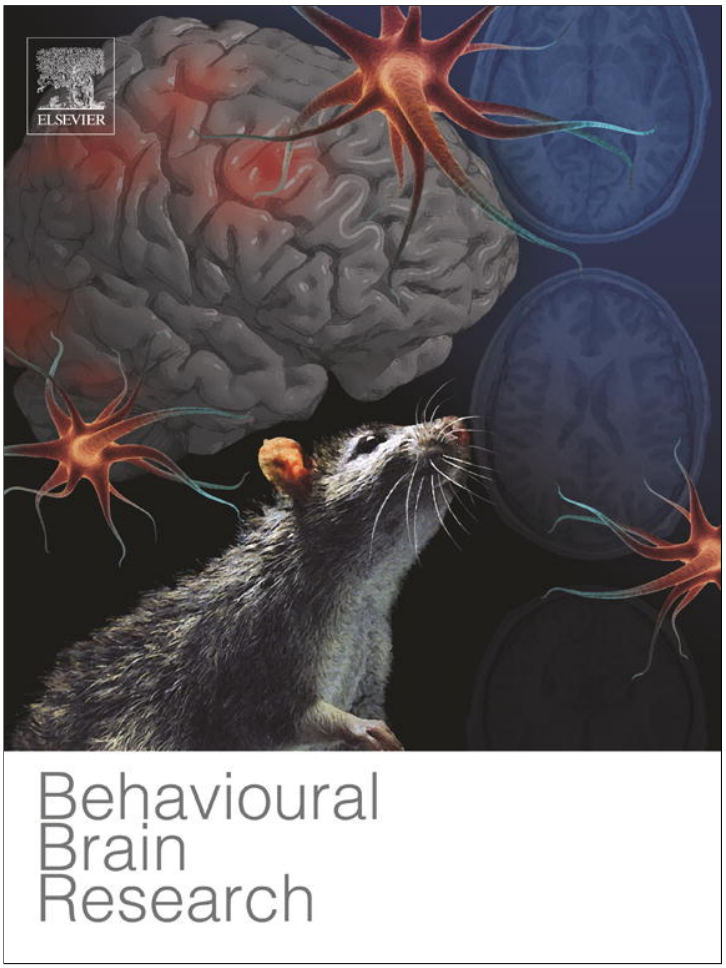

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Research report

Working memory is differentially affected by stress in men and women

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HIGHLIGHTS

- Two studies tested stress effects on working memory (*n*-back task) in men and women.
- The first study used neutral stimuli, the second used emotional stimuli.
- In both experiments a significant sex by stress interaction occurred.
- Stress enhanced *n*-back performance (reaction time) in men but impaired it in women.
- Stimulus emotionality did not interact with the stress effects.

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ABSTRACT

Stress has been shown to influence working memory. However, sex differences and the potential impact of stimulus emotionality have not received much attention. In a first experiment the effects of stress on a neutral working memory (WM) paradigm were tested in male and female participants (Experiment 1). Experiment 2 employed the same paradigm but used emotional stimuli. For this purpose, healthy participants were exposed either to a stressful (Trierer Social Stress Test (TSST)) or to a non-stressful control condition. Subsequently, WM performance in an *n*-back task was assessed. In Experiment 1, single digits were used as stimuli, while in Experiment 2 neutral and negative pictures were additionally employed. Salivary cortisol and Alpha-Amylase (sAA) were measured before and three times after the treatment as a marker of hypothalamus-pituitary-adrenal (HPA) axis- and sympathetic nervous system (SNS) activity. In both experiments, stress caused a substantial cortisol and sAA increase. For WM performance (response time) a stress by sex interaction was apparent. Stress enhanced performance in men, while impairing it in women. In both experiments stress had no effect on response accuracy. No modulating effect of the emotional quality of stimuli on *n*-back performance was observed (study 2). The results indicate that the effect of acute stress on *n*-back performance differs between the sexes. In contrast to long-term memory, the influence of stress on WM appears not to be modulated by the emotionality of the employed stimuli if stimuli are potential targets as it is the case in the *n*-back task.

1. Experiment 1

1.1. Introduction

In humans and other species, the prefrontal cortex (PFC), especially the dorsolateral PFC (DLPFC) is essential for higher cognitive functions such as executive processes and working memory (WM) [1–3]. Besides its importance for cognitive functions, another part of the PFC, the orbitofrontal Cortex (OFC), seems to play a critical role in the processing of motivation and emotion [4,5]. In addition, the PFC is also integrated into a negative feedback system that controls the down-regulation of the hypothalamus-pituitary-adrenal (HPA) axis [6]. The HPA axis is regarded as the major stress system in humans and other mammals, and its activation results in the release of glucocorticoids (GCs) into the blood stream. The stress hormones released (primarily cortisol in humans) can pass the blood–brain barrier and bind to GC sensitive receptors (mineralocorticoid (MR) and glucocorticoid receptors (GR)) in the brain [7]. Histopathological studies in humans, monkeys and rats indicate that, amongst others, the hippocampus, the amygdala and the PFC exhibit a large number of GC sensitive receptors [8–10]. Therefore, it seems reasonable to assume that these brain regions might be susceptible

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to stress effects. Indeed, studies have demonstrated that stress and glucocorticoid administration affect a variety of cognitive processes such as attention [11–13], declarative long term memory [14,15], and working memory [16–18].

Working memory (WM), which is mediated by the PFC, is generally understood as the ability to maintain and manipulate information that no longer exists in the external environment and to shield this information from irrelevant, distracting ones [3]. The results concerning the influence of stress or enhanced GC concentrations on WM are quite heterogeneous with no [19–21], impairing [16,17,22,23], or enhancing effects [24,25] being reported.

One factor which might mediate the effects of stress on working memory is sex. Rodent studies have suggested that female rats show stronger working memory impairments after stress or corticosterone treatment [26]. Most human WM stress studies have tested exclusively males (e.g. [16,17,22,27]. Recently, Cornelisse et al. [24] reported that stress enhanced *n*-back performance in men but had no effect in women. In order to test for the potential presence of sex differences, a comparable number of men and women were tested in the current study. Since a previous study using the *n*-back paradigm showed an equally strong effect of stress on the 2- and 3-back version [22] and in favor of a better understanding the *n*-back task was simplified with only one level of difficulty (2-back).

1.2. Method

1.2.1. Participants

In this study, 59 young healthy male and female university students (men $n = 30$; women $n = 29$) between 19 and 32 years of age (mean ± S.E.M. = 23.53 ± .348) participated. None of the participants self-reported acute or chronic diseases, medical or psychological treatment, or regular intake of medication. All female participants were free of hormonal contraception and were tested outside of menses (self-report). Female participants reported the last two dates of their menses. This information was used in order to allocate the participants in being in the first versus second half of their menstrual cycle. The average body mass index was 24.09 ± .471 kg/m^2 for male and 21.52 ± .441 kg/m^2 for female participants. The participants were recruited and randomly assigned to a stress (men $n = 15$; women $n = 15$) or a control condition (men $n = 15$; women $n = 14$). The study was approved by the national ethic committee of the German Psychological Association (DGPs) and all participants provided written informed consent before their participation.

1.2.2. Stress and control condition

The stress or control treatment was performed 30 min after the arrival of the participants in the laboratory. During this time participants read and signed the consent form, answered several questionnaires and afterwards were allowed to read newspaper magazines. The Trier Social Stress Test (TSST; [28]) was employed in order to induce stress. The TSST is a well-established laboratory stressor that reliably elicits a SNS and HPA response [20,29]. This psychosocial stressor consists of a short preparation time, a videotaped free speech, and a subsequent mental arithmetic task in front of a committee acting in a reserved attitude (duration in total was 15 min). Comparable to the stress group, the participants of the control group participated in a similarly physically and mentally demanding task (speech and math task, but alone in a room), the so-called Placebo TSST [30]. It lacks the stress-inducing components of the TSST (socio evaluative threat; [20,29]) and induces no cortisol increase.

1.2.3. Endocrine and autonomic measures

All testing sessions were conducted in the late morning between 1000 h and 1230 h to control for circadian effects of SNS and HPA activity [31,32]. 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 SNS and HPAA stress response were taken immediately before (baseline), 1 (sample +01), 10 (sample +10), and 25 min (sample +25) after the cessation of the treatment (stress induction vs. control situation). Salivary Alpha Amylase (sAA) served as an indirect measure of SNS activation [33,34]. Saliva was collected using Salivette collection devices (Sarstedt, Nuembrecht, Germany). Free cortisol concentrations were measured using an immunoassay (IBL, Hamburg, Germany). For sAA, a quantitative enzyme kinetic method was used as described elsewhere [35]. Inter- and intra assay variations were below 10%. In some samples, the amount of saliva was insufficient for the analysis of both markers. In such cases the analysis of cortisol was preferred.

1.2.4. Affect measurement

Changes in affect were assessed with the Positive and Negative Affect Schedule (PANAS) [36]. Participants filled out the PANAS at baseline and immediately after cessation of the stressor or the non-stressful situation respectively. The questionnaire consists of 10 items for positive affect (e.g. interested, enthusiastic) and 10 items for negative affect (e.g. upset, ashamed). Participants have to rate the items on a five point scale based on the current strength of the specific emotion or feeling from 1 = "very slightly or not at all," to 5 = "extremely". The ratings of the positive and negative items were summarized into a single negative and positive affect score (negative and positive affect scale), respectively.

1.2.5. Working memory paradigm: n-back task

Working memory was tested with an *n*-back task 10 min after cessation of the treatment (TSST or Placebo TSST). This particular point of time for testing working memory was chosen because cortisol concentrations typically reach their peak approximately 20–30 min after stress onset [29]. The *n*-back task employed in the present experiment is very similar with the paradigm used in a previous experiment [22]. However, some modifications were made. The participants' general task was to monitor the identity of a series of stimuli, 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 before. The single digits were presented in one level of difficulty (2-back) and the participants were instructed to be as fast and accurate as possible. Sixty-two stimuli were shown and the first two trials were excluded, leaving 60 trials to be analysed for each participant. The target stimuli within the remaining trials (same stimulus as *n*-trials before) were presented randomly with a probability of 33%. The stimuli were displayed for 500 ms with an interstimulus interval of 2750 ms.

1.2.6. Statistical analysis

First, an exploratory data analysis was performed to identify individual values which appear to deviate markedly from the data obtained from the entire sample. In SPSS, outliers are defined as individual measurements that are at least 1.5 Inter-Quartil-Ranges above the upper or beneath the lower quartile, respectively. Based on the expected differences in hormone concentrations in male and female participants, the exploratory analyses for the baseline cortisol and sAA concentrations were performed separately for both sex groups. The analysis revealed that some participants showed considerably deviating hormone concentrations compared to the values of their specific comparison-group. Therefore, all hormone samples of participants with conspicuous baseline values (outliers) were excluded from the respective analyses. Thus, the number of participants included in the analyses varies for the different hormones so that the "*n*" is specified at the beginning of each analysis. The exploratory analysis for WM performance was conducted for the reaction time for correct responses and the number of correct responses.

The influence of stress on the dependent variables (salivary stress markers, working memory, and affect) was evaluated with a mixed model analysis of variances (ANOVA) with the repeated measurement factor TIME (2–4 levels dependent on the used measure) and the between group factors TREATMENT (stress vs. control group) and SEX (male vs. female participants).For the analysis of working memory performance, separate univariate ANOVAs were calculated for the percentage of correct responses and reaction time with the fixed factors TREATMENT (stress vs. control group) and SEX (male vs. female participants). Greenhouse–Geisser corrected p values were used when appropriate. To correct for multiple testing, post hoc tests were Bonferroni–Holm corrected. Unless indicated, all results shown in the text and illustrations are means ± standard error mean (S.E.M.).

1.3. Results

1.3.1. Cortisol and sAA responses to stress

To investigate the effects of the TSST and the non-stressful Placebo-TSST on HPA and SNS activity, a 2 (SEX) × 2 (TREATMENT) × 4 (TIME: ba, +01, +10, +25) repeated measurement ANOVA was performed for cortisol and alpha-amylase, respectively. Twenty-six female and 27 male participants were included in the analysis of cortisol. The analyses of the endocrine responses revealed significant main effects of the between subject factors TREATMENT ($F(1, 49) = 33.42$; $p < .001$; $\eta^2 = .405$) and the within subject factor TIME ($F(3, 147) = 16.29$; $p < .001$; $\eta^2 = .249$). In addition, the ANOVA indicated a significant TIME by TREATMENT ($F(3, 147) = 57.04$; $p < .001$; $\eta^2 = .538$), a TIME by SEX ($F(3, 147) = 7.29$; $p < .01$; $\eta^2 = .129$), and a TIME by SEX by TREATMENT interaction ($F(3, 147) = 6.17$; $p < .01$; $\eta^2 = .112$). Bonferroni-Holm corrected independent t-tests revealed separately significant differences for men and women between the stressed and non-stressed subjects on the +01, +10, and the +25 sampling point (all p's $\leq .015$). While no differences were

found between male and female participants in the control group (see Fig. 1), stressed men showed significantly higher cortisol concentrations compared to women at the +25 sample (cortisol concentration at +25 sample women: 16.02 ± 1.76 nmol/l, men: 25.31 ± 2.80 nmol/l) and stronger cortisol increases (average cortisol increases +10 minus baseline; women: 6.48 ± 2.26 nmol/l, men: 14.12 ± 1.91 nmol/l).

For sAA, the data of 48 participants were analysed (23 female and 25 male participants). The analysis showed a significant main effect of TIME ($F(3, 132) = 15.43$; $p < .001$; $\eta^2 = .260$) and a TIME by TREATMENT interaction ($F(3, 132) = 7.38$; $p = .001$; $\eta^2 = .144$). However, post hoc Bonferroni-Holm corrected independent *t*-tests revealed no significant differences between both treatment groups (Fig. 1).

1.3.2. Affect

A repeated measurement ANOVA with the within subject factor TIME (pre- vs. post-treatment measurement) and the between subject factors SEX and TREATMENT was computed separately for the positive and negative affect scale of the PANAS for all participants ($n = 59$).

For the positive affect scale, the ANOVA revealed neither a significant main effect nor significant interactions. For the negative affect scale a significant main effect of TIME ($F(1, 55) = 24.48$; $p < .001$; $\eta^2 = .308$) and a significant TIME by TREATMENT interaction ($F(1, 55) = 28.87$; $p < .001$; $\eta^2 = .344$) was revealed. Post hoc dependent *t*-tests showed significant differences for the control- and TSST-group regarding the affect increase between the pre- and post-measurement. While participants of the control group showed no change of negative affect between both measurements (($t(28) = .783$; $p > .05$; mean negative affect score; pre: 1.35 ± .075; post: 1.33 ± .077) stressed participants revealed a significant increase with higher negative affect immediately after the treatment (($t(29) = -5.49$; $p < .001$; mean negative affect score TSST-group; pre: 1.11 ± .021; post: 1.56 ± .088).

1.3.3. Working memory

1.3.3.1. Reaction time for correct responses. A univariate ANOVA with the fixed factors SEX and TREATMENT was calculated for all participants ($n = 59$) for the dependent variable reaction time (RT) of correct responses. The ANOVA showed no significant main effect of SEX and TREATMENT, but a significant SEX by TREATMENT interaction was found ($F(1,55) = 4.00$; $p = .05$; $\eta^2 = .068$). Descriptive data showed that stressed men were faster compared to non-stressed men (control group: .737 ± .048 s vs. stress group: .634 ± .042 s; Fig. 2), the opposite was true for women with slower RTs in the TSST group than in the control group (control group: .648 ± .043 s vs. stress group: .716 ± .038 s, see Fig. 2)). The descriptive differences between the stress and the control conditions for the two sexes did not reach significance in post hoc independent *t*-tests (both $p > .10$). Effect size calculations for the determination of Cohen's *d* were conducted using G-power software [37]. The effect of stress on RT in men were medium in size ($d = .59$). The effect of stress on RT in women were slightly smaller ($d = .44$).

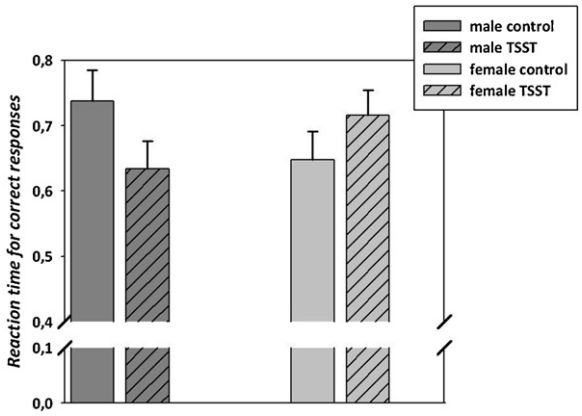

Fig. 2. Experiment 1: Mean reaction time in seconds for correct responses for male and female participants in the 2-back task.

1.3.3.2. Percentage correct responses. The number of correct responses per block was calculated by summing up the number of hits and correct rejections. Analysis of the percentage of correct responses with a univariate ANOVA ($n = 59$) containing the fixed factors SEX and TREATMENT revealed no significant effects. Participants of the control- and stress-groups did not significantly differ regarding the percentage of correct responses.

1.3.4. Possible influence of self-reported menstrual cycle half

Data on menstrual cycle phase (first versus second half of the cycle) was available for 26 participants. Thirteen reported to be in the first half, while the other 13 reported to be in the second half. The distribution of these two groups did not differ between the stress and control condition (Chi Square = 1.42, $p = .44$). Cycle half had no significant impact on the neuroendocrine (cortisol and sAA) or affective response to the stressor (all *p*'s > .10). Finally cycle phase had neither a direct effect on working memory performance (RT and accuracy) nor did it interact with the stress effect (all *p*'s > .10).

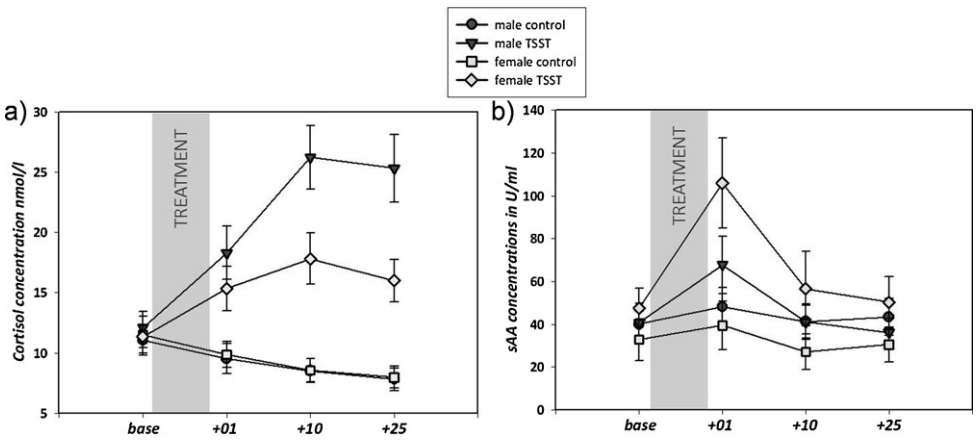

Fig. 1. Experiment 1: Mean cortisol (a) and salivary Alpha-Amylase (b) concentrations for male and female participants in the control and TSST condition.

2. Experiment 2

2.1. Introduction

Most of previous working memory studies used neutral stimuli such as digits or letters [22,24] although it is well established for long-term memory that stimulus emotionality influences memory performance substantially [38,39]. Interestingly, stress effects on long-term memory are most pronounced for emotional material (for review see [14]. GC effects on long-term memory rely on a concurrent sympathetic activation of the beta-adrenergic receptors in the basolateral amygdala (BLA) and interactions of this structure with other brain regions such as the hippocampus and neocortical structures [40,41].

Regarding WM processes, the results are less clear. Studies investigating the effects of task-irrelevant emotional stimuli (distracters) in a Sternberg task have shown an impairing effect of negative distracting pictures on WM performance [42], while task-relevant emotional stimuli appear to have only a mild influence on WM performance [43].

Effects of stress or cortisol on emotional working memory have so far been tested in a Sternberg paradigm only. Here, stress enhanced the impairing effect of emotional distractors [44]. In contrast, cortisol treatment reduced emotional distractibility [27]. This finding supports the hypothesis put forward by Putman and Roelofs [45] stating that cortisol reduces the impact of task irrelevant emotional distractors. This might counteract some of the initial stress effects mediated by catecholamines [46].

The previous studies [27,47] thus explored the extent to which task-irrelevant emotional stimuli interfere with neutral but relevant ones to be maintained in WM. It is an unanswered question whether emotional stimuli also disturb WM performance under stress when they are relevant for task processing. Therefore, in the present study, we wanted to investigate whether acute psychosocial stress affects WM performance in a paradigm with task-relevant emotionally neutral (digits and neutral pictures) and negative (negative pictures) stimuli. For this purpose, the *n*-back task was chosen, since stress effects on this task have been reported in the past [22,24].

2.2. Method

To ensure the comparability of the two experiments, the methods were kept identical as best as possible. For that reason, the general procedure, including timing, measurement of physiological stress parameters and subjective affect markers, was similar to Experiment 1. Thus, this method section contains only descriptions of those methods that deviate from the first experiment.

2.2.1. Participants

One hundred and nine young healthy male and female university students (men $n = 67$; women $n = 42$) between 18 and 40 years of age (mean ± S.E.M. = 23.80 ± .328) participated in the present study. The average body mass index was 23.88 ± .352 kg/m^2 for male and 21.64 ± .368 kg/m^2 for female participants. Exclusion criteria were similar to those of the first experiment, and again all female participants were free of hormonal contraception and testing did not take place during menses.

The participants were recruited and randomly assigned to a stress (men $n = 33$; women $n = 20$) or to a control condition (men $n = 34$; women $n = 22$). The study was approved by the national ethic committee of the German Psychological Association (DGPs) and all participants provided written informed consent before their participation.

2.2.2. Stimulus selection

In a Pilot study, 52 negative and neutral pictures were selected by visual judgement from the International Affective Picture System (IAPS, [48]) according to their visual complexity and the presence of people. Afterwards, 40 students (females $n = 21$; males $n = 19$) were asked to evaluate the pictures with respect to their valence, emotional arousal and visual complexity. The pictures were presented in a randomized order. In order to evaluate valence and emotional arousal, participants had to rate the pictures with the Self-Assessment-Manikin (SAM), an affective 9-point rating scale which was also employed by Lang et al. [48]. The visual complexity was additionally rated on a 9 point scale. Based on the ratings, 10 negative and 10 neutral pictures were chosen from the 52 pictures. Statistical analysis revealed that the groups of negative and neutral pictures were rated significantly different concerning their valence (1 = negative, 5 = neutral, 9 = positive) and arousal scores (1 = calm, 9 = excited), while the evaluation of visual complexity did not differ (see Table 1). A comparison of the normative IAPS ratings and the ratings from the pilot study showed that there was no significant difference in valence and arousal ratings between both samples (all p's > .05).

2.2.3. Working memory paradigm: emotional n-back task

Working memory was tested with an *n*-back task 10 min after cessation of the treatment (TSST or Placebo TSST). The employed task was very similar to that in Experiment 1 concerning the methodological properties such as stimulus presentation time, interstimulus interval and target probability. However, some important modifications were made to the stimuli-set. While single digits only were used in the previous experiment, the present one contained pictures with negative and neutral valence as well as digits. Participants received a total number of ten stimulus blocks (2 practice blocks with feedback and 8 experimental blocks without feedback). The working memory load was varied by alternately using a 2-back and a 3-back condition (task difficulty). In the practice blocks, participants were introduced to the task by working on a 2- back and 3-back task with simple geometric figures as stimuli (e.g. triangle, circle, and square). These neutral stimuli were used in the practice trials in order to avoid the participants being better trained in one group of stimuli (digits or pictures). Of the eight experimental blocks, 4 blocks used digits as stimuli and 2 blocks employed neutral and negative pictures respectively. Number and picture blocks were alternately presented, and in order to avoid order effects, each participant received the stimuli in one of four different sequences and each block consisted of 24 stimulus trials. The first three stimuli of each block were not analysed, while the target stimuli within the remaining trials (same stimulus as *n*-trials before) were presented randomly with a probability of 33%.

2.2.4. Statistical analysis

The statistical analysis is comparable to Experiment 1. At first, exploratory data analyses were performed for hormone and WM data to identify individuals which differ markedly from the data obtained from the entire sample. Participants with deviating data were excluded from the respective analysis so that the "*n*" is specified at the beginning of each analysis.

The influence of stress on the dependent variables (salivary stress markers, working memory, and affect) was evaluated with a mixed model analysis of variances (ANOVA) with the repeated measurement factor TIME (2–4 levels dependent on the used measure), BACK (2-back vs. 3-back), and STIMULUS TYPE (digits vs. neutral vs. negative pictures) for the analysis of working memory performance, respectively. The between group factors were TREATMENT (stress vs. control group) and SEX (male vs. female participants). Greenhouse–Geisser corrected p values were used when appropriate. To correct for multiple testing, post hoc *t*-tests were Bonferroni–Holm corrected. Unless indicated, all results shown in the text and illustrations are means ± standard error mean (S.E.M.).

2.3. Results

2.3.1. Cortisol and sAA responses to stress

In order to investigate the effects of the TSST and the non-stressful Placebo-TSST on HPA and SNS activity, a 2 (SEX) × 2 (TREATMENT) × 4 (TIME: ba, +01, +10, +25) repeated

Table 1
Ratings from the Pilot study from 40 student subjects (mean ± S.E.M).

Mean rating ± S.E.M.	Valence	Arousal	Visual complexity
Negative pictures $n = 10$	2.24 ± .117	6.33 ± .175	4.67 ± .188
Neutral pictures $n = 10$	5.46 ± .097	3.20 ± .153	4.68 ± .211
Paired t-Test	t (39), 22.76; $p < .001$	t (39), −15.03; $p < .001$	t (39), .037; $p = .971$

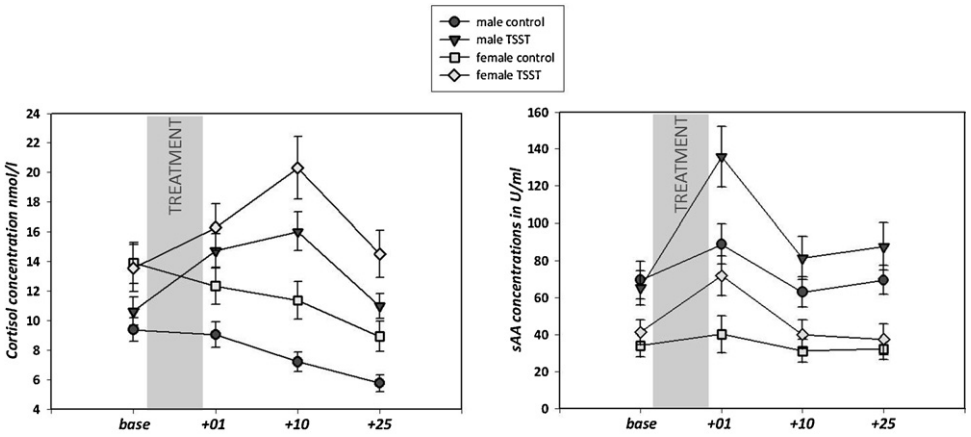

Fig. 3. Experiment 2: Mean cortisol (a) and salivary Alpha-Amylase (b) concentrations for male and female participants in the control and TSST condition.

measurement ANOVA was performed for cortisol and alpha-amylase, respectively. 45 female and 64 male participants were included in the analysis of cortisol. The analyses of the endocrine responses revealed significant main effects of the between subject factors SEX ($F(1, 105) = 10.63$; $p < .01$; $\eta^2 = .092$) and TREATMENT ($F(1, 105) = 21.55$; $p < .001$; $\eta^2 = .170$) and the within subject factor TIME ($F(3, 315) = 26.70$; $p < .001$; $\eta^2 = .203$). In addition, the ANOVA indicated a significant TIME by TREATMENT interaction ($F(3, 315) = 30.24$; $p < .001$; $\eta^2 = .224$). Follow-up analyses with Bonferroni–Holm corrected independent t-tests revealed significant differences between the stressed and non-stressed subjects on the +01, +10, and the +25 sampling points (p's $< .001$). Furthermore, women displayed higher overall cortisol concentrations compared to men (average cortisol concentrations women: $13.96 \pm .995$ nmol/l, men: $10.40 \pm .663$ nmol/l), although the cortisol increase (+10 minus baseline concentration) showed no significant difference between stressed men and stressed women ($t(52) = -.646$; $p > .05$; cortisol increase women: 6.74 ± 2.07 nmol/l, men: $5.40 \pm .936$ nmol/l, see Fig. 3).For sAA, the data of 98 participants were analysed (38 female and 60 male participants). The analysis showed significant main effects of SEX ($F(1, 94) = 17.90$; $p < .001$; $\eta^2 = .160$) and TIME ($F(3, 282) = 30.29$; $p < .001$; $\eta^2 = .244$) and a TIME by SEX ($F(3, 282) = 4.35$; $p = .01$; $\eta^2 = .044$) and a TIME by TREATMENT ($F(3, 282) = 8.72$; $p < .001$; $\eta^2 = .085$) interaction. The post hoc analyses revealed a significant difference between stressed and non-stressed subjects for the +01 sampling point with higher concentrations for the TSST group ($t(96) = 4.93$; $p < .01$; control: 69.86 ± 8.22 U/ml, TSST: 110.99 ± 11.66 U/ml). In contrast to cortisol, men displayed twice as high overall sAA concentrations compared to women ($t(96) = 4.20$; $p < .001$; women: 40.91 ± 4.88 U/ml, men: 82.51 ± 7.24 U/ml; Fig. 3).

2.3.2. Affect

A repeated measurement ANOVA with the within subject factor TIME (pre- vs. post-treatment measurement) and the between subject factors SEX and TREATMENT was computed separately for the positive and negative affect scale of the PANAS.

For the positive affect scale, the ANOVA revealed a significant main effect of TIME ($F(1, 111) = 9.00$; $p < .01$; $\eta^2 = .075$) and a significant TIME by TREATMENT ($F(1, 111) = 7.32$; $p < .01$; $\eta^2 = .062$) interaction. Post hoc dependent t-test showed that only participants from the control group reported significantly more positive affect after the treatment than before ($t(57) = -4.40$; $p < .001$; average pre-measurement: $2.77 \pm .086$ vs. post-measurement: $3.11 \pm .099$) while participants in the TSST group did not show differences between the pre- and post-measurement (average pre-measurement: $2.85 \pm .070$ vs. post-measurement: $2.89 \pm .088$).

For the negative affect scale, a significant main effect TREATMENT ($F(1, 111) = 23.71$; $p < .001$; $\eta^2 = .176$) and TIME ($F(1, 111) = 5.42$; $p < .05$; $\eta^2 = .047$) as well as a significant TIME by TREATMENT ($F(1, 111) = 38.77$; $p < .001$; $\eta^2 = .259$) interaction was found. The control and stress group showed no significant differences in negative affect before (control-group: $1.33 \pm .042$ vs. TSST-group: $1.35 \pm .036$), but after the treatment ($t(113) = -6.40$; $p < .001$; control-group: $1.15 \pm .028$ vs. TSST-group: $1.74 \pm .087$).

2.3.3. Working memory

2.3.3.1. Reaction time for correct responses. For the analysis of WM performance, defined by the reaction time (RT) of correct responses, a 2 (SEX) × 2 (TREATMENT) × 2 (BACK) × 3 (STIMULUS TYPE) repeated measurement ANOVA ($n = 115$) was calculated. The ANOVA showed no significant main effect of SEX, TREATMENT, BACK and STIMULUS TYPE. In addition, no significant interaction was found for STIMULUS TYPE with any other within-or between-subject factors. However, the ANOVA revealed a significant three way interaction of SEX by TREATMENT by BACK ($F(1,111) = 11.68$; $p = .001$; $\eta^2 = .095$). Descriptive data showed slower RTs in stressed female participants for the more demanding 3-back condition compared to females in the control condition (control group: $.657 \pm .042$ sec vs. stress group: $.720 \pm .035$ s; Fig. 4). The opposite picture was found for male participants in the 3-back condition, in which the TSST group displayed faster RTs than the control group (control group: $.710 \pm .039$ s vs. stress group: $.660 \pm .039$ s). The descriptive differences between the stress and the control conditions in the 3-back condition for the two sexes did not reach significance in post hoc independent t-tests (both $p > .10$). Effect

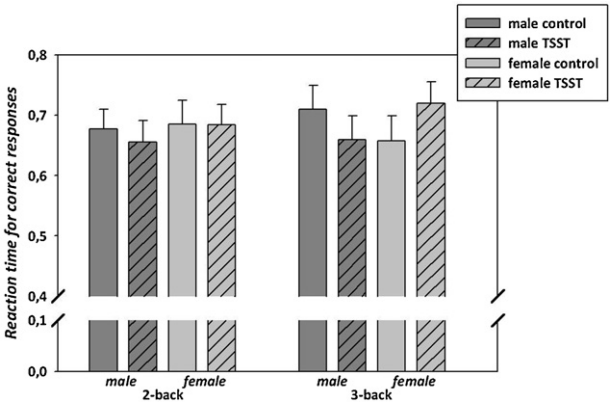

Fig. 4. Experiment 2: Mean reaction time in seconds for correct responses for male and female participants in the 2-back and 3-back condition.

size calculations for the determination of Cohen's *d* [49] were conducted using G-power software [37]. The effect of stress on RT in men were small (*d* = .22). The effects of stress on RT in women were somewhat larger but still small (*d* = .34).

2.3.3.2. Percentage correct responses. The number of correct responses per block was calculated by summing up the number of hits and correct rejections. Analysis of the percentage of correct responses with a 2 (SEX) × 2 (TREATMENT) × 2 (BACK) × 3 (STIMULUS TYPE) repeated measurement ANOVA ($n = 115$) revealed a significant main effect of the within subject factors BACK ($F(1,111) = 177.40$, $p < .001$; $\eta^2 = .615$) and STIMULUS TYPE ($F(2,222) = 4.21$, $p < .05$; $\eta^2 = .037$). As expected, post hoc dependent t-tests showed that participants made more correct responses in the 2-back compared to the 3-back condition ($t(114) = 13.88$; $p < .001$; 2-back: 81.77 ± .883; 3-back: 71.70 ± .977). Regarding the STIMULUS TYPE, post hoc dependent t-tests demonstrated that participants showed significantly more correct responses in *n*-back blocks showing digits (digits vs. neutral pictures: $t(114) = -431$; $p > .05$; digits vs. negative pictures: $t(114) = 2.31$; $p < .05$) compared to those with pictures (neutral vs. negative pictures: $t(114) = 2.31$; $p < .05$; average percentage correct digits: 78,15 ± .935; pictures neutral: 75.82 ± 1.11; pictures negative: 76.23 ± .957). No other significant main effects or interactions were found.

2.3.4. Possible influence of self-reported menstrual cycle half

Data on menstrual cycle phase (first versus second half of the cycle) was available for 40 participants. Seventeen reported to be in the first half, while the other 23 reported to be in the second half. The distribution of these two groups did not differ between the stress and control condition (Chi Square = 1.00, $p = 1.00$). Cycle half had no significant impact on the neuroendocrine (cortisol and sAA) or affective response to the stressor (all *p*'s > .10). Finally, cycle phase had neither a direct effect on working memory performance (RT and accuracy) nor did it interact with the stress effect (all *p*'s > .10).

2.4. Discussion

The objective of the first experiment was to investigate the effect of acute stress on the WM performance in a paradigm with neutral digits. Moreover, we wanted to explore possible sex differences. Data showed strong physiological and psychological stress responses. Effects on working memory differed between men and women as indicated by a SEX by TREATMENT interaction. While stress impaired performance in female participants as indicated by increased response times, the opposite pattern was observed for males. Similar results were detected in the second experiment which was conducted to replicate the sex-dependent stress effects while exploring the impact of stimulus emotionality. Again, results revealed that females were impaired by stress (slower RTs and a constant number of correct responses) while males improved (faster RTs and a constant number of correct responses).

2.4.1. Sex differences in stress responsivity

In both experiments, the stressor induced a strong HPA axis response. In Experiment 2, the cortisol response of men and women was relatively similar, but the two groups differed at baseline. A similar pattern was observed for sAA. In Experiment 1, no baseline differences were apparent, but men showed a more pronounced cortisol response to the stressor than women. The latter finding has been observed repeatedly in our [50,51] and in others laboratories (for a review see [52]). Of note is the fact that despite the differences in cortisol and sAA responses between the two studies, the behavioural findings were highly similar. It is thus unlikely that differences in cortisol reactivity (Experiment 1) or baseline differences in cortisol levels (Experiment 2) are the sole explanation for the observed sex specific effects on working memory, which will be discussed below. In fact, the neuroendocrine observations suggest that other factors besides cortisol are responsible for the observed sex dependent effects. Changes in noradrenergic or dopaminergic activity in the PFC are possible candidates (see below), even though it should be kept in mind that they, of course, interact closely with GCs (see [53]).

2.4.2. Stress effects on WM

Previous studies investigating potential stress effects on WM have reported inhomogeneous results. While some studies have observed impairing effects [17,22,54,55], others have found no [56–58] or enhancing effects [24,25,59].

For male participants, the results of our two experiments are in line with other studies employing the *n*-back paradigm as a WM task. Currently, at least two studies [24,59] have demonstrated that acute stress enhanced WM performance in men in an *n*-back task with neutral stimuli (single digits). In the study by Cornelisse et al. [24] participants took part in the TSST before processing an *n*-back paradigm. Male participants showed faster reaction times after the stress induction compared to the control group. Similar results were found in an fMRI study in which participants had to deal with the *n*-back task after viewing movie clips containing strongly aversive or neutral scenes [59]. Here, too, participants in the stress condition (aversive scenes) displayed significantly faster reaction times but no differences in accuracy compared to the non-stress condition. The authors suggested that the stress-induced enhancement of WM performance might be explained by the interplay of several brain networks. WM performance is suggested to depend on the activation of WM specific brain regions, primarily the dorsolateral PFC (DLPFC), on the one hand, and on the deactivation of the so-called default-mode network (DMN, including hippocampus, amygdala, ventral medial PFC and posterior cingulate cortex) on the other hand. Studies have shown that the ability to deactivate DMN predicts better performance in WM [60] and that stress seems to induce a deactivation in parts of the DMN (hippocampus and amygdala; [59,61]).

In addition, there is evidence that stress and its associated higher state of arousal might affect early attentional processes [11–13]. For example, in one study by Schwabe et al. [13], male participants were exposed to stress before participating in an attentional blink task. Participants in the stress group displayed a diminished attentional blink, which supports the idea of a stress-induced enhancement of attention. This enhancement of attention might also decrease the time it takes to process stimuli and as a result lead to faster RTs in the WM task as observed in our current studies.

However, it must be acknowledged that other studies (including two experiments conducted by the authors) have found impairing effects of stress on WM in male participants [16,17,22,23,55]. One reason for the divergent data might result from the fact that previous studies employed different WM paradigms (Span tasks and Sternberg task) which varied in the demand they put on distinct WM processes (maintaining, updating, manipulating). Nonetheless, in one of our studies, we had reported impairing effects on RT and accuracy in an *n*-back task with neutral stimuli in a male sample [22]. Since several experimental parameters are comparable between studies (such as the time of day when testing was conducted, selection criteria for participants, stress induction method and timing of the *n*-back task) a straight forward explanation for these discrepancies is difficult to find. Our current studies were conducted at a different university within Germany (Bochum versus Bielefeld) and thus with slightly different student populations. These could translate into differences in motivation or arousal at baseline (or post stress). The affective and neuroendocrine stress

markers obtained in these studies however do not show substantial differences between the current two experiments and the one published previously [22]. Recently, evidence has been provided that effects of stress on *n*-back performance are influenced by genetic differences in prefrontal dopamine levels [62]. Only homozygotes for the Met polymorphism showed impaired *n*-back task performance after exposure to the TSST. Thus differences in the genetic composition of the samples might in part be able to explain the inconsistent results obtained in our studies (as well as in studies conducted in other laboratories). Since the relationship between WM performance and dopamine has been described as an inverted U-shaped function differences in basal DA concentrations caused by genetic or environmental influences (e.g. arousal) might conceivably influence the direction of the stress effects. Moreover, differences in coping styles or the tendency to ruminate might be possible moderating variables of interest [63,64].

In contrast to men, stress impaired the WM performance in female participants in both experiments. Women who took part in the TSST displayed slower reaction times compared to women in the control condition (although the effects did not reach significance in post hoc tests). No stress effect was found for task accuracy. These results are in line with previous animal and human studies [18,24,26,59,65–67]. Studies with rodents have repeatedly reported that female rats are more sensitive to stress- or GC-induced working memory impairments [26,67]. While moderate concentrations of stress or pharmacological enhancement of GCs did not affect WM in male rats, the performance of female rats was impaired. The effect was especially pronounced when female rats had high estradiol concentrations. In humans, studies investigating WM processes under stress in women have mostly reported no effects of stress on WM performance in an *n*-back task [24,59]. However, it should be noted that in one study [24], the majority of women used oral contraceptives which considerably influence sex hormone concentrations and blunt the free cortisol response to stress [68]. The second study employed a stressor (strongly aversive films) which did not significantly increase cortisol [59]. Thus, the two experiments presented here are the first to report the impact of a stressor which caused a substantial cortisol increase on working memory in women.

2.4.3. Discussion on sex differences: mechanistic speculations

Previous human stress or cortisol studies have repeatedly observed sex differences in fear conditioning tasks (e.g. [66,69,70]). In other cognitive domains (e.g. long-term memory), sex differences appear to be less pronounced (but see [65,71]). A review on this issue has recently been provided by one of the authors [72].

Our findings are unique in reporting sex-dependent opposing effects of stress on working memory. They thereby share some similarities with rodent studies investigating eye-blink conditioning. Here, female rats under resting conditions showed superior performance compared to male rats. However, the picture reversed after stress as stress enhanced performance in males but impaired it in females [73].

It has been suggested that estradiol mediates differences in stress sensitivity of the PFC, especially with respect to noradrenergic and dopamingergic effects [67]. Thus, the same stressor might enhance performance in males but impair it in females. This might occur either because males and females start off at a different point within the supposedly inverted U-shaped function (see [74] for related thoughts with respect to spatial memories), or because the same stress response translates into stronger changes in the relevant brain areas in females than in males [67]. One animal study which supports these ideas demonstrated that acute stress resulted in an increased dopaminergic activity in the PFC of male compared to female rats [75]. The lack of dopaminergic activation in female rats was interpreted as resulting from significantly higher basal dopamine concentrations in the PFC compared to their male counterparts which possibly exhibit a further activation of the system due to stress. Moreover, strategy changes induced by stress hormones might differ between men and women and could thus be able to account for these complementary findings [74].

2.4.4. No effect of stimulus emotionality

In Experiment 2, the results revealed no evidence for an effect of task-relevant stimuli with negative emotional content on WM performance. This was the case in the control as well as in the stress condition. The missing effects of negative stimuli on working memory stand in contrast to results obtained for long-term memory. Negative emotional content which elicits emotional arousal attains a privileged status in long-term memory [76–78]. The neural structure underlying this effect is the amygdala which mediates emotional learning and facilitates memory consolidation processes in other regions such as the hippocampus [77,79,80].

In contrast to long-term memory, the interaction between WM and emotional stimuli is less well understood. While emotional distractor stimuli seem to impair WM performance (e.g. [42,81]), studies examining the influence of emotional task-relevant stimuli on WM have generated inconsistent results. Kensinger and Corkin, who investigated the effect of negative and neutral emotional stimuli (words, pictures) on WM performance in a number of paradigms (span tasks, self-ordering task, *n*-back task), found WM impairments only for one paradigm but not for others [43]. Another study testing healthy older participants in an *n*-back task with neutral, negative and positive pictures reported no effect of stimulus emotionality [82].

Regarding the interaction between cognitive and affective processes, some imaging studies have argued that the processing of emotional stimuli interferes with cognitive WM processes [42,44]. In contrast, other studies have suggested that attention to the emotional characteristics of the stimuli could be suppressed and redirected to the cognitive aspects of the task in question for the sake of efficient cognitive functioning. This assumption was supported by a study demonstrating that a concurrent WM task disrupted the emotional processing of negative stimuli [83]. In this study, the emotional modulation of the startle eyeblink reflex was significantly reduced when participants were asked to watch neutral and negative pictures and simultaneously deal with a demanding *n*-back task. In addition, other studies imply that the suppression of emotion processing is potentiated by a higher cognitive demand of the task [84–86]. In sum, those WM tasks with task-relevant emotional stimuli have often found no strong effect of negative or positive memory content on performance. Additionally, some studies have suggested that emotional processing is suppressed particularly in tasks with higher cognitive demand.

An interesting side finding of the second study was the fact that accuracy for digits was superior to accuracy for pictures (independent of their emotionality). The findings are thus in contrast to declarative memory studies which have consistently observed superior memory for pictures compared to words (e.g. [87,88]). For working memory performance or at least for working memory paradigms using continuous serial presentations less complex stimuli like digits appear to be associated with enhanced accuracy.

2.4.5. Limitations and future directions

Finally, some limitations of our study need to be addressed. First, our study suggested that stress affects WM differently in male and female participants. However, the underlying mechanisms remain unknown. In the current experiments we only acquired self-reported information about the menstrual cycle phase. Based on this information participants were post hoc grouped into first versus second menstrual cycle half. This factor did neither exert

a substantial influence on the stress response, nor on the stress induced WM performance changes. However, these self-reported measures are problematic, since they often do not match rigorous neuroendocrine measurements. Previous studies investigating specific menstrual cycle phases (follicular phase contrasted with the luteal phase) for example observed a more pronounced cortisol stress response in the luteal phase (which is characterized of high estradiol and progesterone concentrations) of the cycle [68]. Moreover, for the domain of long-term memory evidence has been reported that beneficial effects on memory consolidation do only occur in the luteal phase [89]. In contrast, impairing effects on memory retrieval, as has been repeatedly observed in male participants [20] and mixed sex samples (e.g. [90]), were absent in a sample of women in the luteal phase [65]. Similar studies in the domain of working memory are missing as of today. Given our current findings a more focussed investigation of the impact of sex steroids on the observed stress effects appears indicated.

The two experiments presented in this manuscript were both conducted in the morning hours, a time of high basal cortisol concentrations, accompanied by increased inter-individual variance (see [29]). We had used this time window in order to replicate and extend our previous findings, which had also been obtained in the morning [22]. Based on the strong circadian rhythm of cortisol and the idea of an inverted U-shaped response curve between cortisol and memory some authors have proposed the idea that stress be especially impairing when perceived during the morning. Indeed, one study investigating declarative memories obtained support for this hypothesis [91]. Along these lines we observed in our meta-analysis on cortisol and long-term memory that studies conducted in the morning reported more often negative effects of cortisol on memory. In contrast, studies conducted in the afternoon more often reported beneficial effects [92]. Previous studies in the domain of working memory observed enhancing effects of stress in the morning [24] but also in the afternoon [25]. Similarly impairing effects had been reported from studies conducted in the morning [17] or in the afternoon [16]. However, none of these studies tested the influence of time of day systematically within one experiment. Future WM stress studies similar to those conducted by Maheu et al. [91] or Smeets [90] are needed in order to systematically characterize the potential impact of time of day.

In our current and previous studies [22] WM was tested 10 min after cessation of the TSST. At this time cortisol concentrations had reached their peak but (nor)adrenergic activity (as indexed by sAA) had already returned to pre-stress baseline levels. Studies in rodents could demonstrate that a pharmacological blockage of NA activity prevented the impairing effects of GC treatment on working memory [93]. Similarly in humans WM was impaired in cortisol stress responders if tested during the stressor, but not if tested during the recovery period [94]. It is conceivable that the effects of stress on working memory accuracy and response time might have been stronger if testing had occurred during or immediately after exposure to the TSST.

In both experiments we observed significant sex by stress interactions. However, post hoc tests conducted for both sexes separately were not significant and an effect size analysis indicated that the obtained effects were small to medium. It thus has to be acknowledged that the effects of stress on working memory as measured with the *n*-back task appear to be rather subtle.

Strengths of the current report lie in the fact that we were able to replicate the sex differences in two experiment employing a neutral (Experiment 1) and an emotional *n*-back task (Experiment 2). Moreover, the sample size of both experiments (59 in study 1; 109 in study 2) is larger than those of all previous experiments. It is thus quite unlikely that the results of the two studies present chance findings or findings caused by a few outliers.

2.5. Conclusion

In conclusion, the findings of our two independent studies suggest that WM is influenced by acute psychosocial stress in a sex dependent fashion. Stress appears to enhance *n*-back performance in men, while it appears to impair it in women. Results obtained in males are in contrast to some previous studies and call for additional research aiming at understanding the factors leading to a stress-induced enhancement or a stress-induced impairment in working memory. Findings in women suggest that their PFC-mediated functions are more susceptible to acute stress. Noticeably, this pattern of results was similar in both studies, although baseline levels of cortisol and sAA and the endocrine responsivity varied considerably between the studies. This implies that cortisol is not, at least directly, accountable for the performance differences and that other physiological messenger such as noradrenalin or dopamine might contribute to the observed effects.

In addition, our study did not find evidence for a strong influence of emotional stimuli on WM performance, which is in contrast to findings for long-term memory. The observed results might indicate that emotional and neutral stimuli are processed equally when they are task-relevant, although alternative explanations cannot be ruled out and therefore should be further investigated in future studies.

Disclosure statement

All authors declare that no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations exists that inappropriately influence their work.

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References

[1] Fuster JM. Executive frontal functions. Experimental Brain Research 2000;133(1):66–70.
[2] Arnsten AF, Li BM. Neurobiology of executive functions: catecholamine influences on prefrontal cortical functions. Biological Psychiatry 2005;57(11):1377–84.
[3] D'Esposito M. From cognitive to neural models of working memory. Philosophical Transactions of the Royal Society of London, Series B: Biological Sciences 2007;362(1481):761–72.
[4] Bechara A, Damasio H, Damasio AR. Emotion, decision making and the orbitofrontal cortex. Cerebral Cortex 2000;10(3):295–307.
[5] Cardinal RN, Parkinson JA, Hall J, Everitt BJ. Emotion and motivation: the role of the amygdala, ventral striatum, and prefrontal cortex. Neuroscience and Biobehavioral Reviews 2002;26(3):321–52.
[6] Herman JP, Ostrander MM, Mueller NK, Figueiredo H. Limbic system mechanisms of stress regulation: hypothalamo-pituitary-adrenocortical axis. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2005;29(8):1201–13.
[7] Joels M, Karst H, DeRijk R, de Kloet ER. The coming out of the brain mineralocorticoid receptor. Trends in Neurosciences 2008;31(1):1–7.
[8] Patel PD, Katz M, Karssen AM, Lyons DM. Stress-induced changes in corticosteroid receptor expression in primate hippocampus and prefrontal cortex. Psychoneuroendocrinology 2008;33(3):360–7.
[9] Perlman WR, Webster MJ, Herman MM, Kleinman JE, Weickert CS. Age-related differences in glucocorticoid receptor mRNA levels in the human brain. Neurobiology of Aging 2007;28(3):447–58.
[10] Meaney MJ, Aitken DH. [3H]Dexamethasone binding in rat frontal cortex. Brain Research 1985;328(1):176–80.
[11] Elling L, Steinberg C, Brockelmann AK, Dobel C, Bolte J, Junghofer M. Acute stress alters auditory selective attention in humans independent of HPA: a study of evoked potentials. PLoS One 2011;6(4):e18009.

[12] Shackman AJ, Maxwell JS, McMenamin BW, Greischar LL, Davidson RJ. Stress potentiates early and attenuates late stages of visual processing. Journal of Neuroscience 2011;31(3):1156–61.
[13] Schwabe L, Wolf OT. Emotional modulation of the attentional blink: is there an effect of stress? Emotion 2010;10(2):283–8.
[14] Wolf OT. Stress and memory in humans: twelve years of progress. Brain Research 2009;1293:142–54.
[15] Lupien SJ, McEwen BS, Gunnar MR, Heim C. Effects of stress throughout the lifespan on the brain, behaviour and cognition. Nature Reviews Neuroscience 2009;10(6):434–45.
[16] Schoofs D, Wolf OT, Smeets T. Cold pressor stress impairs performance on working memory tasks requiring executive functions in healthy young men. Behavioral Neuroscience 2009;123(5):1066–75.
[17] Oei NY, Everaerd WT, Elzinga BM, van Well S, Bermond B. Psychosocial stress impairs working memory at high loads: an association with cortisol levels and memory retrieval. Stress 2006;9(3):133–41.
[18] Qin S, Hermans EJ, van Marle HJ, Luo J, Fernandez G. Acute psychological stress reduces working memory-related activity in the dorsolateral prefrontal cortex. Biological Psychiatry 2009;66(1):25–32.
[19] Smeets T, Jelicic M, Merckelbach H. The effect of acute stress on memory depends on word valence. International Journal of Psychophysiology 2006;62(1):30–7.
[20] Kuhlmann S, Piel M, Wolf OT. Impaired memory retrieval after psychosocial stress in healthy young men. Journal of Neuroscience 2005;25(11):2977–82.
[21] Hoffman R, al'Absi M. The effect of acute stress on subsequent neuropsychological test performance. Archives of Clinical Neuropsychology 2004;19(4):497–506.
[22] Schoofs D, Preuss D, Wolf OT. Psychosocial stress induces working memory impairments in an *n*-back paradigm. Psychoneuroendocrinology 2008;33(5):643–53.
[23] Lupien SJ, Gillin CJ, Hauger RL. Working memory is more sensitive than declarative memory to the acute effects of corticosteroids: a dose-response study in humans. Behavioral Neuroscience 1999;113(3):420–30.
[24] Cornelisse S, van Stegeren AH, Joels M. Implications of psychosocial stress on memory formation in a typical male versus female student sample. Psychoneuroendocrinology 2011;36(4):569–78.
[25] Duncko R, Johnson L, Merikangas K, Grillon C. Working memory performance after acute exposure to the cold pressor stress in healthy volunteers. Neurobiology of Learning and Memory 2009;91(4):377–81.
[26] Shansky RM, Rubinow K, Brennan A, Arnsten AF. The effects of sex and hormonal status on restraint-stress-induced working memory impairment. Behavioral and Brain Functions 2006;7(2):8.
[27] Oei NY, Tollenaar MS, Spinhoven P, Elzinga BM. Hydrocortisone reduces emotional distracter interference in working memory. Psychoneuroendocrinology 2009;34(9):1284–93.
[28] Kirschbaum C, Pirke KM, Hellhammer DH. The 'Trier Social Stress Test' – a tool for investigating psychobiological stress responses in a laboratory setting. Neuropsychobiology 1993;28(1-2):76–81.
[29] Dickerson SS, Kemeny ME. Acute stressors and cortisol responses: a theoretical integration and synthesis of laboratory research. Psychological Bulletin 2004;130(3):355–91.
[30] Het S, Rohleder N, Schoofs D, Kirschbaum C, Wolf OT. Neuroendocrine and psychometric evaluation of a placebo version of the 'Trier Social Stress Test'. Psychoneuroendocrinology 2009;34:1075–86.
[31] Rohleder N, Nater UM, Wolf JM, Ehlert U, Kirschbaum C. Psychosocial stress-induced activation of salivary alpha-amylase: an indicator of sympathetic activity. Annals of the New York Academy of Sciences 2004;1032: 258–63.
[32] Kudielka BM, Schommer NC, Hellhammer DH, Kirschbaum C. Acute HPA axis responses, heart rate, and mood changes to psychosocial stress (TSST) in humans at different times of day. Psychoneuroendocrinology 2004;29(8): 983–92.
[33] Nater UM, Rohleder N. Salivary alpha-amylase as a non-invasive biomarker for the sympathetic nervous system: current state of research. Psychoneuroendocrinology 2009;34(4):486–96.
[34] Rohleder N, Nater UM. Determinants of salivary alpha-amylase in humans and methodological considerations. Psychoneuroendocrinology 2009;34(4):469–85.
[35] van Stegeren A, Rohleder N, Everaerd W, Wolf OT. Salivary alpha amylase as marker for adrenergic activity during stress: effect of betablockade. Psychoneuroendocrinology 2006;31(1):137–41.
[36] Watson D, Clark LA, Tellegen A. Development and validation of brief measures of positive and negative affect: the PANAS scales. Journal of Personality and Social Psychology 1988;54(6):1063–70.
[37] Erdfelder E, Faul F, Buchner A. GPower: a general power analysis program. Behavior Research Methods, Instruments, & Computers 1996;28(1):1–11.
[38] Dolcos F, Cabeza R. Event-related potentials of emotional memory: encoding pleasant, unpleasant, and neutral pictures. Cognitive, Affective, & Behavioral Neuroscience 2002;2(3):252–63.
[39] Cahill L, McGaugh JL. Mechanisms of emotional arousal and lasting declarative memory. Trends in Neurosciences 1998;21(7):294–9.
[40] Roozendaal B. Stress and memory: opposing effects of glucocorticoids on memory consolidation and memory retrieval. Neurobiology of Learning and Memory 2002;78(3):578–95.
[41] Roozendaal B, Brunson KL, Holloway BL, McGaugh JL, Baram TZ. Involvement of stress-released corticotropin-releasing hormone in the basolateral amygdala in regulating memory consolidation. Proceedings of the National Academy of Sciences of the United States of America 2002;99(21):13908–13.
[42] Dolcos F, McCarthy G. Brain systems mediating cognitive interference by emotional distraction. Journal of Neuroscience 2006;26(7):2072–9.
[43] Kensinger EA, Corkin S. Effect of negative emotional content on working memory and long-term memory. Emotion 2003;3(4):378–93.
[44] Oei NY, Veer IM, Wolf OT, Spinhoven P, Rombouts SA, Elzinga BM. Stress shifts brain activation towards ventral 'affective' areas during emotional distraction. Social Cognitive and Affective Neuroscience 2012;7(4):403–12.
[45] Putman P, Roelofs K. Effects of single cortisol administrations on human affect reviewed: coping with stress through adaptive regulation of automatic cognitive processing. Psychoneuroendocrinology 2011;36(4):439–48.
[46] Arnsten AF. Stress signalling pathways that impair prefrontal cortex structure and function. Nature Reviews Neuroscience 2009;10(6):410–22.
[47] Oei NY, Tollenaar MS, Elzinga BM, Spinhoven P. Propranolol reduces emotional distraction in working memory: a partial mediating role of propranolol-induced cortisol increases? Neurobiology of Learning and Memory 2010;93(3):388–95.
[48] Lang PJ, Bradley MM, Cuthbert BN. International Affective Picture System (IAPS): technical manual and affective ratings. Gainesville FL: Center for Research in Psychophysiology: University of Florida; 1997.
[49] Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. Journal of Health and Social Behavior 1983;24(4):385–96.
[50] Schoofs D, Wolf OT. Are salivary gonadal steroid concentrations influenced by acute psychosocial stress? A study using the Trier Social Stress Test (TSST). International Journal of Psychophysiology 2011;80(1):36–43.
[51] Preuss D, Wolf OT. Post-learning psychosocial stress enhances consolidation of neutral stimuli. Neurobiology of Learning and Memory 2009;92:318–26.
[52] Kudielka BM, Hellhammer DH, Wust S. Why do we respond so differently? Reviewing determinants of human salivary cortisol responses to challenge. Psychoneuroendocrinology 2009;34(1):2–18.
[53] Butts KA, Weinberg J, Young AH, Phillips AG. Glucocorticoid receptors in the prefrontal cortex regulate stress-evoked dopamine efflux and aspects of executive function. Proceedings of the National Academy of Sciences of the United States of America 2011;108(45):18459–64.
[54] Schoofs D, Hartmann R, Wolf OT. Neuroendocrine stress responses to an oral academic examination: no strong influence of sex, repeated participation and personality traits. Stress 2008;11(1):52–61.
[55] Luethi M, Meier B, Sandi C. Stress effects on working memory, explicit memory, and implicit memory for neutral and emotional stimuli in healthy men. Frontiers in Behavioral Neuroscience 2009;2:1–9.
[56] Smeets T, Jelicic M, Merckelbach H. Stress-induced cortisol responses, sex differences, and false recollections in a DRM paradigm. Biological Psychology 2006;72(2):164–72.
[57] Porcelli AJ, Cruz D, Wenberg K, Patterson MD, Biswal BB, Rypma B. The effects of acute stress on human prefrontal working memory systems. Physiology and Behavior 2008;95(3):282–9.
[58] Weerda R, Muehlhan M, Wolf OT, Thiel CM. Effects of acute psychosocial stress on working memory related brain activity in men. Human Brain Mapping 2010;31(9):1418–29.
[59] Cousijn H, Rijpkema M, Qin S, van Wingen GA, Fernandez G. Phasic deactivation of the medial temporal lobe enables working memory processing under stress. Neuroimage 2012;59(2):1161–7.
[60] Anticevic A, Repovs G, Shulman GL, Barch DM. When less is more: TPJ and default network deactivation during encoding predicts working memory performance. Neuroimage 2010;49(3):2638–48.
[61] Pruessner JC, Dedovic K, Khalili-Mahani N, Engert V, Pruessner M, Buss C, et al. Deactivation of the limbic system during acute psychosocial stress: evidence from positron emission tomography and functional magnetic resonance Imaging studies. Biological Psychiatry 2008;63(2):234–40.
[62] Buckert M, Kudielka BM, Reuter M, Fiebach CJ. The COMT Val158Met polymorphism modulates working memory performance under acute stress. Psychoneuroendocrinology 2012;37(11):1810–21.
[63] Klucken T, Brouwer AM, Chatziastros A, Kagerer S, Netter P, Hennig J. The impact of coping style on gaze duration. PLoS One 2010;5(11):e15395.
[64] Zoccola PM, Quas JA, Yim IS. Salivary cortisol responses to a psychosocial laboratory stressor and later verbal recall of the stressor: the role of trait and state rumination. Stress 2010;13(5):435–43.
[65] Schoofs D, Wolf OT. Stress and memory retrieval in women: no strong impairing effect during the luteal phase. Behavioral Neuroscience 2009;123(3):547–54.
[66] Zorawski M, Blanding NQ, Kuhn CM, LaBar KS. Effects of stress and sex on acquisition and consolidation of human fear conditioning. Learning and Memory 2006;13(4):441–50.
[67] Shansky RM, Glavis-Bloom C, Lerman D, McRae P, Benson C, Miller K, et al. Estrogen mediates sex differences in stress-induced prefrontal cortex dysfunction. Molecular Psychiatry 2004;9(5):531–8.
[68] Kirschbaum C, Kudielka BM, Gaab J, Schommer NC, Hellhammer DH. Impact of gender, menstrual cycle phase, and oral contraceptives on the activity of the hypothalamus-pituitary-adrenal axis. Psychosomatic Medicine 1999;61(2):154–62.
[69] Merz CJ, Stark R, Vaitl D, Tabbert K, Wolf OT. Stress hormones are associated with the neuronal correlates of instructed fear conditioning. Biol Psychol 2013;92(1):82–9.
[70] Jackson ED, Payne JD, Nadel L, Jacobs WJ. Stress differentially modulates fear conditioning in healthy men and women. Biological Psychiatry 2006;59(6):516–22.

[71] Andreano JM, Cahill L. Glucocorticoid release and memory consolidation in men and women. Psychological Science 2006;17(6):466–70.
[72] Wolf OT. Effects of stress on learning and memory: evidence for sex differences in humans. In: Conrad CD, editor. The handbook of stress: neuropsychological effects on the brain. Chichester, West Sussex, United Kingdom: Wiley-Blackwell; 2011. p. 545–59.
[73] Shors TJ. Learning during stressful times. Learning and Memory 2004;11(2):137–44.
[74] Beck KD, Luine VN. Evidence for sex-specific shifting of neural processes underlying learning and memory following stress. Physiology and Behavior 2010;99(2):204–11.
[75] Dalla C, Antoniou K, Kokras N, Drossopoulou G, Papathanasiou G, Bekris S, et al. Sex differences in the effects of two stress paradigms on dopaminergic neurotransmission. Physiology and Behavior 2008;93(3):595–605.
[76] McGaugh JL, Cahill L, Roozendaal B. Involvement of the amygdala in memory storage: interaction with other brain systems. Proceedings of the National Academy of Sciences of the United States of America 1996;93(24): 13508–14.
[77] Cahill L. Sex- and hemisphere-related influences on the neurobiology of emotionally influenced memory. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2003;27(8):1235–41.
[78] Cahill L, Haier RJ, Fallon J, Alkire MT, Tang C, Keator D, et al. Amygdala activity at encoding correlated with long-term, free recall of emotional information. Proceedings of the National Academy of Sciences of the United States of America 1996;93(15):8016–21.
[79] LaBar KS, Cabeza R. Cognitive neuroscience of emotional memory. Nature Reviews Neuroscience 2006;7(1):54–64.
[80] Buchanan TW. Retrieval of emotional memories. Psychological Bulletin 2007;133(5):761–79.
[81] Dolcos F, Kragel P, Wang L, McCarthy G. Role of the inferior frontal cortex in coping with distracting emotions. Neuroreport 2006;17(15):1591–4.
[82] Doehnel K, Sommer M, Ibach B, Rothmayr C, Meinhardt J, Hajak G. Neural correlates of emotional working memory in patients with mild cognitive impairment. Neuropsychologia 2008;46(1):37–48.
[83] King R, Schaefer A. The emotional startle effect is disrupted by a concurrent working memory task. Psychophysiology 2011.
[84] Erthal FS, de OL, Mocaiber I, Pereira MG, hado-Pinheiro W, Volchan E, et al. Load-dependent modulation of affective picture processing. Cognitive, Affective, & Behavioral Neuroscience 2005;5(4):388–95.
[85] Vytal K, Cornwell B, Arkin N, Grillon C. Describing the interplay between anxiety and cognition: From impaired performance under low cognitive load to reduced anxiety under high load. Psychophysiology 2012;49(6):842–52.
[86] Pessoa L. On the relationship between emotion and cognition. Nature Reviews Neuroscience 2008;9(2):148–58.
[87] Paivio A, Csapo K. Picture superiority in free recall: imagery or dual coding. Cognitive Psychology 1973;5:176–206.
[88] Curran T, Doyle J. Picture superiority double dissociates the ERP correlates of recollection and familiarity. Journal of Cognitive Neuroscience 2011;23(5):1247–62.
[89] Andreano JM, Arjomandi H, Cahill L. Menstrual cycle modulation of the relationship between cortisol and long-term memory. Psychoneuroendocrinology 2008;33(6):874–82.
[90] Smeets T, Otgaar H, Candel I, Wolf OT. True or false? Memory is differentially affected by stress-induced cortisol elevations and sympathetic activity at consolidation and retrieval. Psychoneuroendocrinology 2008;33(10):1378–86.
[91] Maheu FS, Collicutt P, Kornik R, Moszkowski R, Lupien SJ. The perfect time to be stressed: a differential modulation of human memory by stress applied in the morning or in the afternoon. Progress in Neuro-Psychopharmacology and Biological Psychiatry 2005;29(8):1281–8.
[92] Het S, Ramlow G, Wolf OT. A meta-analytic review of the effects of acute cortisol administration on human memory. Psychoneuroendocrinology 2005;30(8):771–84.
[93] Roozendaal B, McReynolds JR, McGaugh JL. The basolateral amygdala interacts with the medial prefrontal cortex in regulating glucocorticoid effects on working memory impairment. Journal of Neuroscience 2004;24(6):1385–92.
[94] Elzinga BM, Roelofs K. Cortisol-induced impairments of working memory require acute sympathetic activation. Behavioral Neuroscience 2005;119(1):98–103.