; Stawski et al., 2006). To our knowledge, no study examined the *n*-back WM performance after acute experimentally induced psychosocial stress. However, this is of interest, because this task assesses specific WM processes which differ from those assessed with the Sternberg paradigm (see above Sternberg, 1966; Fletcher and Henson, 2001; Owen et al., 2005).

The objective of this study thus was to examine the influence of acute psychosocial stress and associated endocrine responses of the SNS and HPA axis on WM of male participants. Salivary alpha-amylase (sAA; as a marker of SNS activity; Rohleder et al., 2004; van Stegeren et al., 2006; Ehlert et al., 2006) and salivary cortisol (as a marker of HPA activity; Dickerson and Kemeny, 2004; Kudielka and Kirschbaum, 2005) were assessed before and several times after a stressful or a non-stressful situation. After the treatment WM was assessed in two conditions varying in their demand. In addition, a series of several blocks of both conditions was presented thus allowing a characterization of the temporal course of the stress effects.

2. Methods

2.1. Participants

Forty young, healthy male university students were recruited and randomly assigned to a stress ($n = 20$) or a control ($n = 20$) condition. Four of these 40 subjects (one of the stress and three of the control group) were excluded from data analysis because in at least one block in the WM task they solely pressed one button (only "no" or "yes" answers), probably due to a lack of motivation. All 36 subjects (mean age $\pm$ S.D.: 24.53 ± 3.48) were normally weighted (BMI 23.52 ± 2.19) and none of them suffered from acute or chronic diseases or were taking medications. The study was approved by the national ethic committee of the German Psychological Association (DGPs) and all subjects provided written informed consent before their participation.

2.2. Procedure and tests

2.2.1. Stress induction

The stress induction or the control situation was administered 30 min after the arriving of the subjects at the laboratory. Psychosocial stress was induced with the Trier Social Stress Test; TSST (Kirschbaum et al., 1993), a laboratory paradigm that reliably elicits an increase in HPAA and SNS activity (Dickerson and Kemeny, 2004; Kuhlmann et al., 2005). It consists of a video-taped free speech and a subsequent mental arithmetic task in front of a committee acting with a reserved attitude (duration in total 15 min). The non-stressful control condition was relatively similar in physical and mental demand (speech and math task, but alone in a room) but lacked the stress-inducing components of the TSST (socio evaluative threat (Dickerson and Kemeny, 2004; Kuhlmann et al., 2005).

2.2.2. Endocrine and autonomic measures

All testing sessions were conducted in the late morning between 10:00 and 12:30 h, similar to our previous study, which observed impairing effects of stress on declarative memory retrieval (Kuhlmann et al., 2005). Participants were requested to abstain from eating, drinking, or smoking during the hour preceding the beginning of the testing session. Saliva samples for the analysis of the HPAA and SNS stress response were taken immediately before (baseline), 1 min (sample +01), 10 min (sample +10), and 25 min (sample +25) after the cessation of the treatment (stress induction vs. control situation). Salivary alpha-amylase served as an indirect measure of SNS activation (Rohleder et al., 2004; van Stegeren et al., 2006; Ehlert et al., 2006). Saliva was collected using Salivette collection devices (Sarstedt, Nuembrecht, Germany). Free cortisol levels were measured using an immunoassay (IBL, Hamburg, Germany). For sAA a quantitative enzyme kinetic method was used as described elsewhere (van Stegeren et al., 2006). Inter- and intra-assay variations were below 15%.

2.2.3. Mood measurement

In order to assess the effects of the stressor on affect participants filled out the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988) at baseline and immediately after cessation of the stressor. The PANAS consists of 10 items for positive affects (e.g. interested, enthusiastic) and 10 items for negative affects (e.g. upset, ashamed). Participants have to rate the items on a five-point scale ranging from 1 = "very slightly or not at all," to 5 = "extremely". The ratings were averaged to create a score for positive affect and a score for negative affect.

2.2.4. Working memory testing

Ten minutes after cessation of the treatment (stress induction vs. control situation), at the time of peak cortisol levels WM performance of the participants was tested with an *n*-back task. This particular point for testing WM was chosen because previous studies using the TSST have repeatedly observed that 10 min after cessation of the stressor (25 min after the beginning of the stress exposure) salivary cortisol levels reach their peak (e.g. Kirschbaum et al., 1993; Kuhlmann et al., 2005). This response pattern was also reported in the Meta Analysis of Dickerson and Kemeny (2004).

Subjects were asked to monitor the identity of a series of one-digit numbers from "0" to "9", presented in a random sequence. They had to push one of two possible buttons ("yes" or "no") with the index and middle finger of their dominant hand to indicate whether the currently presented stimulus was the same as the one presented *n*-trials previously. Subjects received in total 10 stimulus blocks (2 practice blocks with feedback and 8 experimental blocks without feedback) in which the WM load varied by alternately using a 2-back and a 3-back condition (task difficulty). Each block consisted of 24 stimulus trials. The stimuli were displayed for 500 ms with an interstimulus interval of 2750 ms. In each block the first three digits were not analysed and within the remaining trials target stimuli (same stimulus as *n*-trials before) were presented randomly with a probability of 33%.

2.3. Statistical analysis

The influence of stress on the dependent variables (salivary stress markers, WM, and affect) was evaluated with a mixed model analysis of variances (ANOVA) with the repeated measurement factor time (two levels (mood ratings) or four levels (cortisol and sAA)) or the repeated measurement factor block (blocks 1–4) for the analysis of WM performance, respectively. The between subject factor was group (stress group vs. control group). Additional factors included in some of the ANOVA models are specified below. Greenhouse–Geisser corrected p-values were used when appropriate. Two-tailed tests were performed for all analyses and p was set to 0.05. Unless indicated, all results shown in the text are means $\pm$ standard deviation (S.D.). For purposes of clarity, data in the figures are illustrated using standard error of the mean (S.E.M.).

Due to the fact that cortisol- and sAA-concentrations are often distributed in a skewed fashion the data were tested for normal distribution. Whereas cortisol showed normal distribution the sAA data were positively skewed distributed. Therefore, the sAA measures were log-transformed and all further analyses were performed with the transformed data.

3. Results

3.1. Cortisol and autonomic responses to stress

A 2 (group) $\times$ 4 (time) repeated measurement ANOVA was performed for cortisol and alpha-amylase, respectively. The analyses of the endocrine responses revealed higher cortisol concentration in the stressed group compared to the control group (see Figure 1a). The ANOVA indicated a significant time $\times$ group interaction ($F(3,102) = 15.51$; $p < 0.01$). Follow up analysis with Bonferroni–Holm corrected independent t-tests revealed significant differences between the stressed and non-stressed group on the +10 and the +25 sampling point (p's < 0.01).

For sAA the analysis showed a significant main effect for time ($F(3,102) = 9.61$; $p < 0.001$) and a time $\times$ group interaction ($p = 0.013$; see Figure 1b), but no main effect of group ($p > 0.05$). While sAA levels rose significantly in the stress group ($p < 0.001$) between the baseline and the +01 measurement it did not so in the control group ($p > 0.10$). However, further analysis yielded no significant differences between the stressed and the control group for the +01 sampling point ($p = 0.10$, uncorrected) or any of the other three sampling points (all $p > 0.10$).

3.2. Affect

A repeated measurement ANOVA with the within subject factor time (pre- vs. post-measurement) and the between subject factor group (stress group vs. control group) was computed separately for negative and positive affect. For negative affect, a significant time $\times$ group interaction was found ($F(1,34) = 16.27$; $p < 0.001$). While both groups did not differ in negative affect before treatment (stress group: 1.43 ± 0.46 vs. control group: 1.46 ± 0.38) they did differ significantly after treatment, with stressed subjects reporting more negative affect (stress group: 1.67 ± 0.59 vs. control group: 1.16 ± 0.16). For positive affect, no significant effect was found (all $p > 0.10$).

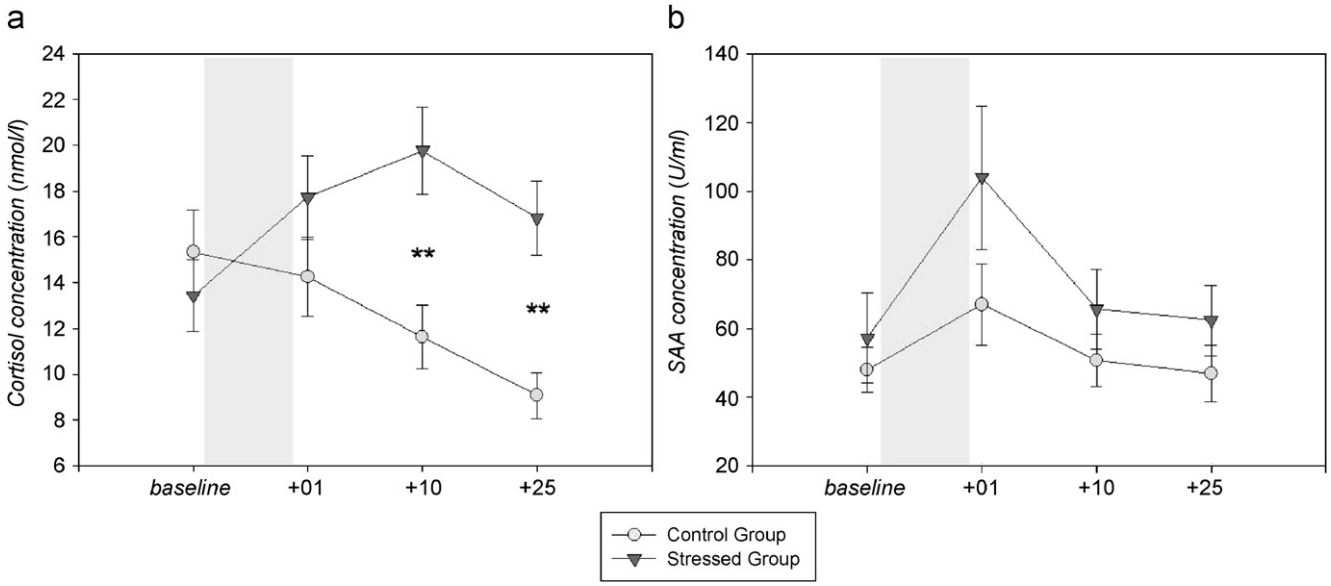

Figure 1 Effects of stress on salivary cortisol and sAA levels. Stressed subjects revealed significant higher cortisol concentrations compared to the control group (a). Corrected independent t-tests revealed significant differences on the +10 and the +25 sampling point (**$p < 0.001$). For sAA (b) the ANOVA revealed a significant group by sampling-point interaction, but no significant between group differences in the post hoc t-tests were detected. Log-transformed data were used for the statistical analysis, but the raw sAA data are used for the display in the graph. Data are presented as group mean $\pm$ S.E.M.

3.3. Working memory performance

For the analysis of WM performance, a 2 (group) × 2 (task difficulty) × 4 (blocks) repeated measurement ANOVA was calculated for reaction time and percentage of correct responses, respectively. The analyses of the reaction times of the correct responses revealed a significant main effect for task difficulty (2-back vs. 3-back) and for block (blocks 1–4; see Table 1 for all ANOVA results for the WM task). Most importantly a significant main effect of group occurred. Stressed subjects showed significantly slower mean reaction times in both task difficulties (mean reaction time 2-back: stress group: 879.69 ± 169.21 vs. control group: 715.32 ± 158.38; mean reaction time 3-back: stress group: 943.26 ± 181.76 vs. control group: 811.97 ± 191.64). In addition, a significant block × group interaction occurred (see Figure 2). For further exploration of the interaction Bonferroni–Holm corrected independent *t*-tests were calculated for each block in the respective level of difficulty. The results revealed significant differences between the stressed and the control group for the first block in both the 2-back and 3-back conditions ($t(34) = -3.07$; $p < 0.001$; $t(34) = -3.18$; $p = 0.003$). In the following blocks stressed subjects still exhibited slower reaction times, but those were no longer significantly different from controls. An additional ANOVA was conducted with the overall reaction time (e.g. correct and incorrect responses, instead of the reaction time for the correct responses only). This analysis leads to almost identical results namely a main effect of group and a group × block interaction (data not shown).

Analysis of the percentage of correct responses (Figure 3) revealed as expected a significant main effect for the within subject factors task difficulty (2-back vs. 3-back) and for block (significant post hoc difference between blocks 1 and 4). Additionally, a significant main effect for the between subject factor group was observed (see Figure 3; Table 1). Participants of the stressed group made fewer correct responses (stress group: 79.29 ± 8.78% vs. control group: 86.59 ± 6.13%). No significant interactions for the between subject factor group (stress group vs. control group) and the

Table 1 ANOVA result summary of the influence of group (stress or control group) on working memory.

Effect	*n*	*F*	*p*
Reaction time of correct responses			
Group	36	6.781	0.014
Task difficulty	36	29.502	<0.001
Task difficulty × group	36	1.258	0.270
Block	36	4.573	0.009
Block × group	36	4.500	0.010
Task difficulty × block	36	0.908	0.435
Task difficulty × block × group	36	0.084	0.963
Percentage of correct responses			
Group	36	8.171	0.007
Task difficulty	36	108.472	<0.001
Task difficulty × group	36	0.522	0.475
Block	36	4.136	0.008
Block × group	36	2.193	0.093
Task difficulty × block	36	1.342	0.265
Task difficulty × block × group	36	0.578	0.631

The ANOVA model contained the between group factor *group* (stress vs. control) and the within group factors *task difficulty* (2-back vs. 3-back) and *block* (four blocks for each condition).

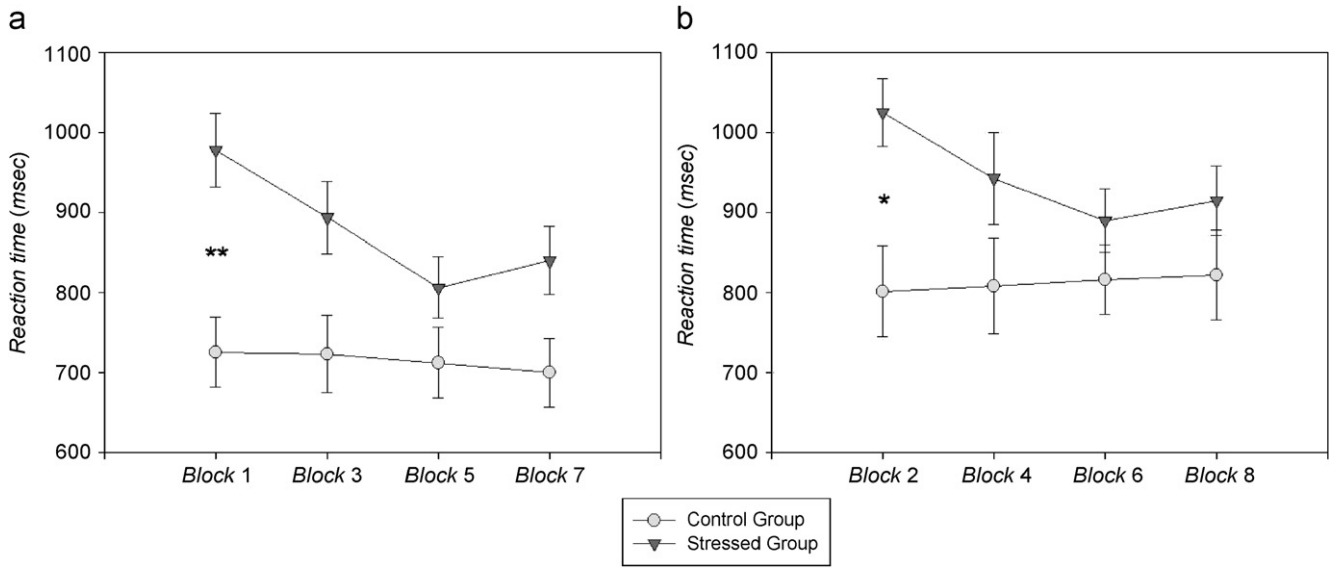

Figure 2 Effects of stress on the *n*-back performance (reaction time). The 2- and 3-back conditions were alternately presented with the 2-back condition starting with block 1 and the 3-block condition with block 2, respectively. Stressed subjects showed significant slower reaction times of correct responses in the 2-back (a) and 3-back working memory condition (b). Corrected independent *t*-tests showed that this effect first was particularly pronounced in the first block in both the 2- and 3-back conditions (*$p < 0.01$; **$p < 0.001$). Data are presented as group mean ± S.E.M.

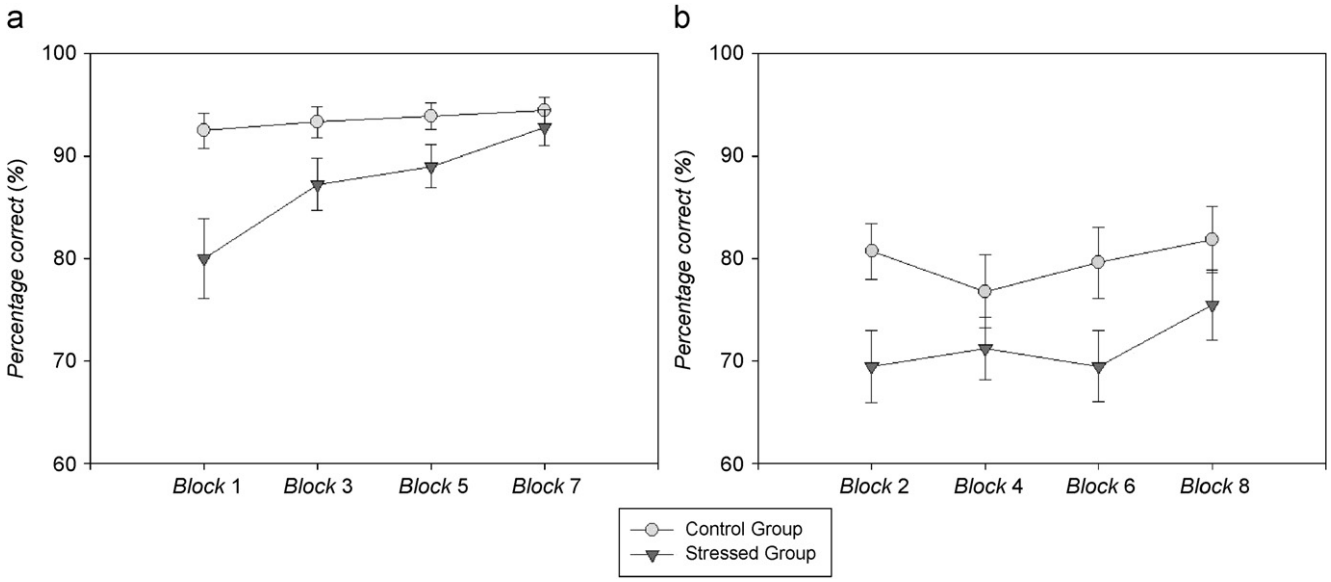

Figure 3 Effects of stress on the *n*-back performance (percentage of correct responses). A main effect for group was observed as well as a higher percentage of correct responses in the 2-back (a) compared to the 3-back task (b; main effect of task difficulty). Data are presented as group mean ± S.E.M.

repeated measurement factors block or task difficulty were found (see Table 1).

3.4. Associations between working memory, neuroendocrine stress markers, and affect

In order to test whether changes in cortisol, sAA, or affect were associated with the averaged reaction time for the correct responses across both back-conditions or the averaged percentage of correct responses in the WM task Pearson correlations were calculated using delta measures for the neuroendocrine and subjective stress measures (post treatment minus baseline). For the cortisol- and sAA-level delta increases were defined as the concentration on the +10 measurement (immediately before the beginning of the WM task) minus baseline. All correlations are presented in Table 2. Results showed a marginally significant correlation between the cortisol and sAA increase. Further on, a larger cortisol increase was correlated with longer response times and tended to be correlated with a lower percentage of correct responses. No associations were found between WM performance and either the sAA increase or changes in affect.

In order to test if the cortisol response would continue to predict WM performance after controlling for group differences a stepwise regression analysis was conducted. For the prediction of WM performance group was entered as the first step and cortisol increase as the second step. This analysis indicated that the cortisol response did not significantly add to the amount of variance already explained by the grouping variable. Thus, the cortisol increase does not qualify as a significant mediator (MacKinnon et al., 2007).

4. Discussion

The main objective of this study was to investigate the effect of acute psychosocial stress and the associated endocrine responses of the HPAA and SNS on WM performance in two levels of task difficulty of a numerical *n*-back task. We observed that stress led to impaired WM. The effects were not modulated by difficulty (2- or 3-back), but vanished over time. Changes in the reaction time of the WM performance were moderately but significantly correlated with the cortisol response, but were not associated with changes in sAA, or changes in affect. Those main findings will be discussed below.

In order to characterize the acute stress response salivary cortisol, sAA as well as mood ratings were assessed. The results revealed significantly increased activity of the SNS and HPA in subjects of the TSST-group as well as enhanced negative affect. These findings are well in line with previous studies (Rohleder et al., 2004; Dickerson and Kemeny, 2004; Kudielka et al., 2004; Nater et al., 2006; Het and Wolf, 2007) and indicate the successful induction of moderate stress.

Subjects of the stress group showed decreased WM performance for the 2-back as well as for the 3-back condition of the *n*-back task. This impairment was reflected in significant slower reaction times and fewer correct responses. Follow up tests indicated that the effects of stress on WM performance were only significant within the first blocks of the 2- and 3-back conditions. The results are in line with studies observing WM impairments after psychosocial stress (Elzinga and Roelofs, 2005; Oei et al., 2006), GC administration (Lupien et al., 1999; Wolf et al., 2001a), or noradrenaline manipulation (Chamberlain et al., 2006). However, they are in contrast to several studies failing to reveal an influence of GCs or psychosocial stress on WM (Monk and Nelson, 2002; Hoffman and al'Absi, 2004; Kuhlmann et al., 2005; Brunner et al., 2005; Smeets et al., 2006).

One explanation for the contradicting results obtained in some of the previous studies might be the employment of different WM paradigms varying in the sensitivity, the involvement of distinguishable WM processes (namely

Table 2 Correlations between neuroendocrine stress indices, working memory performance, and changes in affect.

	Cortisol delta increases	sAA delta increases	WM reaction time	WM % correct	PANAS positive mood	PANAS negative mood
Cortisol delta increases						
R	1	–	–	–	–	–
p						
sAA delta increases						
R	0.333*	1	–	–	–	–
p	0.047					
WM reaction time for correct responses						
R	0.378*	0.208	1	–	–	–
p	0.023	0.223				
WM percentage correct						
R	−0.319	−0.158	−0.525**	1	–	–
p	0.058	0.357	0.001			
PANAS delta increases positive mood						
R	0.193	0.248	−0.035	−0.118	1	–
p	0.260	0.144	0.839	0.493		
PANAS delta increases negative mood						
R	0.318	0.108	0.111	−0.020	−0.109	1
p	0.059	0.530	0.518	0.909	0.529	

The correlation results contained the increase of the cortisol- and sAA response (+10 minus baseline), the working memory performance (reaction time for correct responses and percentage of correct responses), and the changes of positive and negative affects (post-treatment minus baseline) for all 36 subjects.

maintenance, controlled search, and updating) as well as in the demand they place on WM (Sliwinski et al., 2006; Unsworth and Engle, 2007). Regarding the sensitivity the digit span task is considerably shorter as both the Sternberg and the *n*-back task. Additionally, the task difficulty is continuously increased in the course of testing but only two trials with each level of difficulty are to be performed. Another aspect to keep in mind is the type of performance measurement. The number of correct repetitions is the only performance measure. Our study using the *n*-back task as well as studies employing the Sternberg paradigm (Lupien et al., 1999; Oei et al., 2006) suggested that reaction time measures are particularly sensitive for the detection of stress induced WM deficits. In sum, the shorter task duration, the absence of more than one performance criterion as well as the lower demand placed on WM by simple digit tasks (Unsworth and Engle, 2007) might lead to a lack of sensitivity of the digit span task for the detection of acute stress effects.

Two of the previous mentioned studies not reporting WM impairments also employed an *n*-back paradigm (Monk and Nelson, 2002; Brunner et al., 2005). While one of those studies also used an *n*-back task with digits (Brunner et al., 2005), the second study employed more complex stimuli consisting of faces and objects (Monk and Nelson, 2002). Both of those studies used GC administration instead of stress exposure. Furthermore, Brunner et al. (2005) tested prolonged GC effects in a population repeatedly exposed to GCs (neurological patients). In the second study (Monk and Nelson, 2002), healthy subjects received a single administration of 30 mg of hydrocortisone. The 2-back task used in this latter study differed substantially from our task in that different (faces and objects) and fewer stimuli were employed. The differences in the experimental designs and/or in the specifics of the used *n*-back paradigm might be able to explain the discrepancies between those two studies and our current findings.

Moreover, studies showed that the time of day might be critical for testing because of the pronounced circadian pattern of cortisol (Maheu et al., 2005a, b). GC or stress treatment has been reported to impair memory performance in the morning, a time when endogenous GC levels are high. In contrast, some studies suggest that in the afternoon (a time when Monk and Nelson had tested their subjects), a period with lower endogenous levels of cortisol exogenous cortisol application (Lupien et al., 2002) or stress (Maheu et al., 2005a, b) might have enhancing rather than impairing effects on WM.

Finally, the absence of noradrenergic activation might contribute to the divergent results observed in some of the GC treatment studies. Animal and human studies repeatedly demonstrated (Roozendaal et al., 1999, 2004; Elzinga and Roelofs, 2005) that modulation of memory functions involve GC as well as noradrenergic activation. In contrast to the

employment of psychosocial stress induction pharmacological GC administration does not lead to an enhanced release of noradrenaline and thus might only be effective if a certain amount of testing induced arousal is present (Okuda et al., 2004; Kuhlmann and Wolf, 2006a, b).

Another result of our study revealed that both task conditions (2- vs. 3-back) were impaired by psychosocial stress. To our knowledge, there is no other laboratory study comparing the influence of acute psychosocial stress induction on different levels of difficulty on an *n*-back task. Even though a field study observed a relationship between perceived daily stress and the performance in a 2-back task condition but not in a less demanding 1-back version (Sliwinski et al., 2006). Regarding the Sternberg paradigm an impact of task difficulty was observed (Lupien et al., 1999; Oei et al., 2006). These two studies found an impairing effect of GC administration or stress induction only in trials with a high WM load. However, it should be considered that the Sternberg paradigm makes demands on the maintenance and search component of WM while in the *n*-back task the subjects additionally have to continuously manipulate and update the incoming information (Sternberg, 1966; Fletcher and Henson, 2001), which might lead to a higher level of difficulty. This assumption is supported by functional imaging studies which found higher prefrontal activation in manipulation tasks compared to task requiring solely maintenance (D'Esposito et al., 1999; Postle et al., 1999; Veltman et al., 2003). In addition, the inspection of the response behaviour of our stressed subjects showed false response rates of about 13% in the less demanding 2-back condition while Lupien et al. (1999) and Oei et al. (2006) reported considerable lower detection errors rate. This observation provides evidence for the assumption that the *n*-back task employed in our study was more demanding even in the relatively easier 2-back condition. It would be interesting to add a 1-back condition in future studies on this topic, in order to be able to test the effects of stress over a broader range of task difficulty.

As a further interesting result our data showed that the WM impairment is more pronounced in the first blocks of the testing compared to the last. In fact, only in the first block of each difficulty level significant differences occurred in the post hoc tests. However, not until the end of testing the performance of the stressed subjects approached the level of performance of the control group. This was the case for both, the reaction time and the percentage of correct responses. The control group in contrast barely showed a change of performance over time.

Previous studies did not report if they observed changes in WM performance during the process of memory testing after psychosocial stress or GC administration (Lupien et al., 1999; Monk and Nelson, 2002; Brunner et al., 2005; Oei et al., 2006). This could be partially attributed to the fact, that the duration of some WM tests was too short to permit to detect changes over time.

In a recent review by Diamond et al. (2007) it was suggested that the initiation of a strong emotional experience (e.g. stress) almost immediately activates memory related neuroplasticity in the hippocampus and the amygdala but rapidly inhibits prefrontal cortical functioning. It seems that the greater the extent of PFC involvement in the completion of a task, the more likely is a decrease in the task performance. In this context, the precise duration of the inhibition appears to depend on the nature and intensity of the stressor as well as on the magnitude of the stress response. The latter is influenced by the stressor but also by characteristics of the individual (e.g. coping capability, genetic factors; Charney, 2004; de Kloet et al., 2005; Salvador, 2005; Meijer, 2006).

These observations are well in line with results of our study indicating a more pronounced WM impairment in stressed subjects at the beginning of the task while in the later blocks both groups achieved a similar task performance. Our findings are also in line with another human stress WM study, which observed that WM performance was no longer impaired by stress 35 min after cessation of the stressor (Elzinga and Roelofs, 2005).

An alternative explanation might be that the WM performance is particularly susceptible for the influence of stress when tasks are new and marginally trained. According to the dual process theory (Schneider and Shiffrin, 1977; Miller and Cohen, 2001; Schneider and Chein, 2003) processing of new tasks requests a controlled process which is conscious, intentional, and limited in capacity. After sufficient practice the processing becomes automatic and more effective with less demand on cognitive resources. This view is supported by functional imaging studies which observed that practice led to decreased activity in the dorsolateral PFC and increased processing efficiency (Jansma et al., 2001; Milham et al., 2003; Koch et al., 2006). Since the physiological stress response seems to modulate prefrontal cortical functions (Fuchs et al., 2006; Diamond et al., 2007; McEwen, 2007) it might be possible that *n*-back performance is particularly impaired when the task processing strongly occupies the cognitive resources.

As a last observation we found in our study a moderate but significant correlation between the salivary cortisol increase and the response time. Slower reaction times were associated with a stronger increase. This is in line with other studies reporting correlations between stress induced cortisol elevations and changes in WM or declarative memory (Kirschbaum et al., 1996; Lupien et al., 1999; Wolf et al., 2001b; Oei et al., 2006; Smeets et al., 2006).

However, when we controlled for the influence of group membership in a regression analysis the cortisol response was no longer able to significantly explain an additional amount of the variance in WM performance. This suggests that in our data set cortisol is not a strong mediator of the observed effects of stress on WM. This interpretation however is limited by the fact that group membership explained a substantial amount of variance in WM performance, thus making it difficult for a second variable to significantly add to the amount of explained variance. Moreover, group membership and the cortisol response were of course highly correlated. Additional pharmacological studies are needed to characterize the role of cortisol in the observed stress induced *n*-back task impairment.

In contrast, no associations were observed between changes in negative mood and WM. Our results appear to be at odds to studies employing mood induction methods, which observed relationships between negative mood and impairments in cognitive functions, mediated by the PFC (Bartolic et al., 1999; Gray et al., 2002; Schneider et al., 2006). However, it should be noted, that these studies were

restricted to mood induction solely so it is hard to predict the additional effect of endocrine changes. In this context, studies using pharmacological cortisol administration which does not result in changes in mood are of interest. Several of those studies reported decreased WM in the absence of alterations in mood (Lupien et al., 1999; Wolf et al., 2001a). Those pharmacological studies indicate that cortisol can impair WM on its own in the absence of stress induced mood alterations. Thus, while negative mood can influence WM it appears not to be a major factor in the context of stress associated WM impairments.

Some field studies suggest that additional psychological factors influence WM performance in the context of stress (Sliwinski et al., 2006; Stawski et al., 2006). Evidence is presented that stress associated intrusive thoughts negatively impact on attentional resources thereby leading to impaired WM especially in demanding tasks. Future experimental studies in this field might benefit from the assessment of intrusive thoughts and/or rumination in response to the stress induction.

With our design the question as to whether or not the impairment in WM is finally attributable to the endocrine, the affective changes, or an interaction of both remains unanswered. It is likely that those factors interact at multiple levels (e.g. Abercrombie et al., 2006). Future studies combining pharmacological manipulations with stress manipulations are needed to characterize the contribution of these factors.

Finally, some limitations of our study need to be addressed. Firstly, the group of subjects was restricted to a male student sample. It is well documented that sex differences exist in the endocrine stress response with an additional modulating influence of menstrual cycle and hormonal contraception in female subjects (Kirschbaum et al., 1999; Kudielka and Kirschbaum, 2005). In addition, at least in rodents, stress had a stronger influence on WM in female when compared to male rats (Shansky et al., 2006). Thus, our results for male subjects are not necessarily representative for females and thus additional studies are needed. Moreover, the relative small sample size might further confine the generalizability and statistical power of results.

As previously mentioned cortisol has a strong circadian pattern (Van Cauter, 1990). Since all our subjects were tested in the morning we cannot predict how the results would have been if testing had occurred in the afternoon (Lupien et al., 2002; Maheu et al., 2005a, b). Furthermore, for future studies it seems interesting to vary the WM testing within the course of the endocrine stress response. It would be important to characterize how soon the impairments develop and how long they persist after stress termination. In addition, it would be interesting to characterize the magnitude of the stress response needed in order to induce WM impairments. Based on previous observations one might expect that mild stress would result in enhanced WM performance, while moderate stress (as was induced by in the current study) already appears to reduce WM performance.

The conclusion to be drawn from our study is further limited by the selected WM task. Only verbal WM was assessed and it is thus unknown whether or not the findings would have been similar for visual spatial WM tasks. In addition, only two relatively demanding levels of task difficulty (2- and 3-back) were employed. A previous observational study (e.g. Sliwinski et al., 2006) suggests that a less difficult condition (1-back) would have been useful in allowing to answer the question at which level of task difficulty acute stress impairs WM.

At last, it might be advisable to not only examine the influence of stress on WM but additionally to test for changes in basic cognitive processes (e.g. attention, vigilance) even though previous studies found no influence of stress or cortisol treatment on these measures (e.g. Lupien et al., 1999; Kuhlmann et al., 2005).

In sum, we report that WM performance in an *n*-back task is impaired after psychosocial stress. The impairment was characterized by significant slower reaction times and fewer correct responses in both task conditions and particularly pronounced in the first blocks. Future neuroimaging studies are needed in order to characterize the neuronal correlates of this effect.

Role of the funding sources

The funding source had no further role in the design of the study, and in the collection, analysis, and interpretation of the data. In addition, it had no role in the decision to submit the paper for publication.

Conflict of interest

The authors declare that they have no conflict of interest.

Acknowledgements

The work of the authors was supported by a grant from the German Research Foundation (DFG WO 733/6-2). We wish to thank Boris Suchan (Ruhr-University Bochum) and Gernot Horstmann (University of Bielefeld) for their help in programming and implementing the working memory task.

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