



Increased cortisol concentrations in hair of severely traumatized Ugandan individuals with PTSD

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Abstract: The influence of post-traumatic stress disorder (PTSD) on cortisol levels is not yet clear. We examined long-term cortisol levels in severely traumatized survivors of the Northern Uganda civil war - 10 individuals with and 17 without PTSD - by assessing hair cortisol. PTSD patients exhibited higher long-term cortisol concentrations than non-PTSD participants, and the cortisol level was positively correlated with the number of traumatic event types experienced. Our results indicate a chronic stress reaction in PTSD patients, especially under conditions of recurring trauma.

Introduction

Posttraumatic stress disorder (PTSD) constitutes a psychiatric condition which develops after exposure to one or more traumatic event(s) associated with the experience of extreme fear/horror and helplessness (American Psychiatric Association, 2000). The incidence of PTSD increases with the number of different traumatic event types experienced (i.e. with traumatic load) in a dose—response manner — a finding often referred to as building block effect (e.g. Neuner et al., 2004; Kolassa et al., 2010). Previous research on PTSD has frequently studied physiological changes associated with the disorder, with a particular focus on altered activity of the hypothalamic—pituitary—adrenal (HPA) axis. The HPA axis is crucially involved in mediating the physiological response to stress and the secretion of the stress hormone cortisol (McEwen, 1998). It has been proposed that alterations in HPA axis activity might result from exposure to traumatic stressors and perhaps influence the pathophysiology of PTSD (Yehuda et al., 1991).

Previous research on cortisol secretion in PTSD however has produced inconsistent results. The majority of findings suggest a general hypocortisolism in PTSD; e.g. cortisol levels in 24 h urine (e.g. Yehuda et al., 1990, 1995), saliva (e.g. Rohleder et al., 2004; Yehuda et al., 2005) and blood (e.g. Yehuda et al., 1996; Olf et al., 2006) have been found to be attenuated in PTSD patients in comparison to healthy controls. In contrast, a number of studies have also provided evidence for increased cortisol levels in 24 h urine (e.g. Lemieux and Coe, 1995; Maes et al., 1998) and cerebrospinal fluid (Baker et al., 2005) in PTSD patients compared to non-traumatized controls. Similar results of elevated salivary (e.g. Inslicht et al., 2006) as well as 24 h-urinary (e.g. Friedman et al., 2007) cortisol levels in PTSD patients have also been reported when PTSD patients were compared with traumatized controls. Finally, some studies have failed to observe significant differences between salivary cortisol levels of PTSD patients and traumatized controls (Young et al., 2004) as well as between urinary cortisol levels of PTSD patients and healthy controls (Young and Breslau, 2004).

A number of explanations for this heterogeneity of results are conceivable: given the high complexity of PTSD, potential explanations include between-study differences in patient characteristics such as gender, disease comorbidity, medication or drug intake as well as severity, type and frequency of traumatic events (e.g. Rasmusson et al., 2003; Meewisse et al., 2007). In addition to

these, it is however also likely that methodological factors associated with the assessment of cortisol might have contributed to the inconsistency of results (Meewisse et al., 2007). The HPA axis constitutes a highly dynamic system which is influenced by a range of situational factors (e.g. food intake, circadian rhythmicity, psychological stress) and which shows considerable intra- individual variability (e.g. Hellhammer et al., 2007; Stalder et al., 2010a). This means that various characteristics relating to the measurement situation, e.g. participant adherence to the sampling protocol or psychosocial state at the time of cortisol sampling, might present an additional confounding influence on results.

Recently, Eckart et al. (2009) aimed to control for some of these confounding influences by examining the diurnal salivary cortisol profile of severely traumatized survivors of the Rwandan genocide under maximally standardized conditions over three consecutive days. Participants spent the whole study period together, performed the same activities, ate standardized meals and had synchronized light-dark cycles. Interestingly, under these highly controlled conditions no significant differences in salivary cortisol levels between PTSD patients and traumatized controls emerged. Similarly, the building block effect was not reflected in the cortisol data; i.e. there was no significant association between the number of different lifetime traumatic event types and diurnal salivary cortisol levels. A potential explanation for these findings can be seen in evidence suggesting that changes in daily routines and psychological states can acutely affect HPA axis activity (e.g. Stalder et al., 2009). Thus, whilst daily routines were highly controlled in this study, the secure conditions provided by the study context might have meant that participants were examined under conditions of reduced stress that differed markedly from their normal living circumstances. This again might have reduced PTSD-related endocrine changes that are present under more naturalistic conditions.

The challenge of obtaining a methodologically and ecologically valid assessment of cortisol secretion is closely related to the strategy used for measuring cortisol. Previous research examining cortisol levels in PTSD has used blood, salivary or urinary measurements. Whilst particularly the latter two methods allow sampling under naturalistic conditions, they only provide a reflection of cortisol secretion over relatively short time periods, ranging from minutes (in blood or saliva) to hours (in urine). Consequently, situational factors (such as food intake, circadian rhythmicity, psychological stress) can easily superimpose the “real” impact of PTSD on cortisol secretion. In this context, an important new development is the assessment of cortisol levels in human hair which is assumed to provide a retrospective measure of cumulative cortisol secretion over prolonged periods of time (see Gow et al., 2010, for a review). Hair cortisol analysis provides a measure of cortisol secretion under naturalistic circumstances over a longer time span (i.e. months) — depending on the hair length investigated. Another advantage is that it is not influenced by situa-

tional confounding or short-term fluctuations of the HPA axis. Over the past years, the validity of this method has been corroborated in a number of human studies showing characteristically increased hair cortisol levels during the third trimester of pregnancy (Kirschbaum et al., 2009) as well as in patients with Cushing's syndrome (Thomson et al., 2010) and alcohol dependence (Stalder et al., 2010b). Furthermore, several studies have now provided support for the potential of hair cortisol levels to serve as a biological marker of chronic stress (e.g. Kalra et al., 2007; Van Uum et al., 2008; Dettenborn et al., 2010).

The aim of the present study was to utilize hair cortisol analysis to obtain an index of cumulative cortisol secretion in PTSD patients and traumatized controls under naturalistic living circumstances. Similar to Eckart et al. (2009), a severely traumatized population of individuals, this time from Northern Uganda, was examined. Given the political instability and civil war-like circumstances in this area, participants had been exposed to a wide range of traumata including war atrocities, sexual violence and forced displacement. In addition, we set out to investigate whether the previously reported building block effect is reflected in an association between the number of experienced traumatic events and hair cortisol levels.

Methods

Participants

Ten PTSD patients and 22 traumatized controls participated in this study. All PTSD patients and 11 of the traumatized controls were recruited within the context of a larger epidemiological study carried out in "internally displaced people camps" (IDP camps) in the year 2008 in Northern Uganda. From the sample of this initial study, the current participants were recruited based on the severity of posttraumatic stress symptoms using the posttraumatic diagnostic scale (PDS; Foa et al., 1997): traumatized controls were selected based on a score of 0. PTSD patients were chosen based on a score larger than 11 indicating a moderate symptom severity (McCarthy, 2008). Subsequently, PTSD diagnoses were confirmed by a semi-structured interview (Clinician-Administered PTSD Scale; CAPS; Blake et al., 1995) conducted in the native language Luo by trained personnel from the vivo outpatient clinic in Gulu, Northern Uganda. Of these participants, 60% of PTSD patients and 22.2% of traumatized controls experienced traumatic events within the last year. The remaining 11 traumatized controls were recruited in 2009 through personal contacts of the local team of the NGO vivo (www.vivo.org) and comprised individuals who were considered to be in a stable psychological state. Due to practical reasons, PDS scores were not available from these participants.

Descriptive information for the two participant groups is provided in Table 1. All participants had experienced traumatic events in conjunction with the civil

war in Northern Uganda. Of the PTSD group, all patients had been abducted by the Ugandan religious and military group called Lord's Resistance Army (LRA), whilst this was not the case for any of the traumatized controls. At the time of the study, four participants of the control group and one PTSD patient reported suffering from malaria and having used anti-malaria medication. Additionally, one control participant reported the use of anti-malaria prophylaxis whilst another participant reported the use of antibiotics.

All participants provided written informed consent prior to taking part in the study. The ethics committee of the University of Konstanz, Germany, as well as the Ugandan National Council for Science and Technology approved the study procedure. The study was conducted in accordance with the Declaration of Helsinki.

Clinical and psychological measures

Sociodemographic information (age, sex, body mass index, smoking status and alcohol consumption), hair-specific characteristics (washes per week, hair length and coloration) and participants' health status (medication intake and illnesses/ diseases) were obtained using a self-developed questionnaire. The four-item version of the perceived stress scale (PSS-4; Cohen et al., 1983) was used to measure perceived stress over the previous month. The number of different lifetime traumatic events was assessed via a checklist based on the clinical experience of the vivo outpatient clinic which offers Narrative Exposure Therapy to traumatized individuals. The instrument lists 34 unweighted traumatic event types of which 28 are general events (e.g. sexual assault, natural disaster, etc). Due to the specific violent atrocities known to be committed by the LRA, six LRA-specific traumatic events (e.g. threatened to be killed by the LRA, forced to eat human flesh, etc) were further added. A sum score of events experienced or witnessed was built.

Within the context of the epidemiological study in 2008 (see above) some additional clinical instruments were administered. Participant depressiveness and suicide ideation were assessed via the depression scale of the Hopkins Symptom Checklist-25 (HSCL; Derogatis et al., 1974) and the corresponding section of the Mini-International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998), respectively. The validity of the used instruments and the translation procedure are described in detail in Ertl et al. (2010).

Hair cortisol analysis

Hair strands were taken as close to the scalp as possible from a posterior vertex position. Due to the short hair length of most participants, only the scalp-near hair segment (≤ 3 cm) was used for the analysis of cortisol content. Based on an average African hair growth rate of 0.79 cm per month (Loussouarn, 2001), each hair sample was assumed to represent

cumulative cortisol exposure over the period of the previous 15 weeks or less, depending on the length of hair.

The wash procedure and steroid extraction were based on the protocol of Davenport et al. (2006) and has previously been described in detail in Kirschbaum et al. (2009). In brief, 25 mg of powdered hair was used for the analyses of the current study. For the determination of cortisol a commercially available immunoassay with chemiluminescence detection (CLIA, IBL-Hamburg, Germany) was used.

Sufficient hair material to allow for samples to be processed in duplicate was available from 21 participants whilst hair material of the remaining participants only permitted single analyses. For duplicate samples, mean cortisol levels were calculated and used in statistical analyses.

Statistical analyses and data exclusion

Data from four control participants were excluded from hair cortisol analyses due to an insufficient amount of hair (<25 mg), whilst data from another control participant was excluded due to a high outlying cortisol value (larger than two standard deviations above the mean) which was likely to have resulted from high alcohol consumption. This resulted in a total sample of 10 PTSD patients and 17 traumatized controls remaining for analyses. Cortisol data were positively skewed and log transformations most effectively reduced the skewness statistic and were thus applied. For descriptive purposes, mean data in figures are reported in original units (pg/mg).

Group comparisons regarding demographic, hair-related and clinical/psychological characteristics were conducted using *t*-tests for continuous variables and Fisher's exact tests for dichotomous variables. A one-way ANOVA was carried out to compare cortisol levels between PTSD patients and traumatized controls. Additionally, a two-way ANOVA was carried out to examine gender issues. Participants' HSCL scores (only in participants for whom this data was available; see above) and PSS scores were included as covariates but were excluded if no significant influence was found. In addition, associations between hair cortisol levels and the number of lifetime traumatic event types were examined using a Pearson correlation analysis. Participants' HSCL scores (only in participants for whom this data was available; see above) and PSS scores were included as covariates in a regression analysis but were excluded if no significant influence was found.

Results

Table 1 provides results of group comparisons between PTSD patients and traumatized controls regarding sociodemographic, hair-related and clinical characteristics. The table illustrates that the two groups were well-matched

on the examined demographic and hair-related variables. PTSD patients reported having experienced a larger number of different traumatic event types as well as suffering from more acute physical complaints at the time of study. Similarly, as expected, PTSD patients scored significantly higher on measures of depressive symptoms (HSCL) and suicide ideation (M.I.N.I.) than the subgroup of traumatized controls for whom this data was available.

Table 1 Comparison of demographic, hair-related and clinical characteristics of PTSD patients and traumatized controls.

	PTSD patients (n = 10)	Control group (n = 17)	Test statistic	p
Demographics				
Age, year (M, SD)	19.2 (3.2)	20.1 (5.7)	$t_{(24,98)} = 0.5$.62
Male (%)	4 (40)	11 (64.7)	Fisher's exact	.26
Body mass index (M, SD)	22.42 (1.90)	21.44 (2.25) ^a	$t_{(24)} = -1.140$.27
Smoking (%)	0 (0)	4 (23.5)	Fisher's exact	.26
Daily alcohol consumption (%)	0 (0) ^b	3 (17.6)	Fisher's exact	.53
Physical diseases – malaria (%)	1 (10)	4 (23.5)	Fisher's exact	.62
Regular medication (%)	1 (10)	6 (35.3)	Fisher's exact	.20
Acute complaints (%)	9 (90)	1 (5.9)	Fisher's exact	≤.001
Hair-related variables				
Washes per week (M, SD)	6.00 (2.11)	7.78 (4.17) ^a	$t_{(24)} = 1.249$.22
Hair length in cm (M, SD)	2.00 (2.08) ^b	1.38 (1.51) ^c	$t_{(21)} = -0.836$.41
Coloration (%)	2 (20)	1 (5.9)	Fisher's exact	.54
Trauma-related and psychological characteristics				
Abducted by the LRA (%)	10 (100)	0 (0)	Fisher's exact	≤.001
Number of abduction (M, SD)	1.40 (0.70)	n/a		
First age of abduction (M, SD)	10 (4.19)	n/a		
Traumatic events within the last year (%)	6 (60)	2 (22.2) ^b	Fisher's exact	.17
Number of traumatic events (M, SD) ^a	22.90 (3.78)	10.24 (4.59)	$t_{(25)} = -7.36$	≤.001
Age of worst trauma (M, SD)	12.50 (5.23)	16.38 (6.41) ^d	$t_{(20)} = 1.53$.14
PSS score (M, SD)	9.20 (2.62)	7.76 (2.36)	$t_{(25)} = -1.47$.16
HSCL depression score (M, SD)	24.50 (8.76)	4.67 (6.58) ^b	$t_{(17)} = -5.53$	≤.001
M.I.N.I. current suicide risk level (%)	8 (80)	2 (22.2) ^b	Fisher's exact	.02

LRA, Lord's Resistance Army; PSS, perceived stress scale; HSCL, Hopkins Symptom Checklist 25; M.I.N.I., Mini-International Neuropsychiatric Interview.

^a Value refers to n = 16.
^b Value refers to n = 9.
^c Value refers to n = 14.
^d Value refers to n = 12.

Fig. 1 illustrates hair cortisol concentrations of PTSD patients and traumatized controls. The univariate ANOVA revealed that PTSD patients showed significantly higher hair cortisol concentrations than traumatized controls ($F_{(1,25)} = 5.35; \rho = .03; \eta_p^2 = .18$). The covariates revealed no significant influence (p 's > .53) and were thus excluded in the ANOVA. In an additional two-way ANOVA (diagnosis [2] x gender [2]) neither a significant main effect of gender ($F_{(1,23)} = 1.01; \rho = .33; \eta_p^2 = .04$) nor a significant diagnosis x gender interaction ($F_{(1,23)} = 0.37; \rho = .55; \eta_p^2 = .02$) was found.

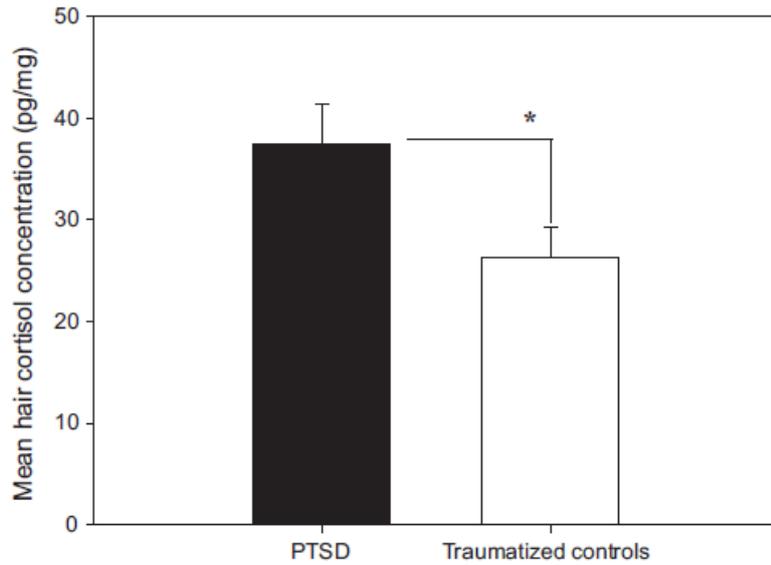


Figure 1

Mean (\pm SEM) hair cortisol concentrations of PTSD patients and traumatized controls $*p \leq .05$. The correlation analysis carried out on data from the complete sample revealed a significant association between the number of traumatic event types experienced and hair cortisol concentrations (see Fig. 2, $r = .41$, $p < .05$, $N = 27$). The covariates revealed no significant influence (p 's $> .31$) and were thus excluded in the regression analysis.

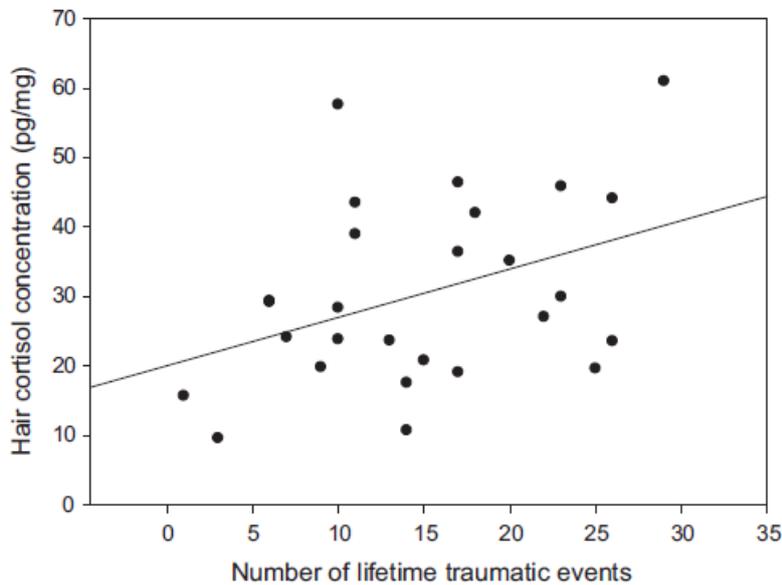


Figure 2 Association between hair cortisol concentrations and the number of lifetime traumatic events ($r = .41$, $p \leq .05$).

Discussion

The current study is the first to investigate cumulative hair cortisol levels in severely traumatized individuals. Results reveal significantly increased hair cortisol levels in individuals with PTSD compared to traumatized controls as well as a positive association between the cumulative exposure to traumatic

stressors and hair cortisol concentrations. If confirmed by future research, the current data suggest that PTSD in severely traumatized individuals who had experienced the last traumatic stressor relatively recently and are still living under unsafe conditions might be associated with general hypercortisolism. The central finding of the current study is that increased hair cortisol concentrations were found in PTSD patients compared to controls who also had been exposed to traumatic stressors, albeit to a lesser extent. Whilst this is in line with previous evidence of elevated basal cortisol levels in PTSD patients compared to healthy controls (e.g. Lemieux and Coe, 1995; Maes et al., 1998; Baker et al., 2005) or traumatized controls (e.g. Inslicht et al., 2006; Friedman et al., 2007), it is at variance with a number of previous studies suggesting decreased (e.g. Yehuda et al., 1990, 1995, 1996, 2005; Rohleder et al., 2004; Olf et al., 2006) or unaltered (e.g. Young and Breslau, 2004; Young et al., 2004; Eckart et al., 2009) cortisol levels in PTSD patients. Despite the fact that a novel method of cortisol assessment was used in the current study in the form of hair analysis, the disparity of the present results with much of the previous literature is surprising and difficult to explain solely on methodological grounds. Hair cortisol levels reflect cumulative cortisol secretion over prolonged periods of time and are thus assumed to be less influenced by situational confounding. Nevertheless, the direction of hair cortisol results should still be in line with the overall tendency of results from previous research based on measures of short-term cortisol secretion, unless confounding had occurred in a systematic manner across studies, which we consider quite improbable. It is thus likely that additional factors, unrelated to the method of cortisol assessment, provide a better explanation of the current results.

A more probable interpretation of the current findings relates to characteristics of the present study sample. Here, particularly the short time interval since the last traumatic stressor and the currently still unsafe living conditions in this sample might be a factor which could have contributed to the current results. Previous research has often investigated cortisol levels in individuals who had suffered from PTSD for many decades (e.g. combat veterans). In contrast, the majority of participants of the present study had experienced the last traumatic stressor relatively recently which might be associated with an initial increase in cortisol levels. The notion that time since trauma plays an important role with regard to cortisol levels is also supported by results of Weems and Carrion (2007) who examined associations between cortisol levels and PTSD symptoms amongst youth with distal and recent traumata. The authors found significant differences in correlation sizes between distal and recent trauma groups, revealing a positive correlation for recent trauma groups and a negative one for distal trauma groups. Furthermore, it is also important to note that many studies suggesting increased cortisol levels in PTSD have studied patient groups with a short time interval since traumatization. For example, Inslicht et al. (2006) found increased salivary cortisol levels in female

PTSD patients (victims of intimate partner violence) of whom a high proportion was still involved with the abuser at the time of endocrine assessment. Similarly, Friedman et al. (2007) reported elevated urinary cortisol levels in women with PTSD due to childhood sexual abuse who had subsequently also experienced adult sexual abuse.

A further explanation of the current results which partly overlaps with the effect of a short time since traumatization relates to the young age of the current study sample. Whilst only a few studies to date have found increased cortisol levels in children or adolescents suffering from PTSD (e.g. De Bellis et al., 1999), it is conceivable that the younger age of participants might be an explanation for the observed hypercortisolism. Pervanidou (2008) has suggested that extreme life stress in early development leads to an elevation in circulating cortisol levels which might decrease over time, leading to hypocortisolism. Since the current population has experienced a continuous period of traumatic life circumstances, i.e. chronic traumatization, it is possible that in the current sample cortisol levels were still elevated and might not have started to decrease yet. Since the two examined study groups did not differ with regard to levels of perceived stress, it is further unlikely that higher cortisol levels in PTSD patients are associated with increased levels of general current life stress but are indeed related to traumatic stress. Future research examining participants repeatedly following traumatic events is needed to determine the specific influence of the time interval since traumatization.

A particular strength of the current research lies in the wide variation and severity of traumatic experiences in the examined population. Since a positive association between the number of lifetime traumatic events and hair cortisol levels was detected in the current data, we assume that the previously reported dose—response relationship between the number of traumatic events and PTSD diagnosis (“building block effect”) is also reflected in our hair cortisol data. Consequently, it is conceivable that the enhanced traumatic load of the PTSD patients might further be important in explaining the finding of increased cortisol levels in this group compared to the less traumatized controls. Based on the current data we are however unable to draw firm conclusions about whether increased cortisol levels in PTSD patients are primarily related to the PTSD symptomatology or cumulative traumatic load. Future studies should thus ideally aim to investigate groups which are characterized by comparable levels of traumatic load in order to examine the specific impact of PTSD diagnosis on cortisol levels.

With regard to the characteristics of experienced traumata, the current sample is similar to the one of Eckart et al. (2009). Whilst these authors did not find significant group differences in diurnal salivary cortisol profiles, respective values were descriptively higher in the PTSD group. It is conceivable that since the current hair cortisol results might not have intermixed chronically persisting HPA axis tendencies with acute reactions to the measurement

situation, the increased power of the current design allowed us to confirm this descriptive result in the present data. If corroborated by future research, this highlights the distinct information that may be derived from different methods of cortisol assessment and suggests that the hair cortisol analysis provides a promising addition to measures of cortisol secretion over shorter time periods.

Some limitations of the current study should be considered. The present results are based on a relatively small number of PTSD participants and thus future research corroborating these findings in a larger sample is warranted. Similarly, due to the political instability and the high extent of traumatic events in Northern Uganda, we were unable to recruit an adequate non-traumatized control group. Thus, the present results do not allow making any inferences about whether hair cortisol values of the two traumatized groups were changed in comparison to healthy non-traumatized controls. This third group should be added — if possible — in future research. Furthermore, the control group was recruited at two different time points, which might have influenced the current results. However, cortisol levels did not differ significantly between the traumatized control groups (results not shown). It is important to note that PTSD patients and controls significantly differed on the following variables: all of the PTSD patients but none of the controls were conducted by the LRA and PTSD patients had significantly higher depression scores. Thus, it cannot be ruled out that differences in cortisol levels between PTSD patients and controls are confounded with one or more of these factors. A further limitation relates to the fact that due to practical reasons, the measurement of participant depressiveness and suicidal ideation was only feasible in the first study episode which considerably reduced statistical power for respective analyses. In addition, since no complete diagnostic interview was administered, it cannot be ruled out that participants might have presented with additional psychiatric comorbidities which in turn might be related to neuroendocrine alterations. Furthermore, hair samples of some participants were of a very short length which might have been associated with a shorter reflected time period of cortisol secretion. However, it is unlikely that this has significantly influenced the current results given that no association between hair length and cortisol levels was found (results not shown). Finally, it must be emphasised, that the current hair cortisol results do not provide specific information about the nature of underlying HPA axis dysregulation. Future research should thus combine hair cortisol analysis with other established measures of HPA axis activity to further enhance the understanding of neuroendocrinological changes in a severely traumatized PTSD sample.

In conclusion, the results of the current study suggest that PTSD characterized by chronic and relatively recent traumatization might be associated with elevated cortisol levels under naturalistic circumstances. Our data yet again illustrate the high complexity of cortisol regulation in PTSD which amongst other things may be particularly influenced by the time interval since

traumatization. Further research closely examining the relationship between PTSD characteristics and alterations in hair cortisol levels is needed.

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Conflicts of interest

The authors have no conflicts of interest to declare.

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