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Early neglect is a key determinant of adult hair cortisol concentration and is associated with increased vulnerability to trauma in a transdiagnostic sample

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ABSTRACT

Background: Childhood adversities and traumatic events have each been associated with hypothalamus-pituitary-adrenal (HPA) axis dysregulation and trauma-related symptoms in adulthood. Hair cortisol concentration (HCC) reflects cumulative cortisol levels over the course of months and is discussed as a potential marker between trauma-induced neuroendocrine dysfunction and trauma-related symptoms. The present study examines this hypothetical link by delineating the impact of exposure to categories of abuse and neglect during development and lifetime traumatic experiences on HCC and trauma-related symptoms.

Methods: The Maltreatment and Abuse Chronology Exposure (MACE) scale, Life Events Checklist, and predictive analytics were used to evaluate the importance of type and timing of maltreatment and trauma load on HCC in inpatients (n = 183) with different psychiatric diagnoses. Additionally, a comparison group of n = 75 controls were recruited from the community. The extent to which the relationship between trauma load and trauma-related symptoms was influenced by childhood adversities and HCC was determined by analysis of variance.

Results: Early neglect, in particular neglect at 3 years, emerged as the most important predictor of adult HCC. Post-hoc explanatory analysis showed that patients with high neglect at age 3 had lower HCC compared to patients with low neglect at age 3 and controls. Patients with high neglect at age 3 and low cortisol reported increased trauma-related symptoms upon trauma exposure.

Conclusion: Results strengthen evidence that inadequate care and neglect during critical periods alter HPA axis biology towards enduring reduction in cortisol, the latter being associated with augmented trauma-related symptoms upon trauma exposure. If validated by longitudinal assessments these cross-sectional findings suggest biological mechanisms of childhood adversities into psychopathology in adulthood.

1. Introduction

Neuroplasticity of the developing organism creates windows of sensitivity during which adverse experiences may affect brain and neuroendocrine development, including hypothalamic-pituitary-adrenal (HPA) axis regulation with potential consequences for psychological disorders (Kuhlman et al., 2017; Lupien et al., 2009; Strüber et al., 2014; Teicher et al., 2016). Adversities include stressful experiences stemming from caregivers and peers such as being emotionally or physically injured (abuse), being left unattended (neglect), and traumatic experiences such as sexual assaults or accidents. Childhood maltreatment and exposure to traumatic events have been associated with altered HPA axis regulation in children, adolescents, and adults with and without mental illness (e.g., Miller et al., 2007), and altered HPA-axis regulation has been related to trauma-related symptoms (e.g., Meewisse et al., 2007). Exposure to adversities is considered a major condition for enduring alterations of the HPA axis biology and increased sensitivity for trauma-related symptoms (Steudte-Schmiedgen et al., 2016; Yehuda et al., 2010). It is still unclear whether the sheer amount or types of adversity experienced during sensitive developmental periods have long-lasting impact on HPA-axis biology (accentuation or suppression), which in turn leads to potential harmful consequences for mental health.

The HPA-axis is crucial for stress regulation as it adapts to short-term as well as long-term challenges and is essential for maintaining homeostasis. Research has often focused on the hormone cortisol in

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various tissues. Whereas saliva, plasma, and urine cortisol measure short-term activity, thereby capturing dynamic aspects of cortisol, hair cortisol concentration (HCC) provides information on long-term regulation over months (e.g., Stalder et al., 2017) and marks effects of past exposure to adversities (meta-analysis: Khoury et al., 2019; review: Steudte-Schmiedgen et al., 2016). However, results on HCC accentuation or suppression upon childhood adversities/ traumatic experiences in adults with and without mental illness are inconsistent (Hinkelmann et al., 2013; Schalinski et al., 2015). In children, reduced HCC emerged in children at age 10–16 upon accumulated early adverse experiences (White et al., 2017). The results of a recent meta-analysis suggested an impact of specific aspects of past adversity and traumatic experiences (e.g., total number or specific types and timing of adversities on HCC; Khoury et al., 2019).

The importance of type of adversity (neglect and abuse) and timing (developmental stage) has been attributed to sensitive periods for brain and neuroendocrine development (e.g., McLaughlin et al., 2014; Kuhlman et al., 2017). Importantly, brain structures affected by adverse experiences such as hippocampus, amygdala, and frontal lobe (review: Teicher et al., 2016) are involved in HPA axis regulation (e.g., Dedovic et al., 2009; Pagliaccio et al., 2014). Evidence from rodents indicates that maternal separation early in the (sensitive) postnatal period has a lasting effect on the glucocorticoid system and behavioral phenotypes e.g., anxious behavior (e.g., Arabadzisz et al., 2010; Curley and Champagne, 2016; Meaney, 2010). Accumulating human evidence suggests potential sensitive periods for HPA axis regulation during both early childhood and adolescence. McLaughlin and colleagues (2015) found a reduced cortisol stress response in children who lived in depriving institutional settings in Romania compared to children from high-quality foster homes. Flannery and colleagues (2017) reported flattened diurnal cortisol slopes in institutionalized children, whereas the time spend with their adoption families during the puberty contributed to steeper diurnal slopes.

Regarding type of experience, both abuse and neglect were related to altered HPA axis regulation in children and adolescents (e.g., abuse: Trickett et al., 2010; e.g., neglect: Flannery et al., 2017; McLaughlin et al., 2015), but also in adulthood (Pesonen et al., 2010; van der Vegt et al., 2009; see Trickett et al., 2010 for longitudinal data). While previous results indicate long-lasting effects of past stressful experiences on the human HPA axis regulation, most results were either based on cumulative adversity load (e.g., Schalinski et al., 2015), or constraint to a specific type (e.g., sexual abuse: Trickett et al., 2010 or neglect: Flannery 2015), or a specific ages of exposure (e.g., neglect in early childhood: McLaughlin et al., 2015). This leaves the element of exposure elusive that crucially and durably relate to HPA-axis regulation.

The percentage of adults with trauma-related psychopathology (e.g., posttraumatic stress disorder, PTSD) increases with a greater exposure to childhood adversities (e.g., Weber et al., 2008). Thus, adverse childhood experiences may sensitize individuals for later stressful and traumatic experiences with consequent trauma-related symptoms (Matz et al., 2010). Distinct neuroendocrine regulation may serve as a predisposing risk factor of this sensitization through childhood experiences (Kuhlman et al., 2017; Yehuda et al., 2010). In addition (or alternatively), increasing exposure to traumatic event types across the lifespan may vary with HCC attenuation, thus indicating an 'endocrine building block', which might then foster trauma-related psychopathology (Steudte-Schmiedgen et al., 2016).

The present study aimed to scrutinize the role of type and timing of adverse experiences and traumatic experiences across the lifespan on HPA axis regulation (indexed by HCC). The study involved patients with different psychiatric diagnoses, following the National Institute of Mental Health (NIMH)-initiated dimensional perspective on psychopathology and symptom manifestations that cut across diagnoses (e.g., Kozak and Cuthbert, 2016). The first research question evaluated more precisely whether abuse or neglect and their timings during childhood (assessed with the Maltreatment of Abuse Chronology of Exposure Scale [MACE]; Teicher and Parigger, 2015) or traumatic experiences across the lifespan (assessed with the Life Event Checklist; Gray et al., 2004) were important predictors for adult HCC. As available evidence is not consistent with respect to the direction of changes in HCC in relation to past adversities (Khoury et al., 2019), present analyses were not guided by specific, directional hypotheses. Because of the high number of potential predictors and the high collinearity of the predictors (in particular at exposure levels of adjacent years), data were analyzed with condition random forest regression (Breiman, 2001). This analysis estimates the importance of a large set of predictors simultaneously, but does not specify the direction of the relationship. Thus, the direction will be determined in post-hoc explanatory analysis. The second research question related the past exposure to the most important predictor and level of HCC to current trauma-related symptoms using analysis of variance.

2. Methods

2.1. Study sample and settings

A total of $n = 183$ patients (44.8% females, mean age of $M = 25.9$, $SD = 6.7$) with different diagnoses (based on the ICD-10; International Classification of Diseases, 10th revision, World Health Organization, 1992) admitted for inpatient treatment at the local Center for Psychiatry were recruited for the present study. Of those, $n = 111$ (60.7%) met ICD-criteria of at least one comorbid diagnosis. The frequency of primary diagnosis of the present sample was $n = 81$ psychotic disorder, $n = 56$ affective disorder, $n = 43$ personality disorder, and $n = 3$ anxiety disorder other than PTSD. Primary and comorbid diagnoses were mental and behavioral disorders due to psychoactive substance use ($n = 49$, 26.8%), with psychotic spectrum disorders ($n = 81$, 44.3%) with affective disorders ($n = 83$, 43%), neurotic, stress-related and somatoform disorder ($n = 59$, 32.2%), behavioral syndromes associated with physiological disturbances and physical factors ($n = 23$, 12.6%), and disorders of personality and behavior ($n = 53$, 29%). Patients were compared to a control sample ($n = 75$, 45.3% females, mean age of $M = 25.4$, $SD = 6.7$) without past and present mental illness (verified with the Mini International Neuropsychiatric Interview, Ackenheil et al., 1999). Control participants were recruited from the community by advertisement in local internet portals, flyers, and mailing lists of the local Center of Psychiatry. Controls were initially screened over the phone or through email correspondence for age, gender, and level of education. Groups did not differ in age, gender distribution, nor years of school education (Table 1). Pregnant women, participants with insufficient hair length (< 3 cm), any serious physical illness (e.g., cancer) within the last year, and inflammatory conditions (e.g., asthma, bronchitis) that required the use of glucocorticoid-containing medications were excluded. Data from $n = 32$ men with insufficient hair length, $n = 1$ participant with a serious physical illness, and $n = 1$ pregnant woman were excluded.

Data of the exposure to adverse childhood experiences as well as psychopathology overlaps with the following studies: Adverse childhood experiences in relation to psychopathology have been reported for a subsample of $n = 79$ patients of the present sample in Schalinski et al. (2016). Furthermore, the impact of childhood adversities on psychotic symptoms was reported for $n = 62$ patients and $n = 61$ controls of the present sample in Schalinski et al. (2018). For a subset of $n = 24$ psychotic patients of the present sample, HCC data were reported in Hirt et al. (2019).

The Institutional Review Board of the University of Konstanz approved the study. All participants provided written informed consent and for patients, the psychologist/psychiatrists in charge verified that patients were in a sufficiently improved state to participant in the current study.

2.2. Instruments and assessment and analysis of HCC

Childhood adversities, traumatic experiences, symptoms of PTSD, and hair samples were collected in interviews with a trained psychologist lasting from 45 min up to 120 min.

Table 1
Demographic data, hair related variables and clinical data for the patient group and the control group without mental illness.

	Patients	Controls	
Demographic data	(n = 183)	(n = 75)	Group Comparison
Gender (females) n (%)	82 (44.8%)	41 (45.3%)	$\chi^2_{(df\ =1)} = 0.01$, p = .939
Age in years M (SD)	25.9 (6.7)	25.4 (6.7)	t(256) = 0.90, p = .552
Years of education M (SD)	11.5 (1.7)	11.6 (1.3)	t(168.97)[d] = -0.29, p = .774
Body mass index M (SD)	24.9 (5.3)	23.4 (3.6)	t(201.75)[d] = 2.22, p = .010
Regular smoking n (%)	116 (63.4%)	23 (30.7%)	$\chi^2_{(df\ =1)} = 23.39$, p < .001
Number of cigarettes per day (only smokers) M (SD)	15.5 (9.5)	8.1 (5.9)	t(137) = 3.57, p < .001
Antidepressants n (%)	71 (38.8%)	0 (0%)	$\chi^2_{(df\ =1)} = 40.15$, p < .001
Atypical neuroleptics n (%)	98 (53.6%)	0 (0%)	$\chi^2_{(df\ =1)} = 64.76$, p < .001
Use of oral contraception n (%)	16 (8.7%)	17 (22.7%)	$\chi^2_{(df\ =1)} = 9.23$, p = .002
Hair-related variables and HCC			
Hair washes per week M (SD)	4.8 (2.3)	5.3 (1.9)	t(256) = -1.62, p = .106
Curls or waves (1 = yes, 0 = no)	72 (39.3%)	25 (33.3%)	$\chi^2_{(df\ =1)} = 0.82$, p = .365
Hair dye (1 = yes, 0 = no)	54 (29.5%)	16 (21.3%)	$\chi^2_{(df\ =1)} = 1.57$, p = .210
Outliers in hair cortisol concentrations n (%)	7 (3.8%)	3 (4%)	$\chi^2_{(df\ =1)} < 0.01$, p = .947
HCC[e] M (SD)	6.95 (5.15)	8.22 (5.77)	$F(1, 245) = 3.50$, p = .062
Indices of adversities			
LEC: trauma load M (SD)	4.7 (2.7)	3.1 (2.2)	t(162.69)[d] = 4.91, p < .001
MACE: duration[a] M (SD)	8.3 (6.5)	2.8 (4.0)	t(216.11)[d] = 8.17, p < .001
MACE: multiplicity[b] M (SD)	3.3 (2.4)	1.2 (1.7)	t(191.38)[d] = 7.79, p < .001
MACE: overall severity[c] M (SD)	33.8 (16.8)	17.6 (12.3)	t(187.82)[d] = 8.59, p < .001

Note. LEC = Life Event Checklist; MACE = Maltreatment and Abuse Chronology of Exposure.
[a] years with a multiplicity score ≥ 1 (ranging from 0 to 18).
[b] number of different forms (ranging from 0 to 10).
[c] severity of childhood adversities (ranging from 0 to 100).
[d] due to unequal variance the Welch test was applied.
[e] HCC (hair cortisol concentration) is reported in original units (pg/mg) and corrected for gender.

2.2.1. Childhood adversities and traumatic experiences

The detailed profiles of exposure to childhood adversities up to age 18 were assessed using the German version of the MACE scale (Isele et al., 2014; Teicher and Parigger, 2015). The scale consists of 75 items and participants indicated whether they experienced each item during their childhood and if so, they checked off each year of occurrence. The scale was developed using item response theory and provides Rasch scales measures of severity of exposure for 8 types of abuse (physical, verbal, non-verbal emotional abuse, witnessing interparental abuse and abuse of siblings, peer-related verbal abuse and physical bullying, and intra-, extra-familial or peer-related sexual abuse), and 2 types of neglect (emotional and physical neglect). The various Rasch scales were based on 4 to 10 items and scaled to range from 0 to 10. The sum score of all subscale severities defines the overall severity (ranging from 0 to 100). The number of subscales with scores exceeding the cut-off severity defined the multiplicity score (ranging from 0 to 10; Isele et al., 2014). Scores were evaluated for each age (timing), for each type (abuse or neglect), and for cumulative measures (severity and multiplicity). A duration index measured the years of multiplicity score ≥ 1 (ranging from 0 to 18). For these analyses, we used the composite scores for abuse and neglect at each age rather than 10 specific maltreatment types in order to minimize the number of predictor variables and because this represents the most fundamental dichotomy between types of experiences (e.g., McLaughlin et al., 2014). MACE scales have demonstrated high convergent validity and acceptable to good reliability (Isele et al., 2014; Teicher and Parigger, 2015). The multiplicity score of the MACE correlated with scores of other scales e.g., Childhood Trauma Questionnaire (CTQ; Bernstein et al., 1994). In the German MACE, the correlation with the CTQ score was $r = .75$ (or $r = .83$ when only similar subscales were considered). Reports of abuse had acceptable to good scores regarding test-retest-reliability from age of 3 on (ranging from $r = .65$ to $r = .88$), and reports for neglect demonstrated acceptable to good reliability for all ages (ranging from $r = .63$ to $r = .88$; Teicher et al., 2018).

Traumatic experiences were measured with 'Life Events Checklist' (Gray et al., 2004), which assesses exposure to 17 different types of traumatic experiences that fulfill the Criterion A for PTSD: involving a serious injury, a life threat or sexual assault to the individual, or the witnessing of it. The overall trauma load was calculated as the sum of different traumatic event types (potentially ranging between 0–17).

2.2.2. Trauma-related symptoms

Trauma-related symptoms and comorbid diagnosis of PTSD were assessed with the PTSD Symptom Scale-Interview (Foa and Tolin, 2000). The interview has demonstrated good to excellent psychometric properties and is comparable to more complex instruments quantifying the severity and diagnosis of PTSD. Responses to all items were given on a scale ranging from 0 (not at all), 1 (once a week or less), 2 (2–4 times a week), to 3 (5 or more times a week). The trauma-related symptom severity was determined by (1) totaling the scores of the 17 items and (2) dividing the total symptom severity by the number of traumatic event types. The resulting score of 'symptoms per traumatic event' best accounts for the dose-dependent relationship between the number of traumatic experiences and trauma-related symptoms (e.g., Neuner et al., 2004). No score was determined for those nine patients, who did not report any traumatic experience in life.

2.2.3. HCC

Hair segments of 3 cm were cut near the scalp from a posterior vertex position, and stored in aluminum foil. Hair samples were analyzed in the laboratory of the Chair of Biopsychology at the Technische Universität Dresden, Germany. The protocol of Davenport et al. (2006) was employed for washing and steroid extraction. Before assaying the external part of the hair was removed. In brief, each hair segment was put into a 10 ml glass container, then 2.5 ml isopropanol was added, and the tube gently mixed on an overhead rotator for three minutes. After decanting, the wash cycle was repeated two times. Then the hair samples were allowed to dry for at least 12 h. Next, the hair segments were weighed out and transferred into a 2 ml cryo vial. Pure methanol (1.5 ml) was added and the steroid extraction was performed for 18 h. Samples were then spun in a microcentrifuge at 10.000 rpm for 2 min, and 1 ml of the clear supernatant was transferred into a new 2 ml glass

vial. The alcohol was evaporated at 50 degrees Celsius under a constant stream of nitrogen until the samples were completely dried. Finally, 0.4 ml of water was added and the tube vortexed for 15 s. Fifty microliters were removed from the vial and used for cortisol determination with a commercially available immunoassay with chemiluminescence detection (CLIA, IBL-Hamburg, Germany). The intraassay and interassay coefficient of variance of this assay is below 8% (C. Kirschbaum, personal communication, August 11, 2018). Analyses were performed in two batches (first batch: $n = 161$; second batch: $n = 97$).

2.3. Statistical analysis

Analyses were performed using R version 3.4.3 and SPSS version 24. The significance level was set at .05. Demographic as well as clinical data were compared with a one-way analysis of variance.

2.3.1. Preparatory analysis of HCC

HCC were transformed using natural log-transformation to reduce positive skewness. Outlying values ($n = 10$) with 3 *SD* above or below the mean were excluded from further analyses (Table 1). In a preparatory analysis prior to hypothesis testing, previously reported covariates (Stalder et al., 2017) as well as the batch were explored using group comparisons for binary variables and correlation coefficients for continuous variables. The batch did not affect the mean level of HCC ($p = .424$), and also the separate analysis of the two batches provided consistent results. As previously reported (see Stalder et al., 2017), men had higher HCC (HCC in pg/mg: $M = 8.04$, $SD = 5.74$) compared to women (HCC in pg/mg: $M = 6.43$, $SD = 4.72$; $t(246) = 2.79$, $p = .006$, Cohen's $d = 0.36$). Neither body mass index ($p = .974$), nor smoking ($p = .427$), nor the use of medication ($p = .347$), nor curls or waves ($p = .195$), nor the use of hair dye ($p = .841$) varied systematically with the HCC. Within the patient group we do not find a significant difference in HCC between patients with and without antidepressant medication ($p = .223$), nor between patients with and without neuroleptic mediation ($p = .212$). Thus, the variable gender was further considered as a covariate in all analysis.

2.3.2. Statistical analysis of the importance of type and timing of maltreatment on HCC

The aim of the first research analysis was to identify type and timing of exposure most predictive of HCC and to determine whether exposure during a specific developmental stage was a more important predictor than overall severity or duration of exposure across childhood. Conventional analytical strategies, such as multiple regression or structural equation modeling, are not suitable as we are endeavoring to ascertain the comparative significance of 42 highly collinear predictor variables. Specific predictors included annual measures of neglect between ages 1–18, annual measures of abuse at ages 3–18, overall duration, severity, and multiplicity of maltreatment during childhood, trauma load across the lifespan, gender, and presence or absence of key diagnostic categories (i.e., psychotic disorders, affective disorders, and personality disorders). Ratings of abuse and neglect at adjacent ages, in particular, tend to be highly correlated. We have found in simulation studies with artificial data that random forest regression with conditional inference trees was superior to other artificial intelligence analytical strategies (e.g., gradient boosted machines, neural networks, support vector machines) in identifying the correct underlying predictors in highly collinear data sets and have used this approach in prior studies to identify the most important type/time predictors of the clinical (e.g., Khan et al., 2015; Schalinski et al., 2016) and neurobiological (e.g., Teicher et al., 2018) consequences of maltreatment.

Briefly, this form of machine learning uses a 'wisdom of the crowd strategy' to regression analysis by creating a forest of decision trees. Each tree is established using a different subset of the data and restricted in the number of predictor variables that can be considered at each branch point. To avoid overfitting, the model is generated based on a training set (75% of the data) and evaluated on the out of bag test set (25% of data). The test set is then run through each tree in the forest and results averaged. Advantages of this method include: better predictive accuracy than conventional regression analyses; ability to consider large numbers of predictor variables; ability to handle highly collinear predictors; no restrictions on the distribution and scaling properties of the data; no assumption of a linear relationship between predictors and outcome and the capacity to model interactions between predictors (Breiman, 2001; Strobl et al., 2007; Strobl et al., 2009). The key limitation of this technique is that it does not provide a clear understanding (such as beta weights) to indicate the relationship between predictor variables and outcomes. This method instead provides a novel metric of the importance of each predictor variable. This measure of variable importance is calculated by sequentially permuting (randomizing to irrelevance) each predictor in the model. Following the permutation of each variable, a new random forest is derived and compared to the original model for goodness of fit as defined by the increase in mean square error (MSE). Permuting important predictor variables results in a poorer fit and a relatively large increase in MSE, whereas permuting unimportant predictors has little impact. Mean levels of importance were derived by repeating this process 100 times with different training and test splits and averaging results. To estimate the statistical significance of these mean importance measures we then performed the random forest analyses 5000 times using reshuffled outcome measures and calculated random chance importance measures and standard deviations for each predictor. *Z* tests were used to determine the probability that observed mean importance levels would have occurred by random chance and then adjusted the *p*-values using Bonferroni correction to control for multiple comparisons.

As a further check on the validity of the model we also performed a cross-validated penalized regression analysis using least absolute shrinkage and selection operator (LASSO) methodology (Tibshirani, 1996). This approach delineates a sparse subset of predictor variables that provide a parsimonious fit to the data. Only those predictors that showed a significant importance in condition random forest regression as well as demonstrated a non-zero beta coefficient in LASSO-penalized regression were considered as "important and significant" predictor/s. These analyses were performed using R libraries 'glmnet', 'party', and 'caret'.

Post-hoc explanatory analysis was used to determine the directionality of the fit, that is whether exposure to important predictors was associated with higher or lower HCC levels. For this purpose, we have applied the k-means clustering algorithm (with $k = 2$) to identify subgroups with similar levels of the predictor/s. This approach appeared to be more appropriate accounting for the distribution compared to an arbitrarily split by the median. Those two patient groups as well as the control group were further used to compare level of HCC.

2.3.3. Statistical analysis of the relationship between adversity-related changes of HCC and current trauma-related symptoms

These analyses aimed to explore the consequences of the adversity-related HCC relationship for trauma-related symptoms. Analysis of variance was used for group comparisons between high and low HCC and high and low exposure due to the low power of tests for interaction with continuous variables (McClelland and Judd, 1993). For this purpose, we used the gender-adjusted level of HCC to split the group into high and low levels identified by k means clustering algorithm (with $k = 2$). Based on this clustering, $n = 86$ patients were assigned to the group with high HCC (HCC in pg/mg: $M = 10.41$, $SD = 3.80$), and $n = 90$ to the group with low HCC (HCC in pg/mg: $M = 3.64$, $SD = 3.89$). The risk for trauma-related symptoms following the exposure to traumatic stress are higher in women than men, therefore gender effect were used as a covariate (e.g., Breslau et al., 1999).

3. Results

3.1. Adverse experiences, HCC, and trauma-related symptoms

Patients reported higher exposure levels compared to controls on all indices of adverse experiences, including childhood adversities and trauma load (all $p < .001$, ranging from 0 to 13 different types of traumatic events, see Table 1). Patients had lower levels of HCC than controls, however, the difference was not significant ($F(1, 245) = 3.50$, $p = .062$, $\eta^2 = 0.01$, see Table 1 for descriptive statistics). However, men had higher levels of HCC than women ($F(1, 245) = 7.77$, $p = .006$, $\eta^2 = 0.03$).

Within the patient sample, 30.6% met the criteria for PTSD diagnosis, and another 19.1% reported symptoms of PTSD without meeting criteria for a PTSD diagnosis. With an average symptom severity of $M = 9.66$ ($SD = 11.55$, range 0 to 39), the score falls in the upper end of the mild severity range for trauma-related symptoms. On average the patient group reported $M = 4.7$ ($SD = 2.7$) different types of traumatic experiences across the lifetime (trauma load). Furthermore, there was a moderate relationship between trauma load and current trauma-related symptoms ($r = 44$, $p < .001$). The respective severity of trauma-related symptoms per traumatic event type was at $M = 2.02$, $SD = 2.6$, ranging from 0 to 13).

3.2. Relation of type and timing of childhood adversities to levels of HCC

Random forest regression with conditional inference trees indicated that neglect ages 1–5 and 9–10 years of age were important predictors of HCC (Table 2). LASSO-penalized regression confirmed that neglect at age 3 was the best predictor followed by neglect at age 5 as these predictors emerged with non-zero beta weights (Table 2). However, only neglect at age 3 was significant according to the Bonferroni-corrected alpha level. Neither trauma load, psychiatric diagnoses, overall severity, multiplicity nor duration of maltreatment emerged as significant predictors (all $p > .530$). The covariate gender obtained a positive importance value but did not achieve significance (Table 2).

We used the severity score of neglect at age 3 to find two subgroups using the k means clustering algorithm. Based on this approach, $n = 55$ patients were assigned to the group with high levels of neglect (with an average neglect score at age 3 of $M = 7.22$ $SD = 1.98$) and $n = 125$ to the group with lower levels (with an average neglect score at age 3 of $M = 1.40$, $SD = 1.50$).

For post-hoc explanatory analysis, patients with high and low score of neglect at age 3 and controls were compared on their levels of HCC. The analysis of variance verified a main effect group ($F(2, 241) = 8.08$, $p < .001$, $\eta^2 = 0.06$), while controlling for the effect of gender ($F(1, 241) = 3.51$, $p = .062$, $\eta^2 = 0.01$). Patients with high levels of neglect at age 3 had lower HCC (HCC in pg/mg: $M = 5.33$, $SD = 5.37$; ln-transformed HCC: $M = 1.67$; $SD = 0.56$) compared to patients with low levels of neglect at age 3 (HCC in pg/mg: $M = 7.63$, $SD = 5.30$; ln-transformed HCC: $M = 2.01$; $SD = 0.54$; $t(171) = 3.67$, $p < .001$, Cohen's $d = 0.61$), and controls (HCC in pg/mg: $M = 8.21$, $SD = 5.26$; ln-transformed HCC: $M = 2.06$; $SD = 0.54$; $t(120) = 3.81$, $p < .001$, Cohen's $d = 0.70$). In contrast, HCC did not differ between patients with low levels of neglect at age 3 and controls ($t(193) = 0.61$, $p = .542$, see Fig. 1a). Patients with high levels of neglect at age 3 showed a 17% reduction in HCC compared to patients with low levels of neglect at age 3 as well as a 19% reduction compared to controls. Fig. 1b displays the regression lines for the relationship between each neglect scores (1–18) and adult HCC, while Fig. 1c shows the regression lines for the relationship of each abuse scores (3–18) and adult HCC.

3.3. Severity of trauma-related symptoms in relation to adverse experiences and HCC

The analysis of variance revealed a significant interaction effect for neglect at age 3 (low and high) and HCC (low and high) on trauma-related symptoms per traumatic event type ($F(1, 165) = 5.03$, $p = .026$, $\eta^2 = 0.03$, see Fig. 2). Additionally, there was a main effect for neglect at age 3 ($F(1, 165) = 7.87$, $p = .006$, $\eta^2 = 0.05$) and a main effect of HCC on trauma-related symptoms per traumatic event type ($F(1, 165) = 4.69$, $p = .032$, $\eta^2 = 0.03$). Furthermore, the covariate gender verified higher levels of symptoms for women compared to men ($F(1, 165) = 14.37$, $p < .001$, $\eta^2 = 0.08$).

After rerunning the analysis of variance for patients with low and high levels of HCC separately, there was a main effect of neglect for patients with low levels of HCC on trauma-related symptoms per traumatic event type ($F(1, 83) = 11.63$, $p = .001$, $\eta^2 = 0.12$), whereas there was no such a difference for patients with high levels of HCC ($F(1, 81) = 0.28$, $p = .600$, $\eta^2 < 0.01$). For both analyses the covariate gender was considered (for patients with low HCC: ($F(1, 83) = 5.55$, $p = .021$, $\eta^2 = 0.06$ and for patients with high HCC: $F(1, 81) = 10.04$, $p = .002$, $\eta^2 = 0.11$). Post-hoc test showed that patients with low levels of HCC that reported high exposure to neglect at age 3 had higher trauma-related symptoms compared to patients with low exposure to neglect at age 3 ($t(84) = 3.57$, $p < .001$, Cohen's $d = 0.79$).

4. Discussion

The present study sought to (1) delineate the type and timing of adversities in childhood and traumatic experiences across the lifespan on adult HCC, and (2) examine the adversity-related changes in HCC on trauma-related symptoms in a larger sample of patients with different psychiatric diagnoses. Results disclosed neglect experiences at age 3 as the most important determinant of adult HCC. In support of the attenuation hypothesis, present findings confirmed that patients with high neglect at age 3 had lower levels of HCC compared to patients with low levels of neglect and controls. Furthermore, findings demonstrated a significant impact of the association of (high) neglect and (attenuated) HCC on increased trauma-related symptoms. Both effects emphasize the strength of detailed exposure chronology for decoding the impact of childhood experiences on long-term modification of HPA axis regulation and potentially, thereby, trauma sensitivity.

This strong impact of being raised in a neglecting environment, in which parents failed to provide basic emotional and physical needs as well as leave their child unattended, may have been overlooked in studies targeting consequences of traumatic experiences, but is progressively acknowledged due to accumulating evidence. In line with previous evidence on the association between early neglect and persistent attenuation of cortisol reactivity, lower diurnal pattern and lower HCC in children and youths (Flannery et al., 2017; McLaughlin et al., 2015; White et al., 2017), these results supports particular sensitivity for neglect during critical periods of neuroendocrine development (Kuhlman et al., 2017). Our finding of a particularly robust association between neglect at age 3 and HCC is most strongly supported by a study of Romania orphans which reported that neglected orphans developed a blunted cortisol response unless they were placed in high quality foster care before 24-months of age (McLaughlin et al., 2015). It should be noticed, that the importance of neglect at age 3 as predictor of adult HCC, as identified by conditioned random forest regression, does not completely rule out an impact of neglect experienced at age 1 to 5 or older, as reports of exposure tend to extend across years. As to what extent the reasonable dominance of caregiver environment on sensitive periods for neuroendocrine development is the only or major determinant of HPA axis regulation and HCC requires systematic variation of the different components (e.g., removal from neglectful environments in early childhood to high quality foster families). The present result adds to the model of long-term attenuated levels of HCC with increasing exposure to past adversities (endocrine building block; Steudte-Schmiedgen et al., 2016). However, while considering comprehensive information of past exposure to adversities, the present results did not confirm a major impact of abuse or traumatic experiences

Table 2
Descriptive statistics and variable importance for all predictors (type and timing of abuse and neglect, further indices of adversities, gender, and diagnostic category) that were simultaneously considered in the random forest regression and non-zero beta coefficients from LASSO-penalized regression analysis.

dependent variable: adult hair cortisol concentration	potential predictors	M (SD), n (%)	[a]variable importance M (SD)	*p-value*	[b]B_{minMSE}
timing for abuse	abuse at age 3	1.9 (4.5)	< 0		
	abuse at age 4	3.5 (6.4)	< 0		
	abuse at age 5	4.8 (7.2)	< 0		
	abuse at age 6	7.0 (8.6)	< 0		
	abuse at age 7	8.5 (9.0)	< 0		
	abuse at age 8	9.7 (9.6)	< 0		
	abuse at age 9	10.5 (10.3)	< 0		
	abuse at age 10	12.0 (10.8)	< 0		
	abuse at age 11	12.6 (11.1)	0.19 (0.03)	.267	
	abuse at age 12	14.0 (10.9)	< 0		
	abuse at age 13	13.1 (10.0)	< 0		
	abuse at age 14	13.0 (10.0)	0.21 (0.04)	.238	
	abuse at age 15	11.9 (10.0)	< 0		
	abuse at age 16	11.3 (9.8)	< 0		
	abuse at age 17	8.8 (8.4)	< 0		
	abuse at age 18	7.9 (8.3)	< 0		
timing for neglect	neglect at age 1	3.1 (3.1)	1.17 (0.09)	.019	
	neglect at age 2	3.0 (3.0)	0.87 (0.05)	.030	
	neglect at age 3	**3.2 (3.2)**	**2.56 (0.13)**	**.0004***	**−0.02**
	neglect at age 4	3.3 (3.3)	0.71 (0.06)	.049	
	neglect at age 5	3.4 (3.4)	1.79 (0.09)	.006	−0.01
	neglect at age 6	3.5 (3.3)	0.24 (0.04)	.195	
	neglect at age 7	3.6 (3.4)	0.51 (0.05)	.086	
	neglect at age 8	3.7 (3.7)	0.53 (0.03)	.075	
	neglect at age 9	3.9 (3.8)	0.78 (0.06)	.029	
	neglect at age 10	4.0 (3.9)	1.02 (0.05)	.019	
	neglect at age 11	4.2 (3.8)	0.25 (0.03)	.190	
	neglect at age 12	4.3 (3.9)	0.10 (0.02)	.344	
	neglect at age 13	4.4 (3.9)	0.03 (0.03)	.460	
	neglect at age 14	4.5 (4.0)	0.08 (0.03)	.359	
	neglect at age 15	4.5 (3.9)	< 0		
	neglect at age 16	4.4 (3.9)	< 0		
	neglect at age 17	4.4 (3.7)	< 0		
	neglect at age 18	4.4 (3.7)	< 0		
indices of adversities	LEC: trauma load	4.7 (2.7)	0.58 (0.04)	.100	
	MACE: [c]duration	8.3 (6.5)	0.26 (0.03)	.248	
	MACE: [d]multiplicity	8.3 (6.5)	0.26 (0.03)	.248	
	MACE: [e]overall severity	33.8 (16.8)	0.14 (0.05)	.323	
demographic variable	gender (female)	82 (44.8%)	0.08 (0.03)	.311	
diagnostic categories	psychotic disorder	81 (44.3%)	< 0		
	affective disorder	83 (45.4%)	< 0		
	personality disorder	53 (29%)	< 0		

[a] Higher values verify higher importance (independent of direction and kind of the underlying relationship with hair cortisol concentration (HCC)). Negative importance scores indicate "unimportant predictors" and are set to < 0.

[b] B_{minMSE} = beta estimates based on the optimal lambda to find the minimum mean squared error in LASSO-(least absolute shrinkage and selection operator) penalized regression analysis. LEC = Life Event Checklist; MACE = Maltreatment and Abuse Chronology of Exposure.

[c] Years with a multiplicity score ≥ 1 (ranging from 0 to 18).

[d] Number of different forms (ranging from 0 to 10).

[e] Severity of childhood adversities (ranging from 0 to 100). The predictor that is highlighted in bold were selected by the LASSO-penalized regression analysis and showed significance (*) according to Bonferroni corrected alpha level ($p \leq .001$).

on adult levels of HCC.

Animal and human studies suggest that early experiences may prompt initial up-regulation of glucocorticoids (for animal models Curley and Champagne, 2016; for human evidence: Trickett et al., 2010; White et al., 2017), which then affect brain structures relevant for the HPA axis biology. Brain structures with high density of glucocorticoid receptors, such as the hippocampus, involved in negative feedback of cortisol regulation (Dedovic et al., 2009), are sensitive to early exposure to adversity (Pagliaccio et al., 2014), and particularly to early neglect (Teicher et al., 2018).

The combination of high neglect at age 3 and low HCC was associated with increased trauma-related symptoms. This finding provides tentative evidence that the neglect-related attenuation of adult HCC reflects aspects of a biological pathway that contributes to the sensitivity to trauma (Steudte-Schmiedgen et al., 2016; Yehuda et al., 2010) and potentially also to further dimensions of psychopathology (Strüber et al., 2014). Yet, present cross-sectional and retrospective results do not allow conclusions on mechanistic trajectories for trauma-related symptoms. Further insight may be gained from prospective longitudinal studies, for instance, in populations, who are at risk for frequent trauma exposure such as soldiers before deployment in war-zones, police officers, firefighters, or first responders.

The present transdiagnostic approach did not confirm importance of diagnostic category as a predictor of HCC. This supports the NIMH-initiated dimensional perspective on symptoms rather than focusing on diagnostic categories (e.g., Kozak and Cuthbert, 2016) and adds to previous findings on HCC differences for various psychiatric disorders (Staufenbiel et al., 2013). Moreover, recent studies indicated that maltreatment is an important predictor of an array of neurobiological measures and that the relationship between diagnosis and neurobiology drops out once maltreatment is included in the analysis (e.g., Ohashi et al., 2017; Teicher et al., 2018).

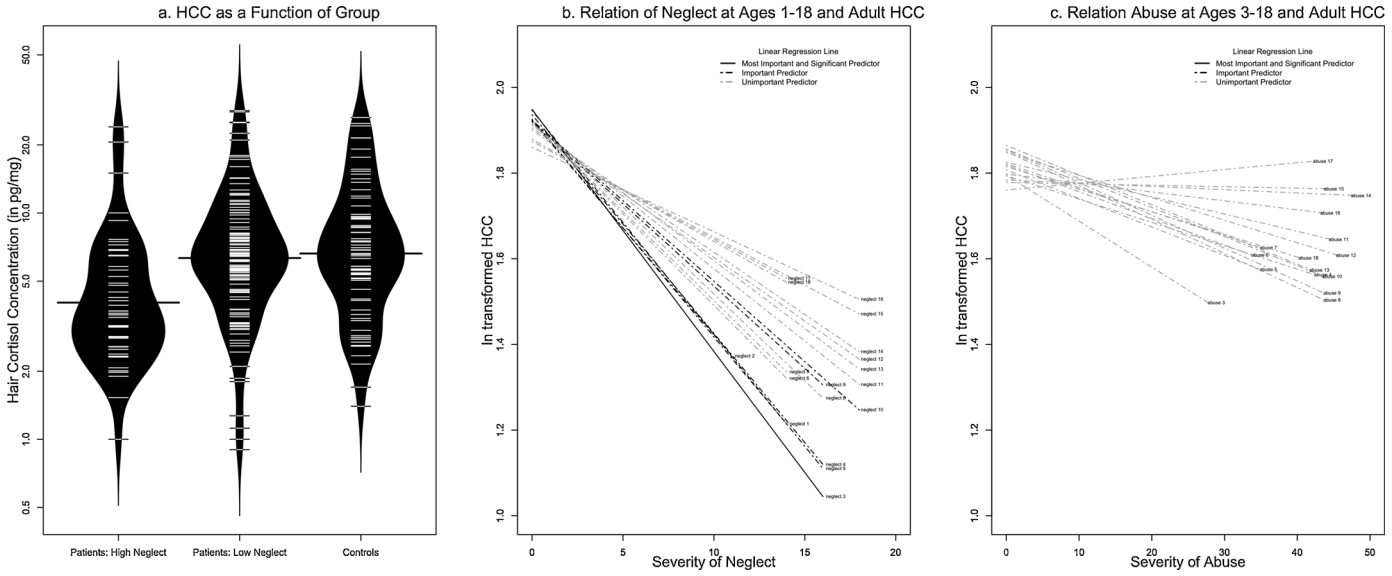

Fig. 1. a) Distribution of the hair cortisol concentration (HCC) as a function of patients with high neglect at age 3 (n = 50), patients with low neglect at age 3 (n = 123) as well as controls (n = 72). HCC are displayed in original units (in pg/mg). The small lines show individual observations, while the long lines represents the mean of the respective group. **b)** The relationship between neglect (from ages 1–18) and adult hair cortisol concentration (HCC) displayed as regression lines. **c)** The relationship between abuse (from ages 3–18) and adult HCC displayed as regression lines: in black solid lines for the most important predictor, black dashed line for important predictors and gray lines for unimportant predictors. The length of the regression line is limited by the minimum and maximum of the severity score at each age.

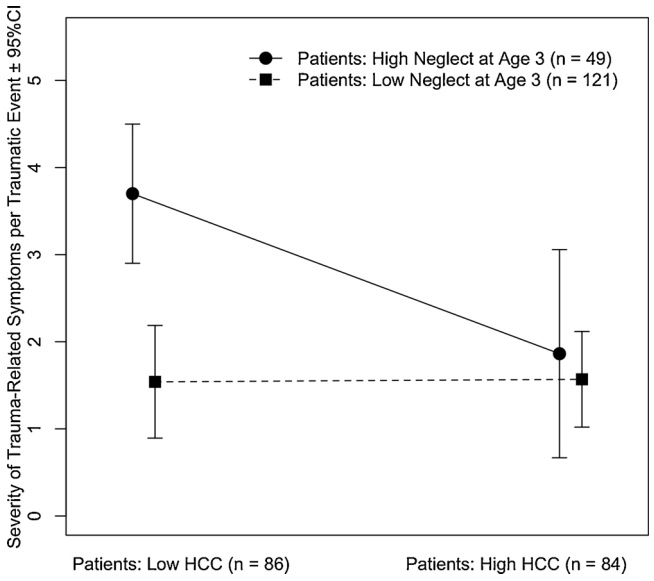

Fig. 2. Severity of trauma-related symptoms per traumatic event type as a function of low and high neglect and hair cortisol concentration (HCC). The error bars present the 95% confidence interval.

Limitations of the study have to be noted: results were obtained in inpatients, most of whom were treated with psychoactive medication for different psychiatric disorders. As psychoactive substances are known to influence saliva cortisol (e.g., Granger et al., 2009), validation of results requires replication in representative sample from the community. Whereas the validity and reliability of type specific reports have been demonstrated in various populations, less is known about the validity and reliability of self-reports capturing the timing of neglect and abuse (Teicher and Parigger, 2015; Teicher et al., 2018). A final limitation is the still ongoing evaluation of the power of conditioned random forest regression to predict outcomes from real exposure data.

5. Conclusion

Exposure to neglectful experiences at age 3 emerged as the most important predictor of average long-term activity of the HPA axis in adults with mental illness. Further, the findings support the notion of a distinct biological phenotype characterized by long-term attenuation of HCC, which, upon trauma exposure, might predispose individuals to develop trauma-related symptoms.

Declaration of Competing Interest

The authors declare that they have no conflict of interests.

CRediT authorship contribution statement

I. Schalinski: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Visualization, Funding acquisition. **M.H. Teicher:** Software, Validation, Formal analysis, Visualization, Writing - review & editing. **B. Rockstroh:** Conceptualization, Resources, Supervision, Writing - review & editing.

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