Behavioral Neuroscience
2009, Vol. 123, No. 5, 1066–1075

0735-7044/09/$12.00 DOI: 10.1037/a0016980

Cold Pressor Stress Impairs Performance on Working Memory Tasks Requiring Executive Functions in Healthy Young Men

Daniela Schoofs and Oliver T. Wolf
Ruhr-University Bochum

Tom Smeets
Maastricht University

The current study investigated the effects of cold pressor stress (CPS) on 2 working memory (WM) tasks differing in the demand they put on maintenance and executive processing. For this purpose 72 healthy young men were exposed either to a stress group or a nonstressful control group. Subsequently, WM performance on the O-Span task (Turner & Engle, 1989) and the digit span task was assessed. Salivary cortisol was measured before and 2 times after the treatment as a marker of hypothalamus–pituitary–adrenal (HPA) axis activity. Results revealed a significant performance impairment of the O-Span and the digit span task backward in stressed subjects that correlated negatively with CPS-induced cortisol increases. Digit span forward was neither affected by CPS nor related to the ensuing cortisol increases. These results indicate that acute stress impairs WM performance for task requiring executive functions that operate on the stored material but not for WM tasks that only require maintenance.

Keywords: working memory, digit span task, O-Span task, cold pressor stress, HPA

Recently an increasing number of studies suggested that stress not only affects declarative memory functions and its associated brain regions (hippocampus and amygdala; Diamond, Campbell, Park, Halonen, & Zoladz, 2007; Joels, Pu, Wiegert, Oitzl, & Krugers, 2006; Roozendaal, 2002) but also influences working memory (WM; Lupien, Gillin, & Hauger, 1999; Oei, Everaerd, Elzinga, van Well, & Bermond, 2006; Schoofs, Preuss, & Wolf, 2008). In their seminal work, Baddeley and Hitch (1974; Baddeley, 2001, 2003) conceptualized WM not as a unitary entity, but as a theoretical concept that includes distinguishable processes such as the temporary maintenance and executive functions as updating and manipulation of stored information (Baddeley, 2001, 2003; Repovs & Baddeley, 2006). These processes appear to mainly depend on prefrontal and parietal brain structures (Baldo & Dronkers, 2006; Fuster, 2000; Muller & Knight, 2006; Petrides, 2000; Wager & Smith, 2003).

Besides the importance of the prefrontal cortex (PFC) for WM functions, it is well known that this area is also involved in the feedback regulation of the hypothalamus–pituitary–adrenal (HPA) axis, one of the major stress systems (Herman et al., 2003; Herman, Ostrander, Mueller, & Figueiredo, 2005). Furthermore, evidence from histopathological studies in rodents, monkeys, and humans indicate a large number of glucocorticoid (GC) receptors within the PFC (Meaney & Aitken, 1985; Patel, Katz, Karssen, & Lyons, 2008; Patel et al., 2000; Perlman, Webster, Herman, Kleinman, & Weickert, 2007), which suggests that PFC mediated functions might be influenced by rising GC levels during stress. In addition, studies in rodents and primates revealing stress-induced impairments in WM performance showed a mediating role for dopaminergic and adrenergic processes within the prefrontal cortex (Arnsten, 1997, 2000; Arnsten & Li, 2005; Murphy, Arnsten, Jentsch, & Roth, 1996). These neurotransmitter systems appear to interact at multiple levels (Ellis & Nathan, 2001; Robbins, 2005).

By and large, human studies have confirmed the negative effects of increased GC levels on WM performance in humans (Elzinga & Roelofs, 2005; Lupien et al., 1999; Oei et al., 2006; Schoofs et al., 2008; Wolf et al., 2001), yet the results are not as straightforward due to the large number of different WM tests and stressors that are employed. For example, pharmacological studies using a single hydrocortisone administration reported significant impairments under high WM load in a Sternberg paradigm (Lupien et al., 1999), whereas for a digit span task either no impairments (Grossman et al., 2006; Kuhlmann, Kirschbaum, & Wolf, 2005) or significant deficits in WM performance were observed (Wolf et al., 2001). Other studies have employed acute laboratory stressors to investigate how GCs affect WM. These can be divided in stressors emphasizing the psychological or psychosocial effect (i.e., nonmetabolically demanding, nonphysical stressors) and those that stronger employ physiological stress inducing components (e.g., heat, handgrip, cold pressor stress) (Dickerson & Kemeny, 2004). Psychosocial stressors typically include performance components that employ cognitive resources (e.g., mathematical tasks) and/or include a social-evaluative component. One often used psychosocial stressor is the Trier Social Stress Test (TSST; Kirschbaum, Pirke, & Hellhammer, 1993), which basically consists of a preparation period, a 5-min free speech, and a 5-min mental arithmetic test that have to be performed in front of a committee while being videotaped. It is known to reliably activate the sympathetic nervous system (SNS) and the HPA axis. Studies using this stressor have found significant WM impairments for the Sternberg (Oei et

Daniela Schoofs and Oliver T. Wolf, Department of Cognitive Psychology, Ruhr-University Bochum; Tom Smeets, Faculty of Psychology and Neuroscience, Maastricht University.

The contributions of Daniela Schoofs and Oliver T. Wolf were supported by a grant from the German Research Foundation (WO 733/6–2).

Correspondence concerning this article should be addressed to Daniela Schoofs, Department of Cognitive Psychology, Ruhr-University Bochum, Universitätsstr. One hundred fifty, D–44780 Bochum, Germany. E-mail: daniela.schoofs@rub.de

al., 2006) and the n-back paradigm (Schoofs et al., 2008), but no impairing effects on digit span were observed in several studies (Hoffman & al'Absi, 2004; Kuhlmann, Piel, & Wolf, 2005; Smeets, Jelicic, & Merckelbach, 2006; but see Elzinga & Roelofs, 2005).

As to the physiological stressors, a study by McMorris et al. (2006) found no effect of heat stress-induced cortisol elevations on verbal and spatial WM. Another stress induction protocol is the Cold Pressor Test (CPS), which also reliably increases activity of the SNS and the HPA axis (Lovallo, 1975). For the CPS subjects were requested to submerge the dominant arm up to the elbow in ice-cold water (0° to 1 °C) for as long as possible with a maximum of 3 min. This procedure activates thermal and nociceptor afferents and elicits a stress response (Lovallo, 1975; McRae et al., 2006; Velasco, Gomez, Blanco, & Rodriguez, 1997). However, it should be noted that the CPS also includes a psychosocial evaluative component because during the procedure an experimenter stays in the experimental room and records the time subjects left their arm in the water. To the best of our knowledge, CPS has been employed only once to examine the influence of stress on WM (Porcelli et al., 2008). In this study, no significant difference between stressed and nonstressed subjects on a modified Sternberg WM task was found. These results might have to do with the small, albeit significant, cortisol increases in response to the stressor obtained in this study.

Conflicting results reported in the stress and WM area may be explained by assuming that more challenging WM tasks (including an additional processing of the stored information; e.g., n-back, Sternberg paradigm, O-Span) require more cognitive resources and thus might be more prone to be affected by stress and GCs than WM tasks assessing the short-term storage of information (e.g., digit span). Specifically, the digit span task forward mainly involves the passive maintenance of information, whereas WM tests such as the O-Span and the n-back task require updating and/or the active manipulation of information retained in WM (Engle, Cantor, & Carullo, 1992; Fletcher & Henson, 2001; Owen, McMillan, Laird, & Bullmore, 2005). Therefore, the current study was designed to specifically examine the effects of CPS on two WM tasks differing in the demand they put on maintenance and executive processing. Thus, we exposed healthy young men either to a stress group that received CPS or a nonstressful control group and subsequently assessed WM performance on the O-Span and the digit span WM test. We hypothesized that compared with the control group, CPS and the ensuing cortisol (i.e., the primary human GC) elevations would result in impaired WM performance for the O-Span and digit span backward task, because those tasks require maintenance and an additional processing of the stored material by executive functions. In contrast, digit span forward, which is a task measuring short-term storage, should not be affected by stress.

Method

Subjects

Seventy-two healthy male undergraduates from Maastricht University were recruited and randomly assigned to either a control condition ($n = 36$) or a CPS session ($n = 36$). One subject of the control group was excluded from data analysis because his body mass index (BMI) was outside the healthy range (i.e., a BMI $>$ 29). The remaining 71 subjects had a mean age of 20.18 years ($SD = 2.80$) and a mean BMI of 21.80 ($SD = 2.37$). None of them reported current or lifetime psychopathology, endocrine, or other serious medical diseases, or were on any kind of medication. The study was approved by the standing human subjects' ethics committee of the Faculty of Psychology and Neuroscience, Maastricht University, and all subjects provided written informed consent prior to participation.

Procedure and Tests

Procedure. The study was a group comparison design and subjects were randomly assigned to the CPS ($n = 36$) or the warm water control condition ($n = 35$). The individual sessions were conducted between 1430 and 1630 to control for the diurnal cycle of cortisol. After arrival in the laboratory, subjects were given a resting phase of 15 min before the first cortisol sample was taken (baseline). Five minutes later (20 min after arrival) subjects attended either the CPS or the warm water control treatment with a maximum duration of 3 min. Immediately after treatment, all subjects had to rest their arm covered by a blanket for 3 min. Following the rest period subjects engaged in the O-Span and digit span tasks. Administration of both tasks was counterbalanced across and within groups and the total time of testing was 15 min (3 min for digit span; 12 min for O-Span task). Further saliva samples were taken 10 min after the onset of the treatment (sample + 10 min) and immediately after the WM testing was finished (sample + 20 min).

Cortisol assessment. Participants were requested to abstain from eating, drinking, or smoking during the hour preceding the beginning of the testing session. Saliva was collected using salivette collection devices (Sarstedt, Nuembrecht, Germany). Samples were taken 5 min before (baseline), as well as 10 (sample + 10), and 20 min (sample + 20) after the onset of the treatment (CPS vs. control condition). Free cortisol levels were measured using an immunoassay (RIA; University of Liège, Belgium), including a competition reaction between ^{125}iodohistamine-cortisol and anticortisol serum made against the 3-carboxymethyloxime-bovine serum albumin conjugate. After overnight incubation at 4 °C of 50 μl of saliva, separation of free and antibody-bound ^{125}iodohistamine-cortisol was performed via a conventional "second antibody" method. Inter- and intra-assay variations were below 10%.

CPS and control condition. The stress or control situation began 20 min after arrival of the subjects at the laboratory. Stress was induced by exposing participants to CPS. The CPS is a widely used, low-risk technique in medical research that induces a reliable and robust increased activity of the sympathetic nervous system and the HPA axis by activation of thermal and nociceptor afferents (Lovallo, 1975; McRae et al., 2006; Velasco et al., 1997). As such, the CPS has been used to investigate the influence of stress on memory functions (e.g., Buchanan, Tranel, & Adolphs, 2006; Cahill, Gorski, & Le, 2003; Smeets et al., 2008). Therefore, subjects were instructed to submerge their dominant arm up to the elbow in ice-cold water (0° to 1 °C) for as long as possible with a maximum of 3 min. They were explicitly told that, as the procedure could be very uncomfortable, they could remove their arm from the ice-cold water at their own discretion without consequences. In the control condition, subjects were asked to place

their arm in warm water (37° to 40 °C) until they were instructed to remove it. This instruction was given pseudorandomly across subjects after 1, 2, or 3 min following arm immersion. The experimenter stayed in the same room and observed the behavior of the subjects while the subjects attended the control or CPS procedure. Assignment to the CPS or control group was single blind that is, participants were not informed beforehand to which group they were assigned until immediately before arm immersion. Following CPS or control situation, participants had to rest their arm covered by a blanket for 3 min.

Subjective rating of discomfort. In line with Cahill et al. (2003), subjects were asked to rate the level of discomfort they experienced during water immersion. To this end, they first were asked to think back at the most intense physical pain they had ever experienced and rate this experience based on a scale ranging from 0 (*no pain or discomfort*) to 100 (*the worst pain or discomfort imaginable*). After this "calibration" scale, subjects rated the peak level of discomfort they had experienced during the CPS on an analogous scale.

WM Testing

Operation span. In the operation-span task (O-Span task; Engle et al., 1992; Turner & Engle, 1989) subjects are requested to solve mathematical operations while simultaneously remembering a set of unrelated words. Thus, the O-Span task is a demanding WM task that includes maintenance and processing of the stored material by executive functions. In the O-Span version used in the present study (Engle et al., 1992; Peters, Smeets, Giesbrecht, Jelicic, & Merckelbach, 2007) subjects are requested to read aloud a mathematical equation that consists of two simple operations: a multiplication or division problem and an addition or subtraction problem (e.g., $6/2 + 5 = 8$). Subsequently, they have to respond whether the solution offered is correct or incorrect. Afterward, a high frequency, one syllable word is displayed on screen and subjects are instructed to remember the presented word. The set size (i.e., number of operation strings) within a trial increased from two to five with every set size being employed three times. At the end of each trial subjects were instructed to write down the words that followed the operation strings in correct order. Altogether, the O-Span task consisted of 12 trials and three practice trials. The O-Span score was calculated according to the partial credit unit scoring procedure (PCU; Conway et al., 2005; Peters et al., 2007). In brief, data were taken into account only if subjects produced more than 85% correct answers in the mathematical equations (accuracy of the processing component; see Conway et al., 2005). The PCU expresses the mean proportion of words that were recalled correctly. For example, when 3 words were remembered correctly in a trial with a set size of 4 words, the trial score would average .75 (4:3). To determine the PCU the scores of all trials were summed and subsequently divided by the number of trials. Thus the PCU could reach a maximum value of 1.00.

Digit span. For the digit span task subjects were asked to listen to a series of digits of increasing length that were read to them at a constant pace of one digit per second. After the last digit was presented, participants had to repeat the numbers in the same (forward condition) or the reverse (backward condition) order. On each successful attempt, the number of digits per list increased. When a participant failed to accurately reproduce a list of numbers on two successive trials, the task was ended. Raw scores for the digit span forward and backward reflect the maximum number of digits correctly recalled.

Statistical Analysis

For evaluation of behavioral effects of the CPS descriptive statistics were done for the duration of arm immersion into the water (duration of immersion) separately for both conditions (CPS vs. warm water control condition). Furthermore, the duration of immersion was compared between both groups by employing an independent samples *t* test. In addition, to investigate a possible effect of duration of immersion on subsequent analyses Pearson correlations were performed between duration of immersion and the (a) subjective discomfort rating, (b) cortisol changes, and (c) WM performance in the O-Span and digit span task.

The influence of the stressor on cortisol as dependent variable was analyzed by using a mixed model analysis of variance (ANOVA) with the repeated measurement factor time (baseline, +10, and +20) and the between-group factor treatment (CPS vs. warm water control group). Because tests for normal distribution showed that cortisol was positively skewed, the data were log-transformed and all further analyses were performed with the transformed data. The subjective rating of discomfort due to the stressor was examined by using an independent samples *t* test.

To evaluate the effect of the CPS on O-Span task performance a two-tailed independent samples *t* test was performed. The performance of the digit span task was investigated by using a mixed model ANOVA with the repeated measurement factor subtest (digit span forward vs. digit span backward) and the between-group factor treatment (CPS vs. warm water control group). Descriptive data is illustrated using mean and standard error of the mean (*SEM*).

In addition, two effect sizes (Cohen's *d*s) were computed by using the meta-analytic software program META (Schwarzer, 1989) with the formula provided by Hedges and Olkin (1985). Both effect sizes were conducted to evaluate the magnitude of the effect of treatment (CPS vs. warm water control) on the WM performance. According to Cohen (1988), effect sizes of 0.50 or larger can be regarded as moderate, whereas effect sizes of 0.80 or larger can be classified as large.

Finally, Pearson correlations were performed with the area under the curve (AUC) with respect to baseline (AUC increase [AUCi], which is the area under the response curve), the delta cortisol increase (cortisol + 20 − cortisol baseline, all cortisol data log-transformed), and the scores of the digit span and O-Span task. The AUCi is used to comprise the information obtained by multiple-cortisol measurement and to reveal possible associations between the cortisol increase over time with others variables (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003).

Results

Behavioral Effects of the CPS

For the cold water condition, 21 of the 36 subjects removed their arm from the water before 3 min were over. Descriptive statistics showed that the shortest duration of arm immersion was 45 s in the CPS group with an average duration of arm immersion of 122.47 s

(*SEM* ± 9.03). Because subjects of the control group also received pseudorandomly the instruction to remove their arm after 60, 120, or 180 s (mean duration of arm immersion in the control group: 118.29 s ± 8.33) an independent *t* test showed no significant differences in the duration between both groups, $t(69) = -0.340$, $p > .10$.

Emotional and Cortisol Response to the CPS

As expected, subjects in the CPS condition reported a far higher rating of discomfort then did subjects in the control condition (40.81 ± 3.22 vs. control group 2.57 ± 1.12), $t(69) = -11.08$, $p < .001$. The ANOVA for the cortisol response yielded significant main effects for treatment, $F(1, 69) = 5.47$, $p = .02$; and for time, $F(2, 138) = 14.76$, $p < .001$; as well as a significant Treatment × Time interaction, $F(2, 138) = 58.46$, $p < .001$. Post hoc Bonferroni–Holm corrected independent samples *t* tests showed a significant difference between the cortisol concentration at the +20 saliva measurement, $t(69) = -4.79$, $p < .001$; see Figure 1, although for the +10 measurement no significant result was found, $t(69) = -1.74$, $p = .086$.

Influence of the Duration of Cold Water Exposure on the Subjective, Endocrine, and WM Data

For investigating possible effects of the duration of arm immersion (duration of immersion) on the feeling of discomfort, cortisol changes, and the WM measurements correlation analyses were done. Therefore, the duration of immersion was correlated with (a) the feeling of subjective discomfort, (b) the cortisol delta increase (+20 − baseline), (c) the AUCi, and (d) the WM performance scores for the O-Span and digit span task. Correlations were calculated separately for the control and the CPS group. The results showed no significant associations between the duration of immersion and any other variable (all *r*s < .28; *p*s > .10).

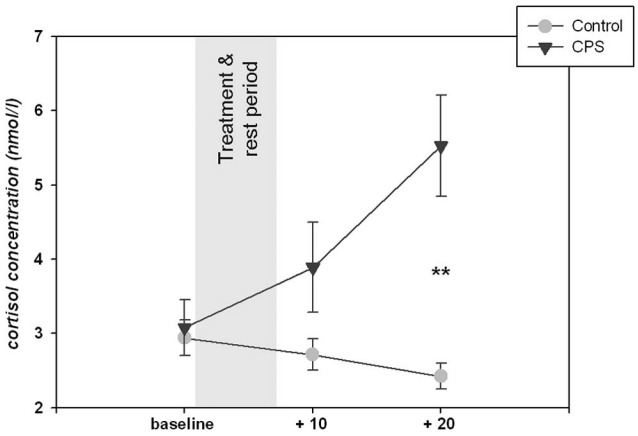

Figure 1. Effects of cold pressor stress (CPS) on salivary cortisol. Bonferroni–Holm corrected independent samples *t* tests revealed that stressed subjects had significantly higher cortisol concentrations compared to the control group at the +20 sampling point (20 min after the onset of treatment; ** $p < .001$). Data are presented as group mean ± *SEM* (raw data). WM = working memory.

Effects of the CPS on WM

Stress impaired performance on the O-Span task, with the *t* test revealing a significant difference between the CPS group and the control group, $t(69) = 3.31$, $p = .001$; see Figure 2. For the digit span task, results revealed significant main effects of subtest, $F(1, 69) = 80.16$, $p < .001$; and treatment, $F(1, 69) = 5.31$, $p < .05$; as well as a significant Subtest × Treatment interaction, $F(1, 69) = 4.49$, $p < .05$. Follow-up analysis with Bonferroni–Holm corrected independent samples *t* tests revealed a significant impairment of the CPS group for the backward condition, $t(69) = 3.27$, $p < .01$; although no significant difference was observed between both treatments for the forward condition ($p > .10$, see Figure 2). Effect sizes for O-Span and digit span backward were .77 and .77, respectively. Thus, according to Cohen, both effects can be considered as moderate to large.

Relationship Between Cortisol Response, Subjective Feeling of Discomfort, and WM

We correlated the cortisol response over time (AUCi) and the delta increase of cortisol (cortisol + 20 − cortisol baseline) with (a) the score of the O-Span task and (b) the score of the digit span forward and backward subtests, respectively. An analysis with all subjects revealed significant negative correlations between the AUCi and the O-Span score ($r = -.40$, $p = .001$) and the score for digit span backward ($r = -.41$, $p < .001$). In contrast, no relationship was found between the AUCi and digit span forward ($p > .05$). A similar pattern of results were observed for the correlations between the delta increase of cortisol and the three WM tasks.

Furthermore, the subjective feeling of discomfort was also correlated with the WM performance in the O-Span, digit span forward, and digit span backward. We observed no correlations between the perceived feeling of discomfort and both digit span conditions. However, the results yielded a significant negative correlation between O-Span scores and subjective feeling of discomfort ($r = -.26$, $p < .05$). Therefore, an additional partial correlation was calculated for the AUCi, the delta cortisol increase, and all three WM measurements with the discomfort rating included as control variable. More importantly, the previously reported pattern of result emerged again (AUCi + O-Span task: $r = -.32$, $p < .01$; AUCi + digit span backward: $r = -.36$, $p < .01$; AUCi + digit span forward: $r = -.19$, $p > .10$) and thus demonstrate that the associations between cortisol and WM performance were not secondary to the impact of discomfort.

When correlations were calculated separately for stressed and warm water control subjects there was no significant correlation observed for the subjects of the control group although for the stressed group again negative correlations were found for the O-Span ($r = -.43$, $p = .01$) and the digit span backward ($r = -.38$, $p < .05$). Again, results yielded no significant correlation between AUCi and the digit span forward ($p > .10$). For the delta cortisol increase the results were comparable with those obtained for the AUCi.

Discussion

The objective of this study was to investigate the effect of an acute laboratory stressor and the associated endocrine responses of

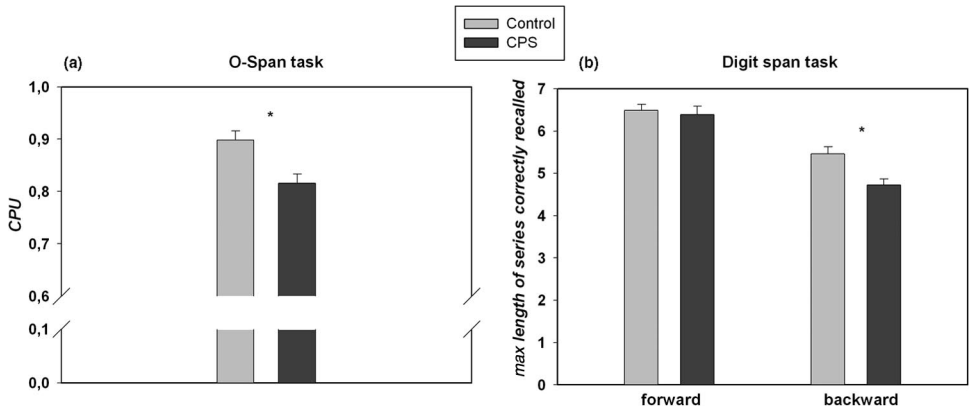

Figure 2. Effects of cold pressor stress (CPS) on the working memory performance in the O-Span (a) and the digit span task (b). A *t* test revealed significant impairments for the O-Span task ($^{*}p < .01$). For the digit span task a significant Subtest × Treatment interaction was found. Post hoc analyses showed a significant impairment of the CPS group in the backward but not in the forward condition. PCU = partial credit unit scoring procedure; max = maximum.

the HPA axis on the performance of two WM sensitive tasks that differed in the demand they make on the WM components of maintenance and executive processing. Results revealed that stress led to impaired WM in the O-Span task and the subtest digit span backward. In contrast, the performance of the subtest digit span forward was not affected by stress. Furthermore, higher cortisol increases were associated with poorer performance in the digit span backward and in the O-Span task although no significant correlations were found for the digit span forward. The present study is to our knowledge the first study that investigated the influence of the CPS on the O-Span and the digit span task.

To characterize the response to the CPS, salivary cortisol and subjective ratings of discomfort were assessed. The results revealed significantly higher ratings of discomfort in the stressed group compared to the warm-water control group as well as an increased activity of the HPA in subjects participating in the CPS. These findings are well in line with previous studies (e.g., Andreano, Arjomandi, & Cahill, 2008; Buchanan et al., 2006; Lovallo, 1975; van Stegeren, Wolf, & Kindt, 2008) and indicate the successful induction of an affective as well as neuroendocrine stress response.

Stress and O-Span Task

In the present study two WM tasks varying in the involvement of executive processing were employed (O-Span and digit span task). Consistent with our hypothesis for the more demanding O-Span task, the CPS group showed poorer WM performance. This impairment was reflected by a significant lower mean proportion of words (PCU) that were correctly recalled. In the O-Span task participants engage in online processing (mental arithmetic) and simultaneously maintain words for subsequent recall (Turner & Engle, 1989). This task puts high demand on the processing as well as the storage aspects of WM (Bayliss, Jarrold, Gunn, & Baddeley, 2003). Indeed, a number of researchers have argued that complex span tasks primarily reflect central executive functions (Redick & Engle, 2006) that are strongly mediated by the prefrontal cortex (Fuster, 2000; Miyake et al., 2000). Therefore, the O-Span task has been repeatedly used as a measure of WM capacity that strongly implicates the operations of the central executive system. Although it is still debated which component of executive functions in particular is measured by the O-Span task results from Miyake et al. (2000) support the hypothesis that this paradigm involves the ability to continuously update and monitor incoming information. Therefore, the O-Span task bears resemblance to other complex WM paradigms such as the n-back (Owen et al., 2005) or the Sternberg task (Sternberg, 1966) that also require continuous updating and monitoring of new incoming information.

Our findings of a stress-induced impairment in the O-Span are in accordance with pharmacological (Lupien et al., 1999) and psychosocial stress studies (Oei et al., 2006; Schoofs et al., 2008) that investigated the acute influence of GC elevations on other complex WM tasks (e.g., Sternberg paradigm, n-back task). These studies found significant decreases of WM performance reflected in longer reaction times and fewer correct responses following GC administration or psychosocial stress induction. Finally, the results are also in line with a previous study investigating the relationship between life stress and WM capacity in a sample of university students (Klein & Boals, 2001).

Stress and Digit Span

For the digit span task, the backward subtest that requires participants not only to remember the digits in the correct sequence but also to reverse the digits before repetition was found to be significantly impaired. The forward subtest, on the other hand, remained unaffected. These differential results are well in line with other studies that collectively suggest detrimental effects of elevated cortisol concentrations on the manipulation and the associated executive component of WM (Scholz et al., 2009; Schoofs et al., 2008). Clinical and nonclinical studies (Curtiss, Vanderploeg, Spencer, & Salazar, 2001; Dobbs, Dobbs, & Kiss, 2001) in turn have led to the assumption that performance on the backward subtest of the digit span represents a measure of central executive function due to the additional requirement of manipulation of

information within the temporary storage (Groeger, Field, & Hammond, 1999; Lezak, Howleson, & Loring, 2004); whereas the digit span forward rather reflects a measure of the capacity to maintain information passively (Baddeley, 2000; but see Ramsay & Reynolds, 1995; Reynolds, 1997; Richardson, 2007). Results obtained by studies using imaging techniques support this view by demonstrating that the processes of maintenance and manipulation rely on different patterns of activity in the brain (Hoshi et al., 2000; Tsukiura et al., 2001; Veltman, Rombouts, & Dolan, 2003). Furthermore, a meta-analysis of D'Esposito and Postle (1999) including 11 studies that employed simple span and delayed response tasks, revealed that none of the patients with lesions in the dorsolateral prefrontal cortex (DLPFC) showed impairments in the forward span tasks. In addition, the only study that tested forward as well as backward digit span (Canavan et al., 1989) demonstrated impaired performance of patients on the backward, but not the forward, subtest.

However, two experiments found an impairing effect of stress (Elzinga & Roelofs, 2005) or hydrocortisone administration (Wolf et al., 2001) on the digit span task. Elzinga and Roelofs (2005) observed a digit span impairment in the forward but not in the backward condition and only for high cortisol responders tested during, but not after, stress exposure. In contrast, Wolf et al. (2001) reported an impairment of the cortisol treated subjects in the digit span with no additionally significant interaction with the factor subtest (forward vs. backward), but this effect only became apparent 3 hr after the treatment. These results are in contrast to previous studies that observed no influence of psychosocial stress (Hoffman & al'Absi, 2004; Kuhlmann, Piel, & Wolf, 2005; Smeets et al., 2006) or pharmacologically induced cortisol increases (Grossman et al., 2006; Kuhlmann, Kirschbaum, & Wolf, 2005) on digit span performance.

One reason for the divergent results might be the varying timing within the different experiments for testing the digit span. The digit span is considerably shorter as other tasks (e.g., Sternberg paradigm, O-Span task). Therefore, the time of testing referring to the onset of stressor might be particularly critical because the cortisol concentrations varies significantly over the course of the stress response. Although in our experiment the digit span was tested when cortisol levels were still rising, in other studies the cortisol peak was already exceeded when subjects were confronted with the WM task (e.g., Kuhlmann, Piel, & Wolf, 2005; Smeets et al., 2006).

An alternative explanation for the empirical discrepancies might be that the digit span as a verbal subtest of the Wechsler memory scale (Wechsler, 1987) was designed as a standardized neuropsychological test procedure for memory functions. As a consequence, the simple span task compared with more complex WM paradigms placed a relatively low demand on WM (Unsworth & Engle, 2007) and might not be sensitive to relatively small performance changes induced by cortisol increases within groups of healthy subjects (D'Esposito & Postle, 1999; Reynolds, 1997). Therefore, in contrast to our study testing a large number of subjects ($n = 71$), studies that employed considerably smaller sample sizes (e.g., Hoffman & al'Absi, 2004; Kuhlmann, Piel, & Wolf, 2005) might not have had sufficient power to detect moderate effects between stressed and nonstressed subjects.

Finally, it should be noted that the present study was the first study that investigated the influence of the CPS on the digit span performance. According to this it is difficult to determine if the divergent results obtained from previous studies could be (at least partially) attributed to the different HPA manipulations employed. In particular, for studies using a single hydrocortisone administration it is well-known that this method results in a relatively isolated increase of cortisol without further affecting other stress responsive systems such as the sympathetic nervous system (SNS; e.g., Kuhlmann, Kirschbaum, & Wolf, 2005; Wolf et al., 2001). However, previous studies investigating declarative long-term memory (Abercrombie, Speck, & Monticelli, 2006; de Quervain, Aerni, & Roozendaal, 2007; Kuhlmann & Wolf, 2006a) and WM (Elzinga & Roelofs, 2005) suggested that the modulation of memory functions through cortisol enhancement require SNS activity or a certain amount of endogenous arousal induced by being submitted to cognitive tests (Kuhlmann & Wolf, 2006b; Okuda, Roozendaal, & McGaugh, 2004). Taken together, cortisol increases alone seem to diminish WM only (a) at rather high cortisol concentrations and/or (b) when the WM task employed puts a high demand on WM (Lupien et al., 1999; Wolf et al., 2001).

Associations Between WM Performance and Cortisol Response

Our results revealed correlations for the cortisol increase (AUCi), the delta cortisol increase, and WM performance in the O-Span and the digit span task backward. The stronger the cortisol response, the larger was the resulting WM impairment on both tasks. These associations were significant for the entire group as well as for the group of subjects exposed to the CPS. No relationship was found between the cortisol increase and WM performance for nonstressed subjects, most likely reflecting the small variance in this group. Furthermore, it was shown that the subjective feeling of discomfort correlated with performance in the O-Span task. However partial correlations revealed that this was secondary to the correlation between the discomfort ratings and the cortisol AUCi. The significant correlations between the endocrine stress response and WM measures are reminiscent of studies that also reported associations between stress-induced cortisol elevations and WM memory alterations (Oei et al., 2006; Schoofs et al., 2008; Smeets et al., 2006). However, it should be noted that the reported correlations in the present study and previous studies accounted on average for about 20% of the variance. When interpreting the size of these correlations it should be noted that both WM functions and the physiological stress response, are quite complex processes, which are influenced by many factors. For WM studies it is well-known that there exist pronounced interindividual differences that (at least) in part depend on individual differences in attentional processes and fluid intelligence (e.g., Awh, Vogel, & Oh, 2006; Unsworth & Engle, 2005). Furthermore, stress influences, beside its effects on the HPA, a variety of important pathways like the sympathetic nervous system and the dopaminergic system (Arnsten & Goldman-Rakic, 1998; Carrasco & Van de Kar, 2003). Both systems are tightly associated with WM functions. For catecholamines (noradrenaline, adrenaline, and dopamine) it is well-known that their concentrations in the PFC are critical for WM performance (Arnsten & Li, 2005; Chamberlain, Muller, Blackwell, Robbins, & Sahakian, 2006). When considering the multifaceted effects of stress on physiological and cognitive systems a correlation between a single, physiological stress

marker and WM performance explaining about 20% of the variance reflects in our view an important finding. In this context it is interesting to note that none of the subjective measures were associated with WM performance. Having said this, the additional measurement of SNS markers (e.g., heart rate, blood pressure or salivary alpha-amylase) would have allowed the comparison of the influence of these two stress systems on WM. In sum, the observed correlations support the hypothesis that WM impairments after stress are (at least in part) caused by the stress-induced activation of the HPA axis. The causal role of heightened cortisol levels for the present findings can only be proven with a pharmacological approach (Lupien et al., 1999).

Stress Effects on WM: Possible Neuronal Correlates

Although results from behavioral studies suggest that WM impairments might be mediated by effects of cortisol on PFC these studies did not allow to draw direct conclusion about the brain areas mediating the observed effects (e.g., Lupien et al., 1999; Oei et al., 2006; Schoofs et al., 2008). However, a couple of studies employing functional Magnetic Resonance Imaging (fMRI) and Position Emission Tomography (PET) techniques provided evidence that stress and/or cortisol modulates the pattern of activation in the PFC (Kern et al., 2008; Wang et al., 2005). Further fMRI studies investigating long term memory also reported significant associations between cortisol and PFC activity (Kukolja, Thiel, Wolf, & Fink, 2008; Oei et al., 2007).

For WM processes, two previous studies examined the effects of acute stress on PFC-based WM systems (Porcelli et al., 2008; Qin, Hermans, van Marle, Luo, & Fernández, 2009). In the first study, subjects were scanned while they were exposed to the CPS or a control condition and simultaneously attended a Sternberg paradigm (Porcelli et al., 2008). The fMRI results showed an increased PFC activation (dorsolateral and ventrolateral PFC) in the stress compared to the nonstressful control condition. In contrast to Porcelli et al. (2008); Qin et al. (2009) found a decreased activation of the DLPFC in subjects engaged in an n-back task after they were stressed by having been shown strongly aversive movies. In both studies, however, the stressor did not substantially alter task performance. In sum, all these human imaging studies suggested that stress has an influence on PFC activation. However, the modulating variables leading to a stress induced increase versus decrease in PFC activation need further characterization. Stressor intensity, task difficulty, and the temporal association between the stressor and the WM task are variables that would need to be considered.

Limitations

Finally, some limitations of our study need to be acknowledged. First of all our study was planned to investigate if WM functions are differentially affected by stress due to a varying demand they put on executive functions. For this purpose we employed two different WM paradigms. We assumed that the digit span forward is a task relying on maintenance capacity while for the backward conditions stored information had to be additionally manipulated and therefore this task in addition relies on executive functions (item manipulation). Furthermore, employing the digit span task allows a comparison of our current study with previously published reports in this area, which most often had used this task. In addition, based on our hypothesis of the importance of an executive demand of the task we selected the O-Span task, which places a heavy load on executive control, for example, by requesting the subjects to solve two different tasks (mathematical task and memorizing words). However, executive control is an umbrella term summarizing a number of cognitive processes like item manipulation, task switching, response inhibition, attention regulation, and so forth (e.g., Arnsten & Li, 2005; Collette & Van der Linden, 2002). The O-Span task does not allow a conclusion as to which specific executive function is important to make WM processes vulnerable to the influence of stress. The findings of impaired digit backward performance, however, suggest that the aspect of item manipulation is critical (or at least sufficient) to create a WM task that is sensitive to the impairing effects of stress. For future studies it would be preferable to use a paradigm that allows a systematically stepwise manipulation of the demand on executive functions while leaving other WM task parameter unchanged.

Furthermore, in the reported study solely a male student sample was tested. However, it has been repeatedly observed that men and women differ in the cortisol stress response with an additional modulating influence of menstrual cycle phase and hormonal contraception in female subjects (Kajantie & Phillips, 2006; Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999; Kudielka & Kirschbaum, 2005). Even though those few studies investigating a mixed sample have found no influence of sex on the effects of psychosocial stress on WM (Elzinga & Roelofs, 2005; Smeets et al., 2006), animal studies reported a stronger influence of stress on WM in female rodents (Shansky, Rubinow, Brennan, & Arnsten, 2006). Thus, further study is needed to clarify whether sex has a modulating influence on the WM performance under stress.

Another limitation of our study is that we did not include measures of sympathetic nervous system activity (e.g., heart rate, salivary alpha-amylase). However, this would have been desirable to better understand the interaction between cortisol and the sympathetic nervous system because previous studies investigating declarative long-term memory (Abercrombie et al., 2006; de Quervain et al., 2007; Kuhlmann & Wolf, 2006a) and WM (Elzinga & Roelofs, 2005) suggested that the modulation of memory functions through cortisol enhancement require concurrent noradrenergic activity. Then again, it should be noted that the CPS stress procedure has been shown to reliably induce sympathetic activity (Lovallo, 1975; McRae et al., 2006; Velasco et al., 1997).

Finally, one limitation of the employed experimental design is the short interval between the treatment and the WM testing. In the cold water condition participants were requested to leave their arm as long as possible in ice cold water. Results showed that this induced significant higher feelings of discomfort in the stressed group. Due to the short time interval between CPS and WM measurement it seems possible, that distraction from pain or other sensations secondary to cold stress had further effects on the cognitive performance measurement of subjects.

Conclusion

In sum, we report that WM performance in the O-Span and the digit span backward task is significantly impaired after exposure to the cold pressor test. In contrast, digit span forward was not

influenced by the stressor. These findings together with other recent studies (Oei et al., 2006; Schoofs et al., 2008) indicate that stress impairs performance in demanding WM tasks requiring maintenance and executive processing of information. Furthermore, the fact that stronger cortisol response were associated with larger WM impairments for the O-Span and digit span task backward suggest that these stress-induced impairments in WM are at least in part brought about by specific effects of cortisol on neurons in the PFC.

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Received January 6, 2009
Revision received June 29, 2009
Accepted June 30, 2009 ■