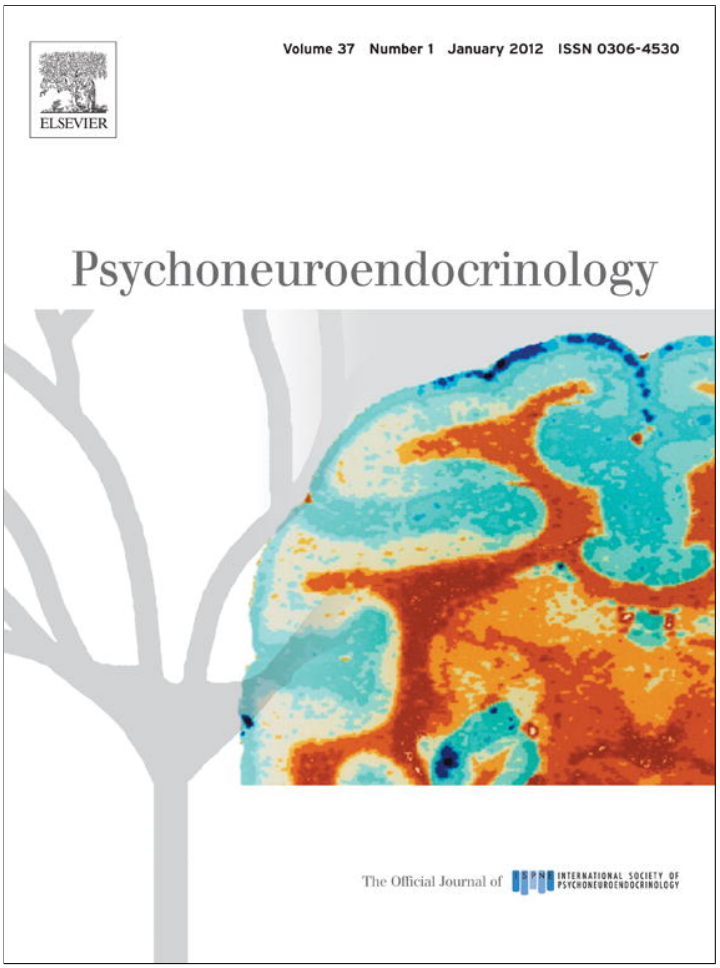

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Psychosocial stress exposure impairs memory retrieval in children

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Development

Summary Negative consequences of stress on working memory and delayed memory retrieval have been observed in adult humans. Little is known about the occurrence of similar effects in children. Forty-four German full-term children, aged 8—10 years, were randomly assigned to a stressful (Trier Social Stress Test for Children — TSST-C) or to a non-stressful control condition. Afterwards, delayed memory retrieval was tested using a computerized version of the well-known card game "Memory". It contained positive, neutral and negative stimuli. In addition, working memory of verbal and non-verbal material was assessed. The stressed children showed pronounced cortisol increases accompanied by a decrease in mood. Children exposed to the stressor performed poorer in the delayed memory retrieval test (memory card game). They committed more errors. No differences were found for working memory. The stress-induced memory retrieval impairment mirrors findings in adults. In contrast, the missing working memory effects could suggest developmental differences in stress sensitivity.

1. Introduction

How do stress and related neuroendocrine responses influence the memory of our children? During their education, they constantly have to manipulate and learn new information as well as retrieve memories in arousing or stressful environments. They have to face presentations, oral or written exams, and a strong pressure imposed by teachers, parents and society. Children are often required to perform well under pressure. In these contexts, some of them fail to retrieve previously learned information. However, few experimental studies exist on this topic compared to the large body of research in adults (reviews in de Quervain et al., 2009; Wolf, 2009) and animals (reviews in Roozendaal, 2002; Joëls, 2006; Cazakoff et al., 2010). One potential reason for the scarcity of studies in children could lie in the observation that the induction of stress in the lab appears to be more difficult in children than in adults (reviewed in Gunnar et al., 2009a).

Stressful events trigger two systems: the sympathetic nervous system (SNS), resulting in the release of catecholamines (noradrenalin and adrenaline), and the hypothalamic—pituitary—adrenal (HPA) axis, resulting in the release of

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glucocorticoids (reviewed in de Kloet, 2003). As in adults, SNS activity in children can be measured using salivary alpha-amylase as an indirect marker (Rohleder and Nater, 2009). However, the few studies reporting sAA concentrations in children after stress exposure yield conflicting results (Strahler et al., 2010; Yim et al., 2010a). Salivary cortisol can be used as a non-invasive marker of HPA axis activity (Kirschbaum and Hellhammer, 1994). Nonetheless, a sizable number of studies have failed to induce a cortisol response in children in the laboratory (reviewed in Gunnar et al., 2009a).

Studies in adults have shown that glucocorticoids can affect memory in a multifaceted way (reviewed in Roozendaal et al., 2006). While consolidation is enhanced (Buchanan and Lovallo, 2001; Cahill et al., 2003), memory retrieval is compromised by elevated glucocorticoid levels (de Quervain et al., 2000, reviewed in Wolf, 2009). These consequences are often more pronounced for emotional material. This idea is supported by rodent data (Okuda et al., 2004; Roozendaal et al., 2004a) as well as by adult human data from pharmacological (Kuhlmann et al., 2005a) or behavioral studies (Buchanan and Tranel, 2008; Smeets et al., 2008). The apparently opposing impact on consolidation and retrieval seems to depend on noradrenergic activity in the basolateral complex of the amygdala (BLA) and its interaction with other brain regions (reviewed in Roozendaal et al., 2009).

With respect to stress effects on working memory (WM), the findings are more controversial. Detrimental effects of stress which appear to be mediated via dopamine, noradrenalin and cortisol have repeatedly been observed in rodents and monkeys (reviewed in Arnsten, 2009). However, results have been less consistent in humans. Some studies using laboratory stressors such as the Trier Social Stress Test (TSST) or the cold pressor stress test (CPS) have shown adverse consequences of stress on WM (Elzinga and Roelofs, 2005; Oei et al., 2006; Schoofs et al., 2008, 2009). Similar findings have been obtained using pharmacological administration of cortisol (Wolf et al., 2001; Terfehr et al., 2011). In contrast, others have failed to replicate these results (Kuhlmann et al., 2005b; Smeets et al., 2006). As in memory retrieval, the modulation of WM also seems to depend on co-activation of the HPA axis and the SNS (Roozendaal et al., 2004b; Elzinga and Roelofs, 2005).

In this context, it might be important to differentiate between distinct components of WM. In typical span tasks attention and storage (as assessed by the forward condition) can be contrasted with manipulation (backward condition). We recently observed that stress selectively impaired performance in the digit span backward task (Schoofs et al., 2009). Here, we suggested that stress might only impair WM tasks with a high demand on executive functions. Other groups, however, have observed the reversed pattern of results (i.e. impaired forward but unimpaired backward performance; Elzinga and Roelofs, 2005). Moreover, WM for verbal and non-verbal material is thought to rely on different brain regions (Owen et al., 2005) as well as on different cognitive processes (reviewed in Baddeley, 2003). Most of the previous studies in the field of stress research have investigated one domain only (verbal or non-verbal) by using the digit span test, the Sternberg task or the n-back task. Recently, however, Li et al. (2010) reported evidence that negative emotions had a stronger impact on the retention of spatial compared to verbal material in WM.

It is unclear whether similar impairing effects of stress on memory retrieval and WM are evident among children. There is evidence for developmental variations in the sensitivity to stress (Gunnar and Quevedo, 2007; Lupien et al., 2009; Sumter et al., 2010). However, the issue of changes in 'cognitive' sensitivity to stress has received little attention. The majority of developmental studies have focused on the physiological response to an acute stressor without addressing its impact on memory.

We currently have knowledge of only two studies investigating the effects of stress-induced cortisol response on memory in children. Quas et al. (2004) reported associations between memory and cortisol response induced by a fire alarm incident, which were further modulated by social support. It was recently reported that a larger cortisol response to a laboratory stressor in children was associated more strongly with accurate memory of this event (tested two weeks later) compared to adults (Quas et al., 2011).

Although several studies indicate no apparent differences in neuroendocrine responses between boys and girls (Khilnani et al., 1993; Yim et al., 2010b), there are examples for sex-differentiated HPA axis responses to stress throughout the human life cycle (reviews in Kajantie and Phillips, 2006; Dedovic et al., 2009). In the Trier Social Stress Test (TSST), adult men typically show a more pronounced response than women (reviewed in Kudielka and Kirschbaum, 2005; Cornelisse et al., 2011). Conversely, higher cortisol in response to TSST-C has been observed in 13-year-old girls (Gunnar et al., 2009b) as well as in 8-year-old-girls (Räikkönen et al., 2010) compared to boys. In line with these findings, a recent study (Strahler et al., 2010) suggested that there is an increase in cortisol response with age in males but not in females. In conclusion, while findings suggest that sex makes a difference in adults, this issue is not clear yet regarding children.

As the memory impact of acute stress in children is still poorly understood, we aimed at investigating whether acute stress and its related hormonal responses affect WM of verbal and non-verbal material, delayed memory retrieval, and immediate recall. We further tested whether stress differentially affects temporary storage (forward) and manipulation processes (backward) of WM. Since it is conceivable that gender could have an impact on the neuroendocrine stress response and its cognitive consequences, we studied this variable in an exploratory fashion. Based on previous findings in adults, we hypothesized that delayed memory retrieval and WM would be negatively influenced by stress in children.

2. Methods

2.1. Participants

Forty-four German full-term children, aged 8 to 10 years, participated in this study and were randomly assigned to a stressful ($n = 22$) or to a non-stressful control condition ($n = 22$). The exclusion criteria included somatic disorders, diabetes, hypertension, cardiovascular diseases, allergy, asthma, neurodermatitis/psoriasis, hepatitis, tuberculosis (TB) as well as sensorial disorders, intellectual disability, dyscalculia, dyslexia, and children taking medication or immunization for at least 3 months prior to the study. Three

Table 1 Sociodemographic characteristics of evaluated children (n = 41).

Characteristics	Treatment			
	Control (n = 19)	TSST-C (n = 22)	Frequency (%)	p
Age mean (SD) (years:months)	9:8 (0:7)	9:8 (0:6)		.97
Range of age (years:months)	8:8—10:9	8:9—10:8		
Sex				.83
Male	11	12	56.1	
Female	08	10	43.9	
Handedness				.37
Right	18	19	90.2	
Left	01	03	9.8	
Education				.40
Third grade	07	11	43.9	
Fourth grade	12	11	56.1	
Birth-size (SD) (cm)	51.2 (2.5)	51.0 (3.1)		.82
Birth-weight (SD) (kg)	3.47 (0.5)	3.45 (0.5)		.88
BMI (SD) (kg/m^2)	16.2 (1.8)	16.5 (1.8)		.52

participants in the control group were excluded from data analysis due to the following reasons: strong self-reported headaches during memory testing (n = 1), misunderstanding of instructions for the cognitive tests (n = 1), and a substantially elevated cortisol baseline value (C_{bas} = 6.27 nmol/l). The latter participant was classified by SPSS analysis as an outlier regarding C_{bas} and C_{+10}. Two participants in the stress group had missing data in the memory card game due to a technical failure. These participants' other data were not affected. Table 1 provides a description of the sample.

The study was approved by the ethics committee of the German Psychological Association (DGP). All children participated voluntarily and written informed consent was obtained from the children as well as from one parent. At the end of experiment, the children received a gift coupon (15 €; approximately US$ 21) and a certificate of attendance. In addition, the parents were given 10 € (approximately US$ 15) as means of compensation for their time and travel expenses.

2.2. Procedures

Sessions were run between 1400 h and 1800 h in order to control for possible circadian rhythm effects (Price et al., 1983; Tzortzi et al., 2009). As shown in Table 2, the entire procedure lasted approximately 2 h. It encompassed the administration of questionnaires and mood scales, endocrine measures (salivary cortisol and alpha-amylase (sAA)), and memory tests. The questionnaires were administered to obtain physical and socio-demographic information about the participants.

2.2.1. Questionnaires

A socio-demographic questionnaire was completed by the parents of the participant. It encompassed the following attributes concerning the participant: Age, handedness, grade of school, size and weight at birth, and current body mass index (BMI).

2.2.2. Self-assessment Manikin (SAM)

The Self-assessment Manikin (SAM) is a visual rating scale commonly used to assess the valence, arousal and dominance of stimuli (Bradley and Lang, 1994; von Leupoldt et al., 2007). In the current study, the SAM was used in two different versions: (1) one adapted version to assess the momentary affective states of participants (happiness, arousal and dominance) before the beginning of the experiment as well as after the Trier Social Stress for Children (TSST-C) or the non-stressful control condition; (2) the original version to obtain the subjective valence and arousal ratings of the memory

Table 2 Timeline of experiment.

Procedures		
Time	Task	Duration (min)
0:00	Questionnaire	05
0:05	SAM	03
0:08	Memory card game (learning phase) — 2 trials	10
0:18	Pause	40
0:58	Salivary samples (C baseline; sAA baseline)	03
1:01	TSST-C or control condition	20
1:21	Salivary samples (C +01; sAA +01)	03
1:24	SAM	01
1:25	WMS-R digits span test	06
1:31	Salivary samples (C +10; sAA +10)	03
1:34	WMS-R spatial span test	08
1:42	Memory card game (retrieval phase)	02
1:44	Story of BASIC-MLT	02
1:46	Salivary samples (C +25; sAA +25)	03
1:49	Ratings IAPS pictures	05
1:54	Debriefing and feedback	05
1:59	End of the session	

Legend: SAM: Self-assessment Manikin; C: cortisol; sAA: alpha-amylase; TSST-C: Trier Social Stress Test for Children; WMS-R: Wechsler Memory Scale Revised; BASIC-MLT: Battery for Memory Assessment in Children-"Merk und Lernfähigkeitstest für 6 bis 16 Jährige"; IAPS: International Affective Picture System. Salivary samples (C and sAA) were collected at four different moments: baseline, +01, +10, +25.

card game pictures by the participants. It was administered in the paper-pencil version, which consists of a 5 point-scale for each dimension of the SAM, respectively. Happiness or valence ranged from a manikin smiling broadly (1 point) to a manikin frowning (5 points). Arousal ranged from a manikin that was not aroused (1 point) to an aroused one (5 points). Dominance ranged from a controlling (biggest manikin — 1 point) to a completely controlled manikin (smallest one — 5 points) (Bradley and Lang, 1994).

2.2.3. Experimental procedure Trier Social Stress for Children (TSST-C) or control condition

As shown in Table 2, after the learning phase containing the memory card game, the children were randomly assigned to a stressful or to a non-stressful control condition. Instructions about the tasks were given for 5 min in both conditions. The stress was induced by an adapted child version of the well-known Trier Social Stress Test (Buske-Kirschbaum et al., 1997, 2003). The Trier Social Stress Test for Children (TSST-C) involves uncontrollability and high levels of social-evaluative threat. It consists of a verbal and a mental arithmetic task in front of a camera and a committee composed of three adult observers who act in a neutral and rather reserved fashion. The speech task involves listening to the beginning of a story, building on it and reporting the thought up part to the committee. After listening to the introduction of the story, the children have 5 min to think about and elaborate on a continuation (preparation) and another 5 min afterwards to tell the committee about their thought up continuation. The arithmetic task (5 min), in turn, consists of serially subtracting the number 7 from the number 758 as fast and as accurately as possible. In the case of an incorrect answer, the committee asks the child to return to the number 758 and start again. The difficulty of the task is increased when the child completes 15 calculations without mistake before the end of the 5-min period. In this case, the child is asked to serially subtract the number 13 from the number 758.

The control condition also involves verbal and mental arithmetic tasks. However, these do not take place in front of a camera and a committee. The children are given 5 min to think about their favorite book or film, which they then tell the examiner about. Instead of the mental arithmetic task, a modified version of the well-known domino game is used. The aim of this game is to obtain the sum of 7 (number of dots on the "open" end of the tile + number of dots on the tile placed by the player = 7). For example, picture the first move of the game, when a single tile is on the table and both of the tile's end halves are still free to use. If the right half of this tile has 3 dots on it and the left half has 2 dots on it, the children can either place a tile with 4 dots onto the right side of this tile (4 + 3 = 7) or one with 5 dots onto the left side of this tile (2 + 5 = 7). The children play this game with the examiner.

2.2.4. Memory assessment

The memory assessment involved the following domains: delayed memory retrieval (memory card game), working memory of verbal (WMS-R digit span test — backward) and non-verbal material (WMS-R spatial span test — backward), and immediate recall (Story subtest of the Memory and Learning test battery BASIC-MLT). In addition, basic attention and passive storage (forward span tasks) were evaluated, since they provide important information for the interpretation of possible effects in the backward version (WM) of the task. The description of each test and of its administration follows below.

2.2.4.1. Memory card game. Delayed memory retrieval was evaluated using a computerized version of the well-known card game "Memory" which was developed in-house (Schwabe et al., 2009). It consisted of 15 animal card pairs arranged in 6 rows. The pictures varied in valence (5 positive, 5 neutral, and 5 negative) and were taken from the International Affective Picture System (IAPS) (Lang et al., 1997).

The memory card game was applied at two different points of time (see Table 2). There was a learning session (prior to the stressful or non-stressful control condition) and a retrieval session (after the stressful or non-stressful control condition). By means of this design, selective effects of stress on memory retrieval could be assessed (Kuhlmann et al., 2005b; Schwabe and Wolf, 2009). Children were given two trials in which to learn the position of 15 card pairs. They were asked to choose one card and afterwards to try to find the correct match. If the second card was different to the first one, it was turned face down again and the participants had to keep looking for the correct match. They could only move on to the next pair after finding the corresponding card. The pictures were randomly arranged between subjects but they were kept constant within subjects. The learning session took place approximately 53 min before the TSST-C or non-stressful control condition and lasted 10 min, as shown in Table 2. Afterwards, there was a pause of 40 min, in which the children performed creative tasks (toy brick building and crafting). The retrieval session took place approximately 21 min after cessation of the stressful or non-stressful control condition and 1 h and 24 min after the initial acquisition and lasted approximately 2 min.

The performance was scored as the number of errors for an entire trial (number of clicks minus correct clicks for all categories combined) as well as for each valence category (positive, neutral, and negative). Valence categories were created based on IAPS norms and validated post hoc by ratings from the participants. The children used SAM scales to classify the emotional valence and arousal dimensions of these pictures. This took place at the end of study (see Table 2). Considering the IAPS norms, the valence of positive stimuli ranged from 7.37 (horse) to 8.34 (puppies) while the valence of negative pictures ranged from 3.17 (cockroaches) to 4.21 (angry dog). The neutral ones showed a range between 4.50 (bees) and 6.37 (duck). In response to the valence and arousal validation of the pictures by the participants, the classification of two pictures was modified. Bees were categorized as negative while the dog was categorized as neutral. In addition to the number of errors, the total time to complete a trial was assessed.

2.2.4.2. WMS-R digit span test. The digit span test (forward and backward) of the Wechsler Scale (Wechsler, 1987) was applied for 4 min after the stressful or non-stressful control condition. The digit span forward task consists of repeating strings of numbers dictated by the examiner. The strings increase in length while there are two trials for each length. Each correct answer was scored with one point. In order to present the test material in a standardized form, the digits

were presented using a recorded CD. The task was terminated if two continuous errors were made at a specific digit length. In the backward condition, the digits had to be repeated in reversed order. While the forward format assesses attention and immediate retention (passive storage), the backward test requires the active manipulation of the stored material (executive functions). The performance in both tests was evaluated using raw scores.

2.2.4.3. WMS-R spatial span test. An analogue visual version of the digit span test, the WMS-R spatial span test (Wechsler, 1987), was administered in a forward and backward condition. In the forward one, the child was asked to copy a sequence of movements made by the experimenter by tapping an array of blocks. In the backward one, the movements were to be repeated in the reverse order. Each correct series of blocks tapped in the correct sequence was scored as one point and the data analysis was performed with these raw scores. As shown in Table 2, this task took place 10 min after cessation of TSST-C.

2.2.4.4. Memory and learning battery test BASIC-MLT. After the retrieval session of the memory card game (see below), the Story subtest of the Battery for Assessment in children BASIC-MLT (Merk- und Lernfähigkeitstest für 6 bis 16 Jährige, German version; Lepach and Petermann, 2008) was administered. This task consists of remembering details of a story immediately after listening to it (via loudspeakers). The task assesses the ability to handle meaningful verbal information and the contribution of comprehension to recall and retention. Each correct part of the story was scored as one point. The maximum score to be obtained was 21 points. The raw scores were used for data analysis.

2.2.5. Neuroendocrine analysis

The activity of the SNS and the HPA axis was evaluated, respectively, by alpha-amylase levels (sAA) (Rohleder and Nater, 2009) and cortisol levels (Kirschbaum and Hellhammer, 1994). Saliva was sampled at four different points of time, using the Salivette sampling device (Sarstedt, Nümbrecht, Germany): baseline, sample +01, sample +10 and sample +25. An immunoassay (IBL, Hamburg, Germany) was used to measure salivary cortisol. To measure sAA, a quantitative enzyme kinetic method was used as described elsewhere (Rohleder and Nater, 2009). Intra- and inter-assay precision expressed as percental coefficient of variation was below 10%.

2.2.6. Statistical analyses

The statistical analyses were performed using PASW Statistics 18. The socio-demographic comparisons between the groups (TSST-C *vs.* control) were performed using Chi—square test (sex, handedness, and education) and independent — samples *t*-test (age, BMI, birth-size, and birth-weight). Before the analysis of cortisol and sAA, these data were tested for normal distribution with the Shapiro—Wilk test. When a deviation from normality was indicated, the data were log-transformed.

The endocrine (cortisol) and autonomic responses (sAA) (salivary stress markers) to the TSST-C were evaluated separately by using a mixed model analysis of variance (ANOVA) with the repeated measurement factor time (baseline, +01, +10 and +25) and the between-subjects factors condition (TSST-C *vs.* control) and sex (girls *vs.* boys). Greenhouse-Geisser correction was used when sphericity assumptions were violated. Effects of the stressor on mood as well as possible differences between the sexes were examined by a two-way MANOVA (condition and sex) with the following dependent variables: happiness, arousal and dominance.

In order to analyze the delayed memory retrieval performance between the two groups as well as the influence of sex, an ANOVA with the repeated measurement factor valence (positive, neutral, and negative) and the between-subjects factors condition (TSST-C *vs.* control) and sex (girls *vs.* boys) was conducted. Effects of the stressor on digit span (verbal) performance and on spatial span (visual-spatial) performance were analyzed separately. Here, a mixed model ANOVA was used with the repeated measurement factor subtest (forward *vs.* backward) and the between-subjects factors condition (TSST-C *vs.* control) and sex (girls *vs.* boys) for each test respectively. The immediate recall performance was analyzed by using a two-way ANOVA (condition and sex). In multiple comparisons, the alpha level was adjusted using the Bonferroni procedure.

Furthermore, effect sizes (Cohens *d*) were computed to illustrate the size of significant effects. They were calculated using G Power software (Faul et al., 2007; see Section 3.8). Effect sizes of .50 or larger can be classified as medium while effect sizes of .80 or larger are considered large (Cohen, 1988).

Finally, bivariate associations between cortisol or sAA and the performance on delayed memory retrieval were investigated by using Pearson correlations (2-tailed). In order to perform this analysis, the repeated neuroendocrine data were transformed into Area under the curve (AUC) index with respect to increase (AUC*i*; see Pruessner et al., 2003). This summary index was computed for cortisol (AUC*i*_co) and sAA (AUC*i*_sAA). Possible associations between delayed memory retrieval performance and changes in the three SAM dimensions (post-stress minus pre-stress) were also analyzed using Pearson correlations (2-tailed).

3. Results

3.1. Description of sample (physical and socio-demographic questionnaire)

As shown in Table 1, there were no significant differences between the groups in the distribution of age, BMI, birth-size and birth-weight. Moreover, there were no differences with respect to sex, education and handedness.

3.2. Response to acute stress — salivary cortisol

Shapiro—Wilk test showed that cortisol data were skewed immediately before exposing the children to the TSST-C or to the control condition ($p < .0001$) and 25 min afterwards ($p < .0001$). In order to obtain a normal distribution, cortisol data were log-transformed. Mauchly's test indicated that the assumption of sphericity had been violated ($\chi^2(5) = 73.47$, $p < .0001$). Therefore, degrees of freedom were corrected using *Greenhouse-Geisser*-estimates of sphericity ($\varepsilon = .51$). A 2 (condition) $\times$ 2 (sex) $\times$ 4 (time) ANOVA for repeated measures revealed significant main

effects of condition ($F_{(1/37)} = 44.60$, $p < .0001$) and of time ($F_{(1.52/56.1)} = 23.11$, $p < .0001$), but no main effect of sex ($F_{(1/37)} = 3.56$, $p = .067$). In addition, a significant interaction between time and condition ($F_{(1.52/56.10)} = 31.75$, $p < .0001$) was found. No interaction between time, condition and sex ($F_{(1.52/56.10)} = .37$, $p = .64$) was observed. Post hoc Bonferroni-corrected independent-samples *t*-tests revealed significant differences between control and TSST-C groups at the +1, +10 and at the +25 sampling ($p < .0001$; see Fig. 1a). The two groups did not differ at baseline ($p = .49$). Effect size analysis indicated a large effect of stress on cortisol concentrations at +10 (Cohens $d = 1.97$). When the effect sizes were calculated according to the method used by Dickerson and Kemeny (2004) (using the baseline SD instead of the pooled SD) the effect size for the cortisol increase was even larger ($d = 6.84$).

3.3. Response to acute stress — salivary alpha-amylase

Shapiro—Wilk test showed that all sAA data were skewed too: baseline, +10, +25 ($p < .0001$) and +1 ($p = .001$). Therefore, these data were log-transformed as well. *Greenhouse-Geisser* corrections ($\varepsilon = .75$) regarding the violation of sphericity ($\chi^2(5) = 21.63$, $p = .001$) were used. The ANOVA for sAA revealed a significant main effect of time ($F_{(2.25/83.24)} = 8.82$, $p < .0001$), but no significant main effects of condition ($F_{(1/37)} = 1.78$, $p = .19$) or of sex ($F_{(1/37)} = 1.10$, $p = .30$). In addition, the condition x time interaction was significant ($F_{(2.25/83.24)} = 4.03$, $p = .017$) while the condition × sex × time interaction was not ($F_{(2.25/83.24)} = 2.10$, $p = .12$). Nevertheless, post hoc Bonferroni-corrected analyses failed to find significant differences between the two groups at any specific points in time (see Fig. 1b): baseline ($p = .92$); +1 ($p = .060$); +10 ($p = .22$); +25 ($p = .12$).

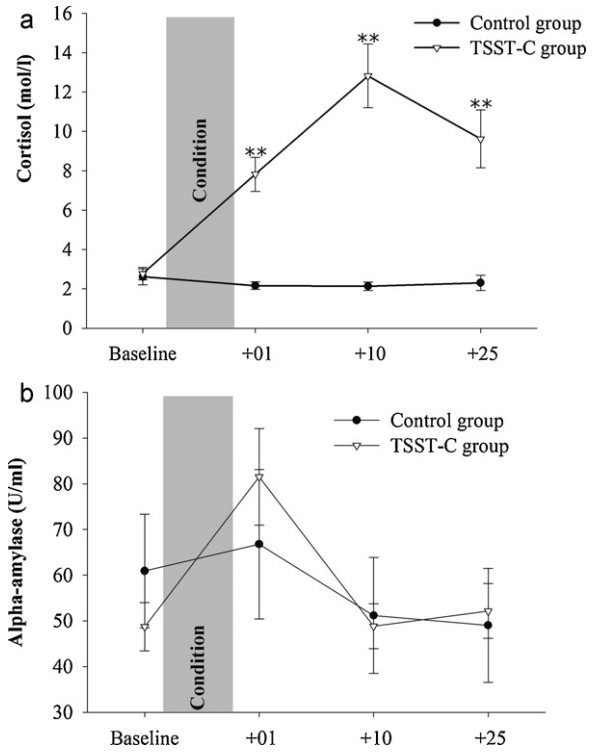

Figure 1 Mean salivary cortisol concentrations (a) and salivary sAA concentrations (b) of children exposed to the TSST-C and the control condition at four different time points. Statistical analyses were performed using log-transformed data. The graphs show raw data. Error bars represent standard error of mean (S.E.M.). For both stress markers a significant condition by time interaction was observed in the conducted ANOVA. However only for cortisol significant between group differences were observed using Bonferroni adjusted *t*-tests (see Section 3 for additional information). $^{**}p < .01$ between the TSST-C and the control group.

3.4. Self-assessment Manikin (SAM)

A two-way multivariate analysis (MANOVA) revealed no differences between TSST-C and control groups before the stress procedure ($F_{(3/34)} = .060$; $p = .98$; Wilks' $\lambda = .99$) on the three dimensions of the SAM scale (data not shown). Likewise, no differences were found between boys and girls ($F_{(3/34)} = .18$; $p = .91$; Wilks' $\lambda = .98$). As expected, mood differences between the two groups (TSST-C *vs.* control) were observed after exposure to the stressor ($F_{(3/34)} = 5.57$; $p = .003$; Wilks' $\lambda = .67$). Stress caused more negative (higher) ratings overall in the SAM. Again, no differences occurred between boys and girls ($F_{(3/34)} = .12$; $p = .95$; Wilks' $\lambda = .99$). Post hoc Bonferroni-corrected univariate tests revealed that participants in the TSST-C reported being unhappier ($F_{(1/36)} = 13.34$; $p = .001$; *Cohens d = 1.22*) and more aroused ($F_{(1/36)} = 6.79$; $p = .013$; *Cohens d = .88*), and felt more like they were being controlled ($F_{(1/36)} = 4.55$; $p = .040$; *Cohens d = .73*) than participants exposed to the non-stressful control condition (see Fig. 2).

3.5. Memory card game

Initially, the data for memory encoding were analyzed. Separate 2 (trial 1 *vs.* trial 2) × 2 (condition) × 2 (sex)

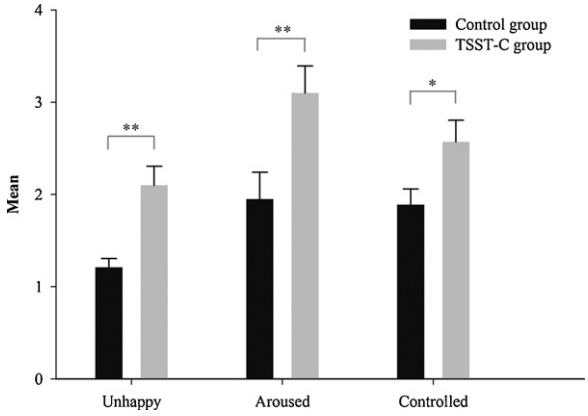

Figure 2 Post stress SAM ratings of children exposed to the TSST-C or the control condition. Ratings of each dimension are given in a 5-point format: happy (1 point) — unhappy (5 points); unaroused (1 point) — aroused (5 points); controlling — controlled (5 points). Error-bars represent standard error of mean (S.E.M.). $^{*}p < .05$ $^{**}p < .01$ between the TSST-C and the control group.

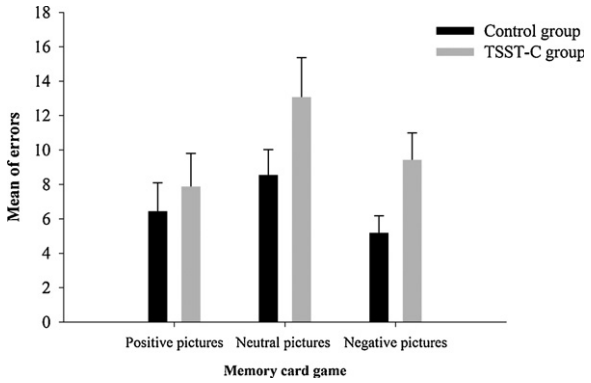

Figure 3 Effects of stress on memory retrieval. A significant main effect of treatment on delayed memory retrieval (number of errors) was observed with stressed participants committing more errors. The valence by condition interaction was non-significant (see Section 3 for additional information). Error bars represent standard error of the mean (S.E.M.).

ANOVAs revealed no condition (TSST-C *vs.* control) or sex differences in number of errors ($F_{(1/35)} = .20$; $p = .66$; $F_{(1/35)} = .011$; $p = .92$) or in total time to complete a trial ($F_{(1/35)} = .63$; $p = .43$; $F_{(1/35)} = .23$; $p = .64$) during initial learning/acquisition, which took place before the experimental stressful or non-stressful control condition. There was a significant reduction of errors committed by children ($F_{(1/35)} = 61.25$; $p < 0001$) in learning trial 2 (mean: 37.10 ± 3.78 S.E.M.) compared to learning trial 1 (mean: 73.79 ± 4.00 S.E.M.). Similarly, there was a significant decrease of total response time to complete the task ($F_{(1/35)} = 117.54$; $p < .0001$): learning trial 1 (mean: 178.57 ± 8.36 S.E.M.); learning trial 2 (mean: 93.24 ± 5.49 S.E.M.).

During the retrieval testing, a 3 (valence) $\times$ 2 (condition) $\times$ 2 (sex) repeated measurement ANOVA showed a main effect of condition on the number of errors committed ($F_{(1/35)} = 4.31$; $p = .045$; see Fig. 3), but no main effect of sex ($F_{(1/35)} = .05$; $p = .82$). The children exposed to the TSST-C made more errors during retrieval (mean: 30.45 ± 4.16 S.E.M.) than control participants (mean: 20.26 ± 2.68 S.E.M.). The effect size for the impairing effects of stress on memory retrieval can be considered medium (*Cohens d* = *.65*). Valence $\times$ condition ($F_{(1.74/61)} = .44$; $p = .61$), valence $\times$ sex ($F_{(1.74/61)} = 1.21$; $p = .30$), as well as valence $\times$ condition $\times$ sex ($F_{(1.74/61)} = .81$; $p = .43$) interactions were not significant. However, descriptively, the impairing effects of stress on memory retrieval were most pronounced for negative stimuli (see Fig. 3). Regarding response time, a 3 (valence) $\times$ 2 (condition) $\times$ 2 (sex) repeated measurement ANOVA showed no significant effect of condition ($F_{(1/35)} = 3.74$; $p = .061$) on total time to complete the task during the retrieval block. Children exposed to the TSST-C (mean: 80.90 ± 8.03 S.E.M.) tended to be slower than control participants (mean: 64.40 ± 3.32 S.E.M.).

3.6. Working memory, passive storage and immediate recall performance

No significant main effects of condition (TSST-C *vs.* control) or of sex were observed regarding performances in the digit span test (condition: $F_{(1/37)} = .86$, $p = .36$; sex: $F_{(1/37)} = .69$; $p = .41$) and in the spatial span test (condition: $F_{(1/37)} = .45$; $p = .50$; sex: $F_{(1/37)} = 1.81$; $p = .19$). Likewise, no significant subtest (forward *vs.* backward) $\times$ condition (TSST-C *vs.* control) interaction and subtest x sex interaction was found for both types of stimuli: verbal (subtest $\times$ condition: $F_{(1/37)} = .59$, $p = .45$; subtest $\times$ sex: $F_{(1/37)} = .40$; $p = .53$) and visual-spatial (subtest $\times$ condition: $F_{(1/37)} = .026$, $p = .87$; subtest $\times$ sex: $F_{(1/37)} = .092$; $p = .76$). With regard to immediate recall of an episode (story subtest of BASIC-MLT), results neither revealed significant differences between the two groups ($F_{(1/37)} = .449$; $p = .51$) nor between boys and girls ($F_{(1/37)} = 1.38$; $p = .25$) (Table 3).

3.7. Relationship between neuroendocrine responses and delayed memory performance

Pearson correlations (2-tailed) for the entire group and for the TSST-C group only were conducted to evaluate whether cortisol or sAA increases were related to delayed memory retrieval. A positive association was found between the AUCi_co and the total number of errors during delayed retrieval of the memory card game ($r = .37$; $p = .021$). More importantly, the analysis within the stress group showed a

Table 3 Immediate recall and working memory performance: control *vs.* TSST-C treatment ($n = 41$).

Memory tasks	Treatment	
	Control ($n = 19$)	TSST-C ($n = 22$)
WMS-R digits span forward	6.16 (1.46)	6.09 (1.77)
95% CI	5.45—6.86	5.31—6.88
WMS-R digits span backward	5.32 (1.00)	4.73 (1.61)
95% CI	4.83—5.80	4.01—5.44
WMS-R spatial span — forward	8.05 (1.50)	7.73 (1.38)
95% CI	7.33—8.78	7.11—8.34
WMS-R spatial span — backward	7.89 (1.45)	7.55 (1.50)
95% CI	7.20—8.59	7.55—6.88
Story (BASIC-MLT)	12.68 (2.81)	13.32 (3.24)
95% CI	11.33—14.04	11.88—14.76

Memory performance (mean (S.D.)). Performance is expressed in raw scores.

positive correlation between these two variables (r = .45; p = .045) as well. Subjects characterized by a larger cortisol response thus committed more errors during delayed retrieval than those who showed a smaller one. However, no significant correlations were observed between total number of errors on delayed memory retrieval and AUCi_sAA in the entire group (r = .13; p = .42) or within the stress group (r = −.08; p = .72).

3.8. Relationship between change in mood and delayed memory performance

No significant associations were observed between change in the three dimensions of mood (post- minus pre-stress) and delayed memory performance: happiness (r = .036; p = .83); arousal (r = .038; p = .82); dominance (r = .011; p = .94).

3.9. Power analyses

In order to calculate the achieved power of the current study post hoc, a formal power analysis was conducted using G* power (Faul et al., 2007). The power to detect an effect of the size of the retrieval impairment (d = .65) observed in the memory card game was .65 ($1 - \beta$) for a one-sided and .53 for a two-sided test. The power to detect an effect of the size of the cortisol concentrations at +10 (d = 1.97) was .99 for a two-sided test.

4. Discussion

The aim of this study was to investigate the acute effects of stress induced by the TSST-C on different memory domains in children. Working memory, delayed memory retrieval and immediate recall were tested. After the TSST-C, the children showed pronounced cortisol increase accompanied by changes in happiness, arousal and dominance. They felt unhappier, more aroused and more like they were being controlled. As in adults, memory retrieval was compromised after stress exposure. In contrast, no impairments were found on WM for verbal or visual-spatial material. As expected, no significant differences were observed for passive storage (forward tests) or immediate recall.

In line with our results, the successful elicitation of the HPA axis in response to the TSST-C or to slightly modified versions of it has been reported in 7- to 14-year-old participants (Khilnani et al., 1993; Buske-Kirschbaum et al., 1997, 2003; Yim et al., 2010b; Quas et al., 2011). Taken together, these findings contradict the idea of a stress hyporesponse period during childhood (reviews in Gunnar and Cheatham, 2003; in Lupien et al., 2009) and suggest that social-evaluative threat activates the HPA axis in children and adults alike (Dickerson and Kemeny, 2004). In fact, the effect size for the cortisol response obtained in our study was substantially larger than those reported in previous studies with adults. However, inducing cortisol responses in the laboratory in the age range present in this study does not appear to be an easy task. A significant number of studies have failed at this point (reviewed in Gunnar et al., 2009a). Gunnar et al. (2009b), for instance, did not observe a significant cortisol increase after TSST-C in 11-year-old children.

In line with several previous reports (Khilnani et al., 1993; Buske-Kirschbaum et al., 1997; Yim et al., 2010b), we did not observe sex differences in the cortisol stress response in children (Kudielka et al., 2004). Sex differences in the response to social-evaluative threat might occur after puberty only, since they appear to reflect activational effects of gonadal steroid changes during the menstrual cycle or in response to the intake of oral contraceptives (Kirschbaum et al., 1999). However, psychological or social explanations (e.g. gender socialization and social learning) need to be kept in mind as well (Dedovic et al., 2009).

Unlike cortisol, results for sAA, an indirect marker of SNS activity (reviewed in Rohleder and Nater, 2009), were less pronounced. A significant condition by time interaction was revealed. An increase in sAA levels (from baseline to +1) occurred within the stress group. However, the two groups did not differ significantly from each other at a single point of time, even though a trend was apparent directly after cessation of the TSST. This indication of SNS response after the TSST-C in 8- to 10-year-old children is in line with other recent findings. Strahler et al. (2010) reported a sAA increase in 6- to 10-year-old children in response to the TSST-C, although it was less strong than in adults. Both studies are in contrast to previous studies (Stroud et al., 2009; Yim et al., 2010a), in which no sAA increase after exposure to the stressor was observed in 7- to 12-year-old participants and in the age range from 9 to 12 years, respectively.

With respect to memory, our findings revealed that delayed memory retrieval in children is impaired by stress. This effect appeared to be most pronounced for negative stimuli, even though the condition by valence interaction was not significant. In addition, participants who showed a larger cortisol response after the TSST-C committed more errors during memory card retrieval than those who showed a smaller one in response to the stressor. These results mirror findings in adults (Kuhlmann et al., 2005b; Buchanan and Tranel, 2008, Smeets et al., 2008; Merz et al., 2010), including the size of the effect (d = .65) (reviewed in Het et al., 2005). We suggest that a possible underlying neuronal mechanism to such impairment might lie in the effects of cortisol on the hippocampus. This interpretation is supported by several recent neuroimaging studies in adults (de Quervain et al., 2003; Oei et al., 2007; Weerda et al., 2010). Unlike the prefrontal cortex (PFC), this brain structure is completely developed by the age of 2 (Giedd et al., 1996). In addition, no age-associated changes have been reported for glucocorticoid receptors messenger RNA (GR mRNA) in the hippocampus (Perlman et al., 2007). Taken together, these data might explain why the detrimental consequences of stress in tasks relying on the hippocampus are similar in adults and children.

The consequences of stress on hippocampus-dependent memory retrieval need to be discussed with respect to the modulating role of the basolateral complex of the amygdala (BLA). Several studies offer evidence on the important influence of the amygdala on cortisol effects (reviewed in Roozendaal et al., 2009). Likewise, behavioral studies on this memory function in adults suggest that the HPA axis and the SNS interact in modulating memory (de Quervain et al., 2007; Smeets et al., 2008). In the current study, stress impaired memory retrieval at a time when cortisol levels were still elevated but sAA levels were back to baseline again. We

suggest that emotional arousal induced by retrieval testing might be sufficient to allow cortisol to be effective (see Kuhlmann and Wolf, 2006; Tollenaar et al., 2008).

As expected, no influence of stress was observed on immediate story recall. This is in line with results from pharmacological studies in adulthood (de Quervain et al., 2000; Elzinga et al., 2005). In contrast to our hypothesis and to several (but not all) studies in adults (Elzinga and Roelofs, 2005; Oei et al., 2006; Luethi et al., 2008; Schoofs et al., 2008), no impairments were found on WM. The power to detect a medium-sized effect comparable to the one observed for memory retrieval was only moderate (power = .65). However, the power was high enough to exclude large effects of .90. In addition, in our opinion, the consistency of the findings across two different WM tests argues against an explanation solely focused on lack of power.

The literature on stress and WM is rather heterogeneous, especially when it comes to simple span tasks. Schoofs et al. (2009) as well as Elzinga and Roelofs (2005) were successful in demonstrating the adverse effects of stress on digit span performance. However, others failed to find them (Kuhlmann et al., 2005b; Smeets et al., 2006). To our knowledge, there is no study investigating the impact of the TSST-C on WM in children yet, so that the current failure to detect effects of stress on WM in children is in need of a replication. Possible mediators such as task complexity, SNS arousal, stressor type and individual differences might explain the variance in studies on acute stress involving adults. For example, Oei et al. (2006) observed most pronounced effects of stress on WM in the Sternberg task at high loads. Why there are divergent findings when the same WM test is used, however, is not well understood. Some methodological differences might be worth noticing. Elzinga and Roelofs (2005) administrated the digit span within a stressful context, i.e., in front of an audience. In contrast, others applied it in a non-stressful context, i.e., in front of an examiner after the stress exposure was already over. Moreover, while Schoofs et al. (2009) induced stress with the cold pressor test (CPT), a short physiological stressor, Smeets et al. (2006) did this using a psychosocial stressor. Taken together, these results suggest that digit span is an adequate measure to use in order to detect the impact of stress on WM. Nevertheless, subtle methodological differences like the exact timing of the task might influence the consequences a stressor has on these tasks. The effects of stress on WM might not be as large as their impact on memory retrieval and might thus be less likely to detect with medium-sized samples. Future studies in children may want to compare effects of stress on different WM paradigms (digits *vs.* *n*-back *vs.* Sternberg).

Whether acute stress affects WM in children the same way it affects WM in adults is thus currently unknown. Findings from the field of developmental neuroscience would favor the interpretation of an age-dependent change in sensitivity to stress (Lupien et al., 2009). In contrast to the hippocampus, the PFC is not completely developed during childhood (reviewed in Casey et al., 2005). The GR mRNA expression levels per cortical layer in the dorsolateral prefrontal cortex (DLPFC) in children are lower than in adolescents and adults (Perlman et al., 2007). Such data suggests that the PFC of children might be less sensitive to the effects of acute stress. Consequently, there were no differences in WM between stressed and control groups in the present study. Taken together, the developmental evidence might explain our oppositional findings with two different functions: working memory (PFC) and memory retrieval (hippocampus). Following this line of reasoning, only prolonged (chronic) stress in childhood might induce WM and attention impairments. Clinical findings or those related to chronic stress have shown deficits in WM and attention (Elison et al., 2007), although the findings are also heterogeneous when it comes to WM (reviewed in Matheson et al., 2003). Supporting our interpretation, a study with young rodents observed spatial WM impairments only after a longer duration of corticosterone treatment, but not after shorter period (Coburn-Litvak et al., 2003).

Some limitations of our study need to be acknowledged. We used a visual-spatial memory task (memory card game) for the assessment of delayed memory retrieval. In contrast, a structured verbal task (story recall) was used for the assessment of immediate recall performance after stress exposure. We had chosen these two quite different tasks in order to reduce the amount of possible interference. It thus remains to be shown whether stress also impairs the delayed retrieval of verbal material (structured or unstructured) in children as it does in adults (Kuhlmann et al., 2005b; Merz et al., 2010).

In summary, our results demonstrate that the TSST-C is a potent laboratory stressor if used on children between the age of 8 and 10. Stressed children showed a pronounced cortisol increase, sAA elevations and a decrease in mood. The stress response was accompanied by detrimental effects on delayed memory retrieval, mirroring effects in adults. Moreover, the cortisol stress response was correlated with the amount of errors committed during retrieval. These findings are of relevance for educational settings, since they might be able to explain why some children underperform in the context of a stressful exam. The efficiency of different measures to minimize the detrimental consequences of stress on memory retrieval in children (e.g. stress management training, social support) should be investigated. In contrast, stress had no effects on verbal and visual WM. These divergent results of stress on delayed memory retrieval and WM (detrimental *vs.* missing effects) could, to some extent, reflect developmental differences of hippocampus and PFC. Additional studies on the cognitive impact of acute stress in children and explanations as to how developmental differences can influence them need to be carried out.

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Conflict of interest statement

The authors declare that they have no conflict of interest regarding this manuscript.

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