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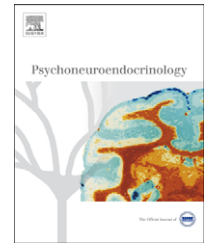
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# Diminished cortisol responses to psychosocial stress associated with lifetime adverse events

## A study among healthy young subjects

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### KEYWORDS

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Trauma;  
Psychosocial stress;  
Resilience;  
Stress inoculation

### Summary

**Background:** Animal and human studies have found that prior stressful events can result in an altered reactivity in the HPA axis. The aim of the present study was to investigate the role of adverse events in childhood on cortisol reactivity to psychosocial stress in young healthy subjects ( $n = 80$ ).

**Methods:** Salivary cortisol levels were measured before, during and after exposure to a psychosocial stress task in healthy men and women with high ( $n = 33$ ) and low ( $n = 47$ ) exposure to adverse childhood events.

**Results:** A significant blunted cortisol response was found in individuals with a history of adverse events compared to individuals with no adverse life events, with no differences in baseline cortisol levels. This finding appeared to be primarily driven by men. The groups did not differ on any other physiological or subjective stress measure, including heart rate, blood pressure, and subjective tension.

**Conclusions:** These findings suggest that, at least in healthy young males, adverse childhood events are associated with changes in HPA-axis functioning. Longitudinal studies are needed to investigate whether the blunted cortisol response is a risk factor in the etiology of psychiatric disorders or rather reflects resiliency with regard to the development of psychopathology.

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## 1. Introduction

Compelling evidence is accumulating that early trauma, including sexual, physical and emotional abuse, is associated with an increased risk to develop a variety of psychiatric disorders in adulthood, including posttraumatic stress disorder (PTSD), depression, dissociative disorders, alcohol and substance abuse, and borderline personality disorder (Beitchman et al., 1992; Bremner et al., 1993; Draijer and Langeland, 1999; Kendler et al., 1993; McCauley et al., 1997; Mullen et al., 1996; Stein et al., 1996). Given the fact that childhood abuse may affect as many as one in five individuals (McCauley et al., 1997), it is very important to understand the psychological and neurobiological processes underlying the increased stress vulnerability associated with childhood abuse.

In preclinical studies, there is a growing body of evidence demonstrating that early adverse events may have a lasting impact on the neurobiology of the stress response, particularly on the stress-regulating hypothalamic–pituitary–adrenal (HPA) axis (see Heim and Nemeroff, 2001; Kaufman et al., 2000; Sanchez, 2006, for reviews). The HPA axis is activated during prolonged stressful events resulting in a marked increase in the release of the stress-hormone cortisol (or corticosterone, depending on the system) from the adrenal. Cortisol release from the adrenal is regulated by the adrenocorticotropine releasing hormone (ACTH) from the pituitary, which in turn is primarily regulated by corticotropin releasing factor (CRF) from the paraventricular nucleus of the hypothalamus. The responses of the HPA axis are regulated by a complex negative feedback system, exerted by glucocorticoids.

Numerous studies in rodents and primates have shown that early life stressors, such as (prolonged) maternal separation, may result in chronic increases in plasma glucocorticoid levels and ACTH and a potentiation of glucocorticoid responsiveness to subsequent stressors in adulthood, which is primarily driven by an enhanced CRH drive (Anisman et al., 1998; Coplan et al., 1996; Ladd et al., 1996, 2000; Levine et al., 1993; Plotsky and Meaney, 1993; Plotsky et al., 2005; Sapolsky, 1997). Besides the enhanced neuroendocrine responses, prolonged early life stress in animals is also associated with enhanced anxiety, decreased social interaction, and impaired cognitive performance later in life (Kaufman et al., 2000).

Exposure to brief (intermittent) stress early in life, in contrast, has been associated with a diminished activation of the HPA axis to novel stressors later in life (Parker et al., 2004, 2006; Anisman et al., 1998; Denenberg, 1999), together with diminished anxiety and relative unimpaired cognitive functions. Neuroendocrine stress resistance in rodents is mediated, in part, by enhanced glucocorticoid-feedback sensitivity (Meaney, 2001), although evidence for this mechanism was not found in primates (Parker et al., 2006).

Taken together, these observations suggest that in animals exposure to early life stress may lead to an increase in HPA-axis reactivity to novel stressors after exposure to relatively severe or chronic stress, and to a decrease in cortisol reactivity after minor or brief stressors. The effects of stress exposure on HPA-axis functioning depend on many factors, however, including the nature, timing, frequency, duration,

and perceived intensity of the stressful events. Other factors that may moderate the outcomes of early adversity are social support (e.g., nurturing versus neglecting caregiver), gender, and genetic factors on individual variability in vulnerability (see Heim et al., 2004; Sanchez, 2006; Sanchez et al., 2001).

In humans, studies on the effects of early abuse on the reactivity of the HPA axis to stressors later in life are scarce, and have so far almost exclusively been conducted in patients with mood or anxiety disorders. Heim et al. (2000b) found that adult women with a history of childhood abuse and a current major depression (and comorbid PTSD) exhibited increased cortisol and ACTH responses to a psychosocial stress task compared to women with a current major depression and no abuse history, and to women without a psychiatric disorder either with or without an abuse history. Interestingly, peak cortisol responses were predicted by a history of childhood abuse, the number of separate abuse events, the number of daily hassles and the severity of the depression (Heim et al., 2002). Moreover, among male and female patients with PTSD related to a history of early abuse, Bremner et al. (2003) found elevated cortisol levels in anticipation and during a cognitive challenge task compared to healthy controls with no PTSD or early abuse, which appeared to be primarily driven by men. Neither a control group with a history of abuse without PTSD, nor a group with PTSD and late trauma were included in this study, however. Therefore it is not possible to disentangle the effects of PTSD symptomatology from the impact of the abuse itself on cortisol responsiveness to the cognitive challenge. Nevertheless, these studies are consistent with a model of HPA-axis sensitization after early trauma, so that subsequent exposure to stressful events may lead to increased stress responses.

Contrary findings have also been reported, however. A recent study that assessed cortisol reactivity to a physical stress task (i.e., a cold pressor task) among PTSD patients with either a history of early or late trauma found that patients with early trauma had lower cortisol levels both at baseline and throughout the testing period compared to PTSD patients with late trauma and to controls without PTSD or trauma history (Santa Anna et al., 2006). Lower basal cortisol levels have also been reported in rape victims with a history of childhood sexual abuse soon after the rape when compared to women without early abuse histories (Resnick et al., 1995). Moreover, the women with previous abuse were also more likely to have developed PTSD 3 months later (Yehuda et al., 1998).

Taken together, these studies suggest that among patients with a current psychiatric disorder, early sexual and/or physical trauma is related to changes in HPA-axis reactivity, of which some are suggestive of enhanced cortisol reactivity and blunted basal cortisol levels. These studies are very important in illustrating the chronic impact of adverse life events on stress reactivity in psychiatric patients. One major limitation in interpreting these findings is, however, that in most studies (except for the study of Heim et al., 2000b) the effects are confounded with current psychiatric symptoms. Hence, what remains unknown is whether changes in HPA-axis reactivity constitute a premorbid risk factor that was present before the development of the disorder, or rather are related to the current psychiatric status.

To the best of our knowledge, no studies have investigated cortisol reactivity among healthy male and female individuals with varying amounts of adverse life events who have *not* developed any psychiatric disorder (yet). The purpose of the present study was therefore to investigate cortisol reactivity to a psychosocial stress task (TSST) in a sample of healthy men and women who had experienced either very few or relatively many adverse life events.

## 2. Method

### 2.1. Participants

Eighty college students participated for financial or course credit (52 men and 28 women, age: mean  $\pm$  S.D.:  $21.6 \pm 3.61$  years) in three studies on the effects of stress exposure on cognitive functioning (Elzinga and Roelofs, 2005; Roelofs et al., 2007; Tollenaar et al., *in press*). Participants between 18 and 37 years old were recruited from the University of Leiden through announcements. Exclusion criteria were: any psychiatric disorder on AXIS-I, including substance abuse (DSM-IV) using the Mini-International Neuropsychiatric Interview (MINI; Sheenan et al., 1998), any clinical significant medical disease, and use of medication (oral contraceptives were allowed in the study of Roelofs et al., 2007). Participants were asked to minimize physical exercise during the hour preceding the experiment and not to take large meals, coffee, drinks with low pH or cigarettes, because these variables can have an influence on cortisol levels. All procedures were carried out with the adequate understanding and written signed informed consent of the participants. All three studies were approved by the local ethics committee.

### 2.2. Assessments

#### 2.2.1. Trier Social Stress Task (TSST; Kirschbaum et al., 1993)

This psychosocial stress test, which mainly consists of a free speech and mental arithmetic task of 15 min duration has repeatedly been found to induce significant endocrine and cardiovascular responses (Kirschbaum et al., 1993). In a review paper on acute laboratory stressors, the TSST was found to be the strongest elicitor of cortisol elevations (Dickerson and Kemeny, 2004). Participants received instructions in which they were told that they would be taking on the role of a job applicant. Participants were given 5 min to prepare a 5-min free speech to an audience of three psychologists. They were told that the speech would be videotaped, that the psychologists were trained to monitor non-verbal behavior, that a voice frequency analysis would be performed, and that the speech would be critiqued on content and presentation style. Following preparation time, the audience entered the room and prominently switched on the camera and microphone. Participants were instructed to stand in front of a table with the audience sitting at the other side and the chairmen asked the participant to describe his/her qualifications for the job. Participants were expected to utilize the entire 5 min for the speech as described by Kirschbaum et al. (1993). For the mental arithmetic task, participants were instructed to serially

subtract 13 from 1587. The audience responded to any mistakes by instructing participants to "Start from the top. Subtract 13 from 1587". In the study of Elzinga and Roelofs (2005) and Tollenaar et al. (*in press*), the mental arithmetic task was shortened to 3 min and was followed by a working memory task (to assess the effects of stress-induced cortisol elevations on working memory). Participants were tested at either 10.00 a.m. (study 1), 11.30 a.m. or 13.30 a.m. (study 2), or 14.15 a.m. (study 3).

#### 2.2.2. Stress measures

Salivary cortisol was measured to investigate the effects of exposure to early adverse events on the reactivity of the HPA axis. To assess the specificity of this association, other (physiological and psychological) stress measures were assessed as well, including heart rate, blood pressure and subjective tension. All physiological assessments and the subjective measure of distress were obtained at five assessment points over a 75-min period, at approximately -20, -1, +15, +40, +55 min with reference to the start of the stressor.

**2.2.2.1. Cortisol.** Saliva samples were obtained using Salivette collection devices (Sarstedt, Rommelsdorf, Germany). Saliva samples were stored at  $-20^{\circ}\text{C}$  before assaying. Biochemical analysis of free cortisol in saliva was performed using a competitive electrochemiluminescence immunoassay (ECLIA; Elecsys 2010, Roche Diagnostics), as described elsewhere (van Aken et al., 2003). The within-run precision of the cortisol assay in saliva was 2.7% at the level of 11.5 nmol/L and the between-run precision was 7.2% at the level of 7.72 nmol/L. Cortisol was LOG transformed to normalize distribution. The area under the curve increase (AUCi) was measured using the equation from Pruessner et al. (2003).

**2.2.2.2. Heart rate.** Heart rate was recorded continuously by an Ambulatory Monitoring System (AMS; Vrije Universiteit Amsterdam) version 3.6, a small battery powered device for ambulatory recording. It was measured via three Ag-AgCl disposable electrodes (ConMed), placed just above the sternum, at the left side of the chest, and at the bottom right side of the chest. For each subject, heart rate was averaged for 2 min starting from a marker given at each of the five assessment points.

**2.2.2.3. Blood pressure.** Systolic and diastolic blood pressure was measured from the non-dominant arm using a blood pressure monitor (Omron 705CP).

**2.2.2.4. Subjective tension.** Subjective tension was assessed on a visual analogue scale ranging from 0 to 100.

#### 2.2.3. Traumatic Experiences Checklist (TEC; Nijenhuis et al., 2002)

The TEC is a reliable and valid self-report inventory that assesses emotional abuse and neglect, physical abuse, sexual harassment, and sexual abuse, as well as general traumatic events, including loss of significant others, life threat by disease, parental divorce, and psychopathology of parents (i.e., alcohol or drug abuse). The TEC has primarily been validated in psychiatric outpatients (Nijenhuis et al., 2002), but has recently also been studied in a non-clinical sample ( $n = 73$ ; Näring and Nijenhuis, 2005), showing that the TEC is also sensitive enough to measure in the low range.

The TEC version that was used in the present study contains 26 items, with the total score ranging from 0 to 26. Besides the total score, there are scores for the presence of emotional abuse (emotional neglect and emotional abuse in various settings, six items), physical abuse (physical abuse in various settings, intentional threat to life, and intense pain, five items), and sexual abuse (sexual harassment and sexual abuse in various settings, six items). For each item it was assessed whether the event happened yes or no, at which age the event first took place, at which age the event ended, and the impact of the event on a scale from 1 (not at all) to 5 (very much). All items are preceded by the phrase: "Did this happen to you?" An example of sexual harassment is: "Sexual harassment (acts of a sexual nature that DO NOT involve physical contact) by your parents, brothers, or sisters?" A sexual abuse item is: "Sexual abuse (unwanted sexual acts involving physical contact) by your parents, brothers, or sisters?"

Cronbach's  $\alpha$  for the TEC total score is 0.86. Cronbach's  $\alpha$  for emotional abuse is 0.78, for sexual abuse 0.65, and for physical abuse 0.77. Test-retest reliability of the TEC total score is  $r = 0.91$ . The test-retest for the specific type's of abuse: emotional abuse,  $r = 0.80$ ; physical abuse,  $r = 0.86$ ; sexual abuse,  $r = 0.88$  (all  $p < 0.0001$ ). Concurrent validity as measured by the correlation between the TEC and the Stressful Life Events Screening Questionnaire total score (SLESQ; Goodman et al., 1998) is strong,  $r = 0.77$ ,  $p < 0.0001$ .

#### 2.2.4. Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983)

The scale consists of 14 items equally divided between anxiety and depression subscales. Each item is rated on a scale from 0 to 3 and the respondents rate the response which comes closest to how they have been feeling in the past week. A recent review of over 700 studies using the HADS found it to have good psychometric properties and to perform well in assessing anxiety and depressive disorders in health settings and in the general population (Bjelland et al., 2002). In a recent study, among students, internal consistency using Cronbach's  $\alpha$  for the HADS anxiety scale was 0.82 and for the depression scale 0.74. Correlations between the scales were between 0.52 and 0.63 (Andrews et al., 2006).

#### 2.2.5. Statistical analysis

To analyze the effects of the TSST on cortisol, blood pressure, heart rate, and tension, analyses of variance (ANOVA) for repeated measures were used with Time as within-subjects factor. To compare the two groups on these measures, ANOVA for repeated measures were used with Group (low versus high AE group) as between-subjects factor and Time as within-subjects factor. For the regression analysis, a stepwise regression was performed. Analyses were performed using SPSS 11.5. The criterion for statistical significance was  $p < 0.05$ , two-tailed.

### 3. Results

#### 3.1. High versus low adverse events (AE) groups

Individuals with a total score of 1 or 0 on the TEC were assigned to the low adverse events (AE) group ( $n = 47$ ),

whereas individuals reporting 2 or more adverse events were assigned to the high AE group ( $n = 33$ ; see Table 1 for participant characteristics). The two groups differed significantly on reported number of adverse events, but not on age, gender, or anxiety or depression scores as measured with the HADS (see Table 1). None of the participants in the low AE group reported a severe traumatic event, such as sexual abuse or severe physical abuse. In the low AE group, the majority (63.8%,  $n = 30$ ) reported no adverse event, and 36.2% ( $n = 17$ ) reported one event. Moreover, in the low AE group 4% ( $n = 2$ ) reported emotional abuse, 8.5% ( $n = 4$ ) reported (mild) physical abuse, and none of the participants reported sexual abuse. In the high AE group, the majority (72.7%,  $n = 24$ ) reported three or more adverse events, whereas 27.3% ( $n = 9$ ) reported two adverse events. Moreover, 53.4% ( $n = 14$ ) reported emotional abuse, 51.5% ( $n = 17$ ) reported physical abuse, and 21.3% ( $n = 7$ ) reported sexual abuse. In all individuals in the high AE group at least one of the adverse event(s) started before the age of 18. The mean age at which the adverse events first took place was: 7.7 ( $\pm 6.0$ ) years for emotional abuse; 13.3 ( $\pm 6.3$ ) years for physical abuse, and 14.0 ( $\pm 2$ ) years for sexual abuse. We made a distinction between abuse lasting less than a year (including single events) and abuse with a duration of more than a year. For emotional abuse, one individual reported that the abuse took place during  $< 1$  year, whereas the mean duration for the other participants ( $n = 13$ ) was 9.3 ( $\pm 7.0$ , range 2–25) years. For physical abuse, eight individuals reported that the event lasted  $< 1$  year, whereas the mean duration for the other participants ( $n = 9$ ) was 5.9 ( $\pm 4.1$ , range 1–13) years. For sexual abuse, one individual reported a duration of  $< 1$  year, whereas the mean duration for the other participants ( $n = 6$ ) was 4.5 years ( $\pm 5.1$ , range 1–12). The mean impact of the adverse events (on a scale from 1 to 5) was: 2.7 ( $\pm 0.7$ ) for emotional abuse, 2.7 ( $\pm 0.9$ ) for physical abuse, and 2.6 ( $\pm 0.8$ ) for sexual abuse.

**Table 1** Subject characteristics of the high ( $n = 33$ ) versus low ( $n = 47$ ) adverse events (AE) groups.

|                 | High AE<br>( $n = 33$ ),<br>mean $\pm$ S.D. | Low AE<br>( $n = 47$ ),<br>mean $\pm$ S.D. | $p$ -Value<br>two-tailed |
|-----------------|---------------------------------------------|--------------------------------------------|--------------------------|
| Mean age        | 21.79 $\pm$ 3.71                            | 21.47 $\pm$ 3.58                           | n.s.                     |
| Gender          | 23 M/10 F                                   | 29 M/18 F                                  | n.s.                     |
| TEC total       | 3.58 $\pm$ 1.62                             | 0.36 $\pm$ 0.49                            | 0.0001                   |
| Emotional abuse | 0.79 $\pm$ 1.02                             | 0.04 $\pm$ 0.20                            | 0.0001                   |
| Physical trauma | 0.64 $\pm$ 0.70                             | 0.08 $\pm$ 0.28                            | 0.0001                   |
| Sexual abuse    | 0.27 $\pm$ 0.57                             | 0.00 $\pm$ 0.00                            | 0.005                    |
| HADS total      | 7.15 $\pm$ 4.02                             | 6.60 $\pm$ 3.89                            | n.s.                     |
| HADS anxiety    | 4.87 $\pm$ 2.62                             | 4.51 $\pm$ 2.31                            | n.s.                     |
| HADS depression | 2.34 $\pm$ 2.25                             | 2.13 $\pm$ 2.11                            | n.s.                     |

TEC, Traumatic Experiences Checklist; HADS, Hospital Anxiety and Depression Scale.



### 3.2. Stress induction

One cortisol sample was missing for three participants (two from the low and one from the high AE group, resulting in  $n = 45$  for the low AE, and  $n = 32$  for the high AE group). ANOVA rm with Time as within subjects factor for mean (log transformed) cortisol levels showed significant increases over time ( $F(4,312) = 24.13$ ,  $p < 0.0001$ ). Post-hoc  $t$ -tests showed that there was an overall significant increase between cortisol levels right before the TSST at  $-1$  min ( $7.69 \pm 3.72$  nmol/L) and cortisol levels right after the TSST at  $+15$  min ( $10.17 \pm 7.81$  nmol/L), ( $t(79) = 8.95$ ,  $p < 0.0001$ ),  $+40$  min ( $12.23 \pm 6.67$  nmol/L,  $t(81) = 7.95$ ,  $p < 0.0001$ ) and  $+55$  min ( $10.46 \pm 6.50$  nmol/L,  $t(81) = 4.63$ ,  $p < 0.0001$ ).

When Gender was entered as covariate in the repeated measures, a main effect of Gender ( $F(1,77) = 60.08$ ;  $p < 0.0001$ ) and a significant interaction between Time and Gender ( $F(4,308) = 3.04$ ;  $p < 0.01$ ) was found. Consistent with previous findings (Kirschbaum et al., 1999) men had higher cortisol levels and showed a larger cortisol response (cortisol levels at  $-1$  min ( $8.90 \pm 3.76$  nmol/L) versus  $+15$  min after the TSST ( $15.06 \pm 6.16$  nmol/L) ( $t(53) = 7.80$ ;  $p < 0.0001$ )) than women (cortisol levels at  $-1$  min ( $5.36 \pm 2.26$  nmol/L) and  $+15$  min after the TSST ( $6.76 \pm 3.41$  nmol/L) ( $t(27) = 2.45$ ;  $p < 0.05$ )). When added as an additional covariate, neither significant effects were found for either the factor Sample (i.e., the three separate studies) ( $F(4,304) = 0.44$ ; n.s.), nor for Time of day ( $F(8,296) = 0.49$ ; n.s.). Based on these outcomes Gender was entered as a covariate in the between group analyses on cortisol reactivity, and Sample and Time of day were not.

Separate ANOVA rm for heart rate, systolic and diastolic blood pressure and subjective tension also showed significant increases on all stress measures over time: heart rate ( $F(4,308) = 88.17$ ,  $p < 0.0001$ ), systolic blood pressure ( $F(4,324) = 99.56$ ,  $p < 0.0001$ ), diastolic blood pressure ( $F(4,324) = 77.91$ ,  $p < 0.0001$ ), and tension ( $F(4,324) = 65.95$ ,  $p < 0.0001$ ). Post-hoc  $t$ -tests indicated that compared to baseline all measures were elevated at  $+15$  and  $+40$  min (all  $p < 0.0001$ ). Subsequently, Sample and Gender were entered as covariates for all measures. Gender was a significant covariate for tension ( $F(4,320) = 3.60$ ,  $p < 0.01$ ) and systolic blood pressure ( $F(4,320) = 5.13$ ,  $p < 0.001$ ), related to the fact that women had more sustained elevated tension and systolic blood pressure at  $+40$  min compared to men. Sample was a significant covariate for heart rate ( $F(8,300) = 13.93$ ;  $p < 0.0001$ ) and diastolic blood pressure ( $F(8,316) = 5.11$ ;  $p < 0.0001$ ), which was related to the fact that the increase in heart rate and systolic blood pressure were smaller in the third sample (Roelofs et al., 2007). Again, to control for these effects all significant variables were entered as covariates in the designated between Group rm analyses.

### 3.3. Stress reactivity in high versus low adverse events groups

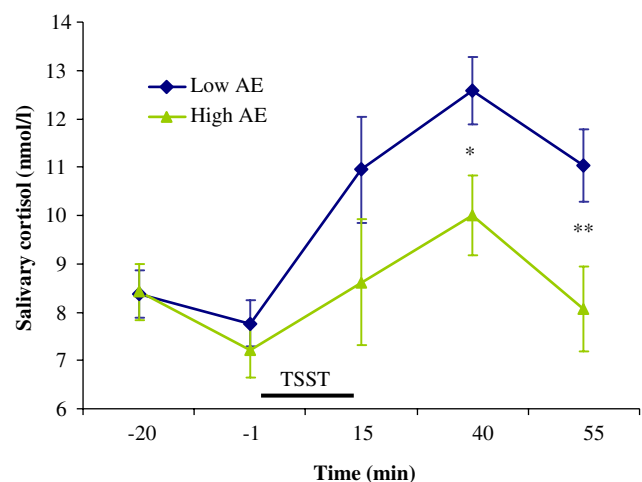
Using ANOVA rm with Group (high versus low AE group) as between subjects factor and Gender as covariate and (log transformed) cortisol as dependent variable, a significant Group  $\times$  Time interaction was found ( $F(4,296) = 3.36$ ,

$p < 0.01$ ). Post-hoc analyses (Bonferroni corrected) showed that the low AE group had higher cortisol levels after the TSST compared to the high AE group, at  $+40$  min ( $F(1,77) = 6.55$ ,  $p < 0.05$ ), and  $+55$  min ( $F(1,77) = 7.46$ ,  $p < 0.01$ ), but not at baseline ( $-20$  min, ( $F(1,76) = 0.00$ , n.s.);  $-1$  min ( $F(1,77) = 0.18$ , n.s.)), or immediately after the TSST at  $+15$  min ( $F(1,75) = 2.74$ , n.s.) (see Figure 1). Due to the higher levels at  $+40$  and  $+55$  min, a trend for a main effect of group was found ( $F(1,74) = 3.48$ ,  $p = 0.07$ ). The main effect of Gender and a Time  $\times$  Gender did not interact with Group ( $F(4,292) = 0.27$ , n.s.). If the rm ANOVAs were conducted separately for men and women, the effects were stronger for men ( $F(4,188) = 2.80$ ,  $p < 0.08$ ), and where not significant in women ( $F(4,104) = 1.48$ , n.s.) (see Figure 2a and b).

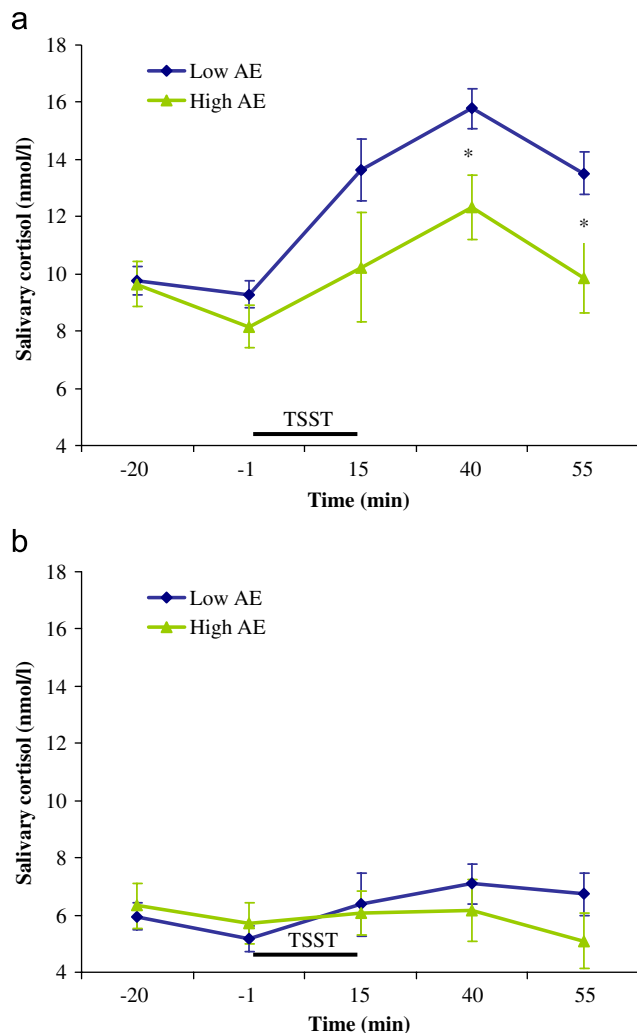
Univariate analysis of variance with (log transformed) cortisol AUCi as dependent factor and Group as between subjects factor and Gender as covariate confirmed the group interaction, showing a significantly smaller cortisol AUCi for the high AE compared to the low AE group ( $F(1,78) = 6.42$ ,  $p < 0.05$ ).

With regard to the other stress indices, the two groups did not differ with respect to heart rate (Group  $\times$  Time ( $F(4,296) = 1.00$ , n.s.), main effect of Group ( $F(1,74) = 0.16$ , n.s.)), systolic blood pressure (Group  $\times$  Time ( $F(4,308) = 0.37$ , n.s.), main effect of Group ( $F(1,77) = 0.25$ , n.s.)), diastolic blood pressure (Group  $\times$  Time ( $F(4,308) = 0.55$ , n.s.), main effect of Group ( $F(1,77) = 0.01$ , n.s.)), or subjective distress (Group  $\times$  Time ( $F(4,308) = 0.13$ , n.s.), main effect of Group ( $F(1,77) = 0.00$ , n.s.)) see Figure 3a-d.

Because of the arbitrary nature of a median split, the same between-group analyses were conducted with extreme groups, i.e., participants that reported no adverse event ( $n = 30$ ) versus those that reported three or more adverse events ( $n = 24$ ). In this Group  $\times$  Time analyses with Gender as covariate, again a significant interaction emerged, showing a smaller cortisol increase in participants with a history of adverse events compared to those who did not



**Figure 1** Mean ( $\pm$ S.E.M.) free salivary cortisol (in nmol/L) in response to psychosocial stress induction (TSST) in the low ( $n = 47$ ) versus high adverse events (AE) groups ( $n = 33$ ). Note: \* $p < 0.05$ ; \*\* $p > 0.001$ .



**Figure 2** Mean ( $\pm$ S.E.M.) free salivary cortisol (in nmol/L) in response to psychosocial stress induction (TSST) for men in the low ( $n = 27$ ) versus high adverse events (AE) groups ( $n = 22$ ) (Figure 2a) and for women in the low ( $n = 18$ ) versus high adverse events (AE) groups ( $n = 10$ ) (Figure 2b). Note: \* $p < 0.05$ .

report any adverse events ( $F(4,192) = 3.61$ ,  $p < 0.01$ ). Univariate analysis of variance with (log transformed) cortisol AUCi as dependent factor and extreme groups as between subjects factor and Gender as covariate confirmed the group interaction, showing a smaller cortisol AUCi for the group reporting more than three adverse events versus the group with no history of adverse events ( $F(1,52) = 3.68$ ,  $p < 0.06$ ), although this was only trend significant.

### 3.4. Regression analysis

Finally, to analyze the role of depression or anxiety symptoms on the cortisol response, and to investigate whether the number of separate adverse events is predictive of the cortisol increase after the TSST, a stepwise regression analysis was computed with (log transformed) cortisol AUCi as dependent variable and Gender entered as a

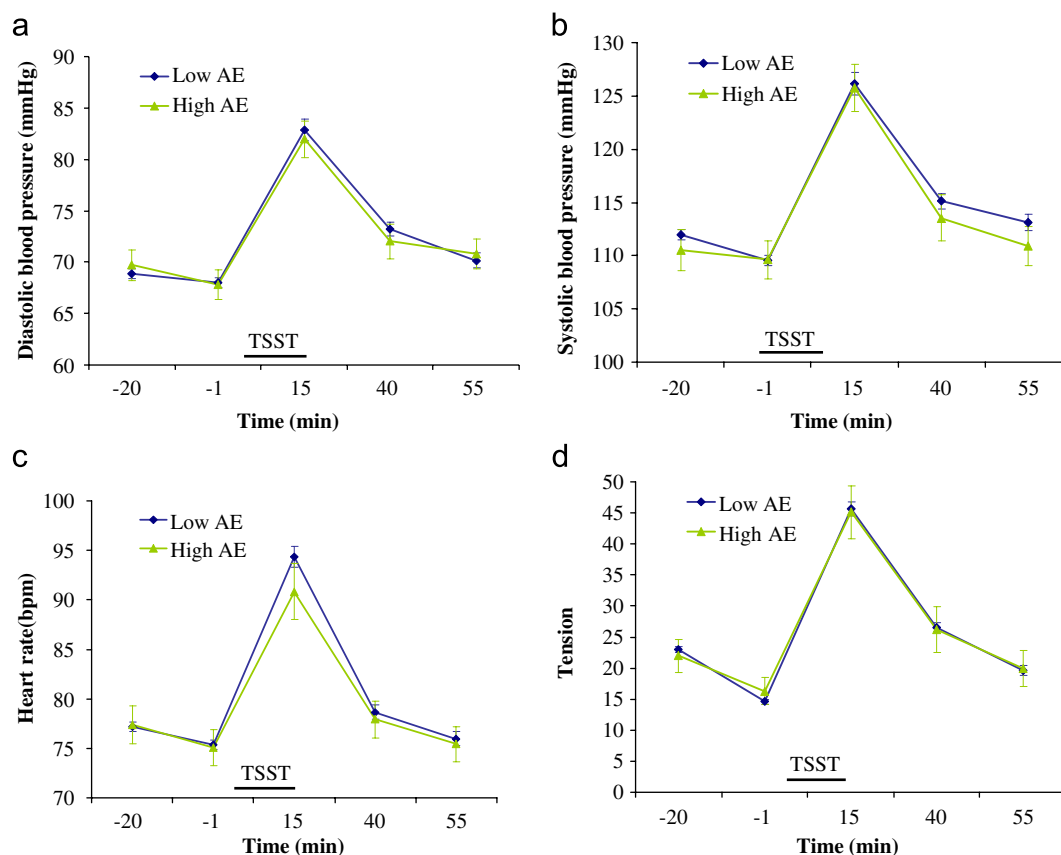
first step, HADS Anxiety and Depression as a second step, and TEC total score as a third step. Consistent with the ANOVA analyses, gender was a significant predictor ( $F(1,76) = 4.73$ ,  $p < 0.05$ ). Depression (but not anxiety scores) scores explained some additional variance in the cortisol AUCi ( $F(3,76) = 3.26$ ,  $p < 0.05$ ). In line with the significant differences between the high and low AE group, the number of adverse events as measured with the TEC total score was a significant predictor of cortisol AUCi, even after controlling for gender and anxiety and depression scores ( $F(4,76) = 3.79$ ,  $p < .01$ ; see Table 2).

## 4. Discussion

In the present study, we found that non-clinical individuals that have been exposed to a relatively high number of adverse events had a significantly lower cortisol reactivity to a psychosocial stress task compared to individuals who had experienced none or one adverse event, while the two groups did not differ at baseline cortisol levels. In line with the findings of the group analysis, a regression analysis showed a significant linear (negative) association between the number of adverse events and cortisol levels as measured by the AUCi. Interestingly, the two groups did not differ with regard to blood pressure, heart rate, and subjective distress either at baseline or in response to the psychosocial stress task, suggesting a specific effect of GC reactivity in the absence of any changes in sympathetic arousal or subjective distress. To our knowledge, this is the first study among young healthy individuals showing that adverse life events are related to altered HPA-axis functioning in individuals who have no current psychiatric disorder.

Second, analyses conducted separately in men and women revealed that the blunted cortisol reactivity associated with a history of adverse events was primarily driven by men, whereas the differences in females were not significant. This is consistent with the finding of Heim et al. (2000b) in which the control group consisting of healthy women with or without a history of abuse did not show any difference in cortisol reactivity to the TSST. It is also in line with a study among PTSD patients showing altered HPA reactivity only in male PTSD patients, but not in females (Bremner et al., 2003). Based on our study, it cannot be concluded that there are no effects of exposure to adverse life events on the functioning of the HPA axis in women, however, as women as a group did not show a clear cortisol response to the TSST. This is probably due to the use of contraceptives and the influence of the menstrual cycle on the HPA axis (see e.g., Kirschbaum et al., 1999; Kudielka and Kirschbaum, 2005; Kajantie and Phillips, 2006). Future studies that include women who are not taking oral contraceptives and who are carefully selected with regard to the menstrual cycle are needed to investigate the role of adverse life events on HPA-axis functioning in women.

One interesting observation is that the present findings differ from those in patients with a psychiatric disorder. In women with a history of early trauma and a depressive disorder, trauma history was associated with enhanced cortisol and ACTH responses to a psychosocial stress task compared to depressed patients without early life time trauma (Heim et al., 2000b). Moreover, PTSD patients with



**Figure 3** (a–d) Mean ( $\pm$ S.E.M.) systolic and diastolic blood pressure, heart rate, and subjective distress in response to psychosocial stress induction (TSST) in the low ( $n = 47$ ) versus high adverse event groups ( $n = 33$ ).

early childhood abuse showed enhanced cortisol levels during the anticipation phase of a cognitive challenge (Bremner et al., 2003) and also during exposure to traumatic scripts (Elzinga et al., 2003). Apparently, current psychiatric status is an important factor when determining the role of adverse events on HPA functioning after stress. Hence, it is important that this is taken into account in future studies (see also Tarullo and Gunnar, 2006).

In terms of explanatory models, reduced cortisol reactivity could be related to either enhanced feedback associated with a downregulation of CRF receptors and increased negative glucocorticoid feedback, or to a reduced release of cortisol by the adrenal glands. Taken these considerations into account, three main hypotheses can be put forward for the blunted cortisol reactivity in the high AE group.

First of all, differences in GC reactivity could be related to an enhanced stress resistance in the high AE group. Of note is that the high AE group consists of a highly selective sample of healthy individuals who are highly educated (i.e., all university students) and who, despite having experienced a number of adverse events, have low depression and anxiety rates and did not develop a psychiatric disorder. Possibly, the blunted cortisol response constitutes a very sensitive and specific marker for resiliency to stress, as it was the only stress-related variable that differentiated between the two groups.

The blunted cortisol response as a marker of enhanced resiliency may have been present a priori, before the

**Table 2** Linear stepwise regression analyses on cortisol AUCi (log transformed) in response to psychosocial stress induction as a function of gender, anxiety and depression as measured with the HADS, and adverse life events as measured with the TEC ( $n = 80$ ).

| Variable        | $\beta$ | $R$  | $\Delta R^2$ |
|-----------------|---------|------|--------------|
| Step 1          |         | 0.24 | 0.06*        |
| Gender          | 0.24*   |      |              |
| Step 2          |         | 0.34 | 0.06         |
| HADS anxiety    | 0.02    |      |              |
| HADS depression | −0.25*  |      |              |
| Step 3          |         | 0.42 | 0.06*        |
| TEC             | −0.24*  |      |              |

TEC, Traumatic Experiences Checklist; HADS, Hospital Anxiety and Depression Scale.

\* $p < 0.05$ .

adverse events took place. Recent genetic studies suggest that approximately 60% of the variance in glucocorticoid levels may be attributable to genetic individual differences (Bartels et al., 2003). Moreover, specific candidate genes related to increased (e.g., Bcl1 and N3635; Wust et al.,



2004) and diminished (Uhart et al., 2004) cortisol responses to the TSST have been identified.

The blunted response may also (in part) be a consequence of the stress exposure. The so-called 'stress inoculation' hypothesis assumes that exposure to mildly stressful events early in life may make an individual more resilient to adverse events later in life. There is some evidence in rodents and non-human primates for decreased pituitary–adrenal responses and diminished anxiety to future stressors after mildly stressful events early in life, such as brief handling involving removal of rat pups from their dams for 15 min per day (Zaharia et al., 1996; Anisman et al., 1998). The development of rodent stress resistance is thought to be mediated, at least in part, by the increase in maternal care by the mother, rather than the handling procedure (Caldji et al., 1998; Francis et al., 1999; Liu et al., 1997; Plotsky and Meaney, 1993). In a study of Parker et al. (2006) in primates, however, evidence for stress inoculation was also found in the absence of increased maternal care.

Also in humans, there is some evidence that exposure to mildly aversive life events may make a person more resilient to novel stressors, although studies have not been related to HPA-axis functioning. For example, in a study among women who had been raped, it was found that those women who had experienced minor life stressors in the past were least traumatized in response to the rape compared to women with no previous life stressors. Women with major life changes were most traumatized, on the other hand (see Ruch et al., 1980). Another study, among healthy subjects from a 'risky family background' (harsh parenting style), found decreased amygdala activation when viewing angry or fearful faces compared to subjects from non-risky backgrounds (Taylor et al., 2006). Taken together, these studies are consistent with the hypothesis that exposure to moderately adverse life events may be associated with diminished stress reactivity. In most (animal and human) studies described above the stressors were rather mild, however, and hence it is unclear whether stress inoculation can occur after the type of adverse events that have been reported by the high AE group. In sum, the finding of blunted cortisol reactivity in a group of healthy, well-performing individuals may be a sensitive marker of resiliency. Longitudinal studies are clearly needed to further unravel the interplay between genetic influences and the role (and specific characteristics) of adverse life events on cortisol reactivity to stressful situations later in life.

A second hypothesis that cannot be dismissed is that, rather than a marker of resiliency, the blunted cortisol response is related to an *increased* vulnerability to stress, constituting a risk factor in the development of a psychopathological disorder. The interpretation of the blunted cortisol reactivity as a marker of increased vulnerability to stress is in line with studies in humans showing that chronic, sustained stress early in life may be associated with basal *hypocortisolism*, which could be a result of chronic glucocorticoid hypersecretion, associated with a downregulation of CRF receptors and increased negative glucocorticoid feedback (Heim et al., 2000a). Basal *hypocortisolism* has been observed in healthy individuals living under ongoing stress (Heim et al., 2000a), in women with a history of early abuse who have recently been raped (Resnick et al., 1995), and after early life stress in patients with PTSD (Stein et al.,

1997; Santa Anna et al., 2006). A major limitation is, however, that all the studies mentioned above report on basal cortisol levels, whereas in our study we specifically found differences in cortisol *reactivity*, while baseline cortisol levels did not differ between the two groups.

Consistent with the hypothesis that lower cortisol levels could also constitute a risk factor in the etiology of psychiatric disorders, there are some indications that low cortisol levels after exposure to a traumatic event constitute a risk factor for the development of PTSD symptoms later on. This is in line with findings that if not enough GR receptors are occupied, the body is not optimally prepared to cope effectively with stressors (Sapolsky et al., 2000). For example, Delahanty et al. (2000) reported that patients who met acute PTSD diagnostic criteria 1 month following an motor vehicle accident excreted lower levels of urinary cortisol in the immediate aftermath of the trauma than did those who did not develop PTSD, and cortisol levels mediated the relationship between trauma history and acute PTSD symptoms (Delahanty et al., 2005). Very interesting in this regard is a recent study in rats showing that genetically manipulated blunted cortisol levels enhanced the prevalence of both baseline and stress-induced increases in anxiety-like behaviors (Cohen et al., 2006). Taken together, these studies suggest that basal low cortisol levels associated with chronic early life trauma may be a marker of enhanced susceptibility to develop mood or anxiety disorders later on in life. However, it should be noted that this *contrasts* with the findings that brief exposure to stress early in life has been not only associated with decreased cortisol reactivity but also relatively decreased anxiety-like behavior and enhanced learning. This discrepancy further underlines the need for longitudinal studies investigating whether individuals with lower cortisol reactivity are more prone to develop psychopathological disorders than the low AE group, or vice versa.

A third possible explanation for the findings that participants with previous trauma showed a blunted cortisol response is that individuals from the high AE group may have been less involved and more detached during the TSST as a result of an avoidant coping strategy related to previous adverse events. There is evidence in early psychoendocrine research that low cortisol levels observed in sustained stress have a psychogenic component (see Mason et al., 2001). For example, disengaging coping strategies have been related to decreased cortisol levels in a sample of PTSD patients (see Mason et al., 2001). However, if the high AE group would have been less engaged and more detached from the psychosocial stress task, one would expect a blunted stress reactivity on all stress measures, particularly on the subjective scales, which was not the case.

Taken together, this study may be considered as a first step to investigate the effects of exposure to adverse events on HPA-axis functioning in healthy individuals. In this study, the TSST was used as a validated measure to assess cortisol reactivity in response to a general psychological stressor (see Dickerson and Kemeny, 2004). Given the present findings, there are many other aspects of the HPA axis that merit investigation in future research. In order to get a more complete understanding of the effects of a history of adverse events on the regulation of the HPA axis, it will be also important to assess the initial components of the stress

response, by measuring ACTH. Moreover, pharmacological studies challenging the HPA axis (e.g., using the Dex/CRH test) or by blocking glucocorticoids (e.g., using metyrapone) are needed to investigate in more detail at which level of the HPA axis alterations may occur, i.e., at the level of the hypothalamus, pituitary, and/or adrenal gland. It would also be interesting to investigate whether the current findings extrapolate to physical stress (e.g., by measuring physical exercise or cold pressure stress). Other factors that might be taken into account in future studies are the effects of social support and current levels of stress as mediating factors (see also Tarullo and Gunnar, 2006). Moreover, future studies may consider the use of clinical interviews as a more reliable tool to assess (early) adverse life events, although some individuals may be less inhibited to report traumatic experiences on self-report measures than in the context of a face-to-face trauma interview.

In conclusion, in a relatively large sample, we have found the intriguing result that the HPA axis is blunted in healthy individuals, primarily males, that have been exposed to prior stressful events, which was significantly related to the number of adverse life events. As noted, longitudinal prospective studies are needed to investigate whether the blunted cortisol response reflects resiliency with regard to the development of psychopathology or rather is a risk factor in the etiology of psychiatric disorders.

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## Conflict of interest

There is no conflict of interest.

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