Dissociative stress response corresponds with downregulation of the HPA-axis

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ABBREVIATIONS

ACTH	Adrenocorticotropin Hormone
AIC	Akaike Information Criterion
AT	Adult Trauma
BDI	Beck Depression Inventory
Bf-S	Zerssen Mood Scale
BIC	Bayesian Information Criterion
CADSS	Clinician-Administrated Dissociative States Scale
CAPS	Clinician Administrated PTSD-Scale
COPE	Brief Stress Coping Questionnaire
CORT	Cortisol
CRH	Corticotropin-Releasing Hormone
CTE	Checklist for Traumatic Experiences
DES	Dissociative Experiences Scale
DHEA	Dehydroepiandrosterone
DRC	Democratic Republic of Congo
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSP-I	Dissociative Subtype of PTSD Interview
DSS-acute	Dissociation-Tension-Scale acute
DST	Dexamethasone Suppression Test
DS-PTSD	Dissociative Subtype of PTSD
ELT	Early Life Trauma
ELT+AT	combined Early Life and Adult Trauma
FVTS	Fear of Death and Dying Questionnaire
HC	Healthy Controls
hCORT	hair Cortisol
HPA-axis	Hypothalamus-Pituitary-Adrenal axis
LPA	Latent Profile Analysis
M-CIDI	Munich Composite International Diagnostic Interview
M.I.N.I.	Mini International Neuropsychiatric Interview
MD	Major Depression
mPTSD	mild PTSD

NS	No Symptoms
ntHC	non-traumatized Healthy Controls
pCORT	plasma Cortisol
PD	Panic Disorder
PHQ-9	Patient Health Questionnaire
PSSI	PTSD Symptom Scale Interview
PTSD	Posttraumatic Stress Disorder
PTSD-NR	PTSD non-responders
PTSD-R	PTSD responders
RIQ	Response to Intrusions Questionnaire
SCID-D	Structured Clinical Interview for Dissociative Disorder
sCORT	salivary Cortisol
SF-A	Sleep Questionnaire for the last night
SF-B	Sleep Questionnaire for the last two weeks
SPQ	Spirit Possession Questionnaire
sPTSD	severe PTSD
ssBIC	sample-size adjusted Bayesian Information Criterion
STAI	State-Trait Anxiety Inventory
SVF-78	German Stress Coping Questionnaire
TAS	Tellegan Absorption Scale
TE	Trauma Exposure
tHC	traumatized Healthy Controls
TSST	Trier Social Stress Test
VAS	Visual Analogue Scale
WSAS	Work and Social Adjustment Scale

SUMMARY

The term „dissociation“ (from Latin: *dissociare*, disuniting, separating) is used in natural sciences to describe processes of falling apart, disintegration, and separation. In the psychology it is defined as lost of information or control over mental processes that, under normal circumstances, are available to conscious awareness, self-attribution, and sensory experience (Cardeña & Carlson, 2011). The relationships between dissociation, stress, trauma exposure and the development of psychopathology, such as Posttraumatic Stress Disorder (PTSD), have been frequently documented (Frewen, Brown, Steuwe, & Lanius, 2015; Soffer-Dudek, 2017; van Dijke, Ford, Frank, & van der Hart, 2015; Vonderlin et al., 2018). However, biological stress processes accompanying dissociative symptoms are still broadly unknown (Brand, Lanius, Vermetten, Loewenstein, & Spiegel, 2012). For this reason, in my dissertation, I focused on mechanisms of psychobiological stress processing in traumatized and non-traumatized healthy controls as well as in PTSD patients. Especially, I was interested in dissociation understood as a stress coping strategy through cognitive distance and emotional downregulation (Ehlers & Clark, 2000; Lanius et al., 2010).

The data was gathered in two studies. In the first study, I conducted standardized stress experiments (Trier Social Stress Test, TSST, Kirschbaum, Pirke, & Hellhammer, 1993) in female PTSD patients, traumatized and non-traumatized female healthy controls at the Max Planck Institute of Psychiatry in Munich. At four assessment times, concentrations of blood stress hormones (among others cortisol) as well as parameters of psychological stress reactivity were examined. The second study took part in the Nakivale refugee camp in Uganda, where I conducted interviews on trauma exposure and its clinical consequences, with focus on dissociative symptomatology. Hormonal stress response was examined in saliva samples collected at three different assessment times. Further stress markers were determined in hair samples. In both studies, I aimed at finding relationships between the studied psychological and biological variables. The results from both studies were presented in three papers.

In **Paper 1**, which replicated and extended the findings from my previous work (Zaba et al., 2015), in PTSD patients, two subgroups of hormonal stress response were identified. One PTSD group showed a significant increase of stress hormone, cortisol, that did not differ from that of a control group consisted of non-traumatized, healthy controls. In the second PTSD group, cortisol levels decrease, despite the presence of significant psychological stress response, was observed. The missing biological stress response was accompanied by trauma-

related dissociation, psychiatric comorbidity as well as by early life trauma and was best predicted by severity of trauma-related dissociation. Interestingly, traumatized healthy controls showed elevated cortisol levels together with high levels of non-pathological dissociation (absorption) that were comparable with those of PTSD patients.

In **Paper 2**, I focused on the identification and clinical characterization of the Dissociative Subtype of PTSD (DS-PTSD, American Psychiatric Association, 2013) in a highly trauma exposed, non-Western population. The DS-PTSD was identified with an established, statistical stratification method (Latent Profile Analysis) in 14% of all studied individuals and in 26% of all PTSD cases. Sexual trauma, high levels of depressive symptoms, low general functionality as well as elevated suicidality were found as correlates of the DS-PTSD. Interestingly, similar correlates were found in already studied Western populations (e.g., Hansen, Ross, & Armour, 2017).

The results of **Paper 3** showed that assessments of trauma exposure and its clinical consequences did not evoke a significant biological stress response, within the studied sample. However, a subset of individuals (29% of the whole sample) with high levels of PTSD, especially re-experiencing, and depressive symptoms as well as low levels of emotional and instrumental support as coping strategies, exhibited a significant biological stress response. Similarly to the results from the first study, low reactive cortisol levels were best predicted by sexual trauma, low emotional coping and high dissociative tendencies.

Both studies demonstrated that stress- and trauma-related dissociative symptoms correspond with downregulation of the hormonal stress system. This shows that focusing on the emotional stress response can broaden our understanding of the complex relationship between trauma exposure, psychopathology and stress hormone activity. Dissociative symptoms, transdiagnostically and transculturally, have frequently been associated with large illness burden and reduced treatment outcome (Lyssenko et al., 2018; McKinnon et al., 2016, **Paper 2**). For this reason, prospective studies on the possible causal link between dissociation and downregulation of biological stress system are urgently needed.

ZUSAMMENFASSUNG

Der Begriff „Dissoziation“ (v. lat. *dissociare*, trennen, scheiden) wird in Naturwissenschaften verwendet, um Prozesse des Auseinanderfallens, Zerfalls oder der Trennung zu beschreiben. In der Psychologie wird sie als Verlust von Informationen oder der Kontrolle über mentale Vorgänge, die unter normalen Umständen dem Bewusstsein, der Selbstattribution sowie dem sensorischen Empfinden zugänglich wären (Cardeña & Carlson, 2011), beschrieben. Ein Zusammenhang zwischen Dissoziation, Stress und Traumatisierung sowie der Entwicklung der Psychopathologie wie Posttraumatischer Belastungsstörung (PTBS) wurde mehrmals nachgewiesen (Frewen et al., 2015; Soffer-Dudek, 2017; van Dijke et al., 2015; Vonderlin et al., 2018). Trotzdem bleibt weitestgehend unbekannt, durch welche Vorgänge im biologischen Stresssystem dissoziative Symptome begleitet werden (Brand et al., 2012). Aus dem Grund konzentrierte ich mich in meiner Dissertation auf die psychobiologischen Mechanismen der Stressverarbeitung bei nicht-Traumatisierten, Traumatisierten sowie bei an PTBS-Erkrankten Personen. Das besondere Augenmerk richtete ich dabei auf die Dissoziation als eine Art des Stressumgangs durch die kognitive Distanzierung sowie Unterregulation des emotionalen Erlebens (Ehlers & Clark, 2000; Lanius et al., 2010).

Die Datenbefunde erhob ich in zwei Studien. In der ersten Studie führte ich standardisierte Stressexperimente (Trier Social Stress Test, TSST, Kirschbaum, Pirke, & Hellhammer, 1993) an PTBS-Patientinnen, traumatisierten und nicht-traumatisierten gesunden Probandinnen am Max-Planck-Institut für Psychiatrie in München durch. Dabei wurden Stresshormone (u. a. Cortisol) im Blut sowie Parameter der psychologischen Stressreaktion untersucht. Die zweite Studie fand im Nakivale Flüchtlingslager in Uganda statt, wo ich Interviews zu Traumata und deren klinischen Folgen, insbesondere zu dissoziativen Symptomen, durchführte. Die hormonelle Stressantwort auf die Befragung wurde mithilfe von drei zu verschiedenen Zeitpunkten entnommenen Speichelproben bestimmt. Zusätzlich wurden weitere hormonelle Stressmarker in Haarproben untersucht. In beiden Studien untersuchte ich die Zusammenhänge zwischen den erhobenen psychologischen und biologischen Faktoren. Die Studienergebnisse präsentierte ich in drei Artikeln.

Im **Paper 1**, das die Ergebnisse meiner vorherigen Arbeit (Zaba et al., 2015) repliziert und erweitert, wurden bei PTBS-Patientinnen zwei Subgruppen der hormonellen Stressreaktion identifiziert. Eine PTBS-Gruppe zeigte einen signifikanten Anstieg des Stresshormons Cortisols, der sich von dem einer Vergleichsgruppe von nicht-traumatisierten, gesunden

Kontrollprobandinnen nicht unterschied. Bei der zweiten PTBS-Gruppe war ein Abfall der Cortisol-Werte bei Anzeichen einer signifikanten psychologischen Stressreaktion zu beobachten. Die fehlende biologische Stressantwort ging mit einer Trauma-bezogenen Dissoziation, psychiatrischer Komorbidität sowie mit frühkindlicher Traumatisierung einher und konnte von der Trauma-bezogenen Dissoziation vorhergesagt werden. Interessanterweise zeigten traumatisierte, gesunde Kontrollprobandinnen eine erhöhte Cortisol-Antwort. Zugleich wies diese Probandengruppe eine vergleichbar starke Ausprägung der nicht-pathologischen Dissoziation (Absorption) wie bei PTBS-Patientinnen auf.

Im **Paper 2** fokussierte ich mich auf die Identifizierung und klinische Charakterisierung des Dissoziativen Subtyps der PTBS (DS-PTBS, American Psychiatric Association, 2013) in einer stark traumatisierten, nicht-westlichen Population. Mit einer etablierten, statistischen Stratifizierungsmethode (Latent Profile Analysis) wurde der DS-PTBS bei 14% der Probanden aus der gesamten Stichprobe sowie bei 26% aller PTBS-Fälle identifiziert. Sexuelle Traumatisierung, starke Ausprägung der depressiven Symptome, niedriges Funktionsniveau sowie erhöhte Suizidalität konnten als Korrelate des DS-PTBS gefunden werden. Interessanterweise ähnelten diese Korrelate denen bei bereits zuvor untersuchten westlichen Populationen (e.g., Hansen et al., 2017).

Die Ergebnisse aus dem **Paper 3** zeigten, dass die Befragung zu Traumata und deren klinischen Folgen keine systematische biologische Stressantwort erzeugte. Allerdings wies der Teil der Probanden (29% der Gesamtstichprobe) mit stark ausgeprägter PTBS- sowie depressiver Symptomatik und niedrigen Werten der emotionalen und instrumentellen Unterstützung als Stressverarbeitungsstrategien eine signifikante biologische Stressantwort auf. Vergleichbar mit den Ergebnissen aus der ersten Studie konnten niedrige reaktive Cortisol-Werte mittels sexueller Traumatisierung und dissoziativer Tendenzen vorhergesagt werden.

Beide Studien belegten, dass Stress- und Trauma-bezogene dissoziative Symptome mit der Unterregulation des hormonellen Stresssystems einhergehen. Dies zeigt, dass die Berücksichtigung der emotionalen Stressverarbeitung unser Verständnis des komplexen Zusammenhanges zwischen Traumatisierung, Psychopathologie und Stresshormonen-Aktivität erweitern kann. Dissoziative Symptome sind transdiagnostisch und transkulturell mit hoher Krankheitsintensität sowie mit schlechter Therapieprognose assoziiert (Lyssenko et al., 2018; McKinnon et al., 2016, **Paper 2**). Daher sind weitere, vor allem prospektive Studien zur Kausalität zwischen Dissoziation und Unterregulation des biologischen Stresssystems von großer Bedeutung.

1. GENERAL INTRODUCTION

Worldwide, a lifetime prevalence (over 70%) of trauma exposure (TE), i.e., witnessed or direct experience of threatened death, serious injury or sexual violence (American Psychiatric Association, 2013), was found in representative study populations (Benjet et al., 2016; Kessler et al., 2017; Liu et al., 2017). Although TE constitutes a *conditio sine qua non* for a subsequent development of posttraumatic stress disorder (PTSD), this disorder develops only in a relatively small subset (7-12%) of exposed individuals (Breslau, 2009; Kessler et al., 2017). This suggests that psychobiological processing of TE may be more decisive for the subsequent PTSD development than TE itself (Bandelow et al., 2017; Walker, Pfingst, Carnevali, Sgoifo, & Nalivaiko, 2017). However, PTSD prevalence of nearly 100% was found in severe traumatized populations, meaning that indeed any individual may develop PTSD once TE is extremely high (Conrad et al., 2017; Kolassa, Kolassa, Ertl, Papassotiropoulos, & De Quervain, 2010; Neuner et al., 2004).

PTSD, a highly debilitating disorder, is characterized by re-experiencing of traumatic memories, avoidance of trauma-related stimuli, hyperarousal (according to the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders, DSM-IV, American Psychiatric Association, 2000) as well as, according to the latest, fifth edition of DSM, negative thoughts and feelings associated with the TE (DSM-5, American Psychiatric Association, 2013). The large individual and societal burden of PTSD results from its high comorbidity with other psychiatric and somatic conditions (e.g., Price, Legrand, Brier, & Hébert-Dufresne, 2019; Richardson et al., 2017; Spinhoven, Penninx, van Hemert, de Rooij, & Elzinga, 2014), long symptom persistence (Kessler et al., 2017; Morina, Wicherts, Lobbrecht, & Priebe, 2014), and still insufficient treatment methods (e.g., Bernardy & Friedman, 2015; Carpenter et al., 2018; Visser, Gosens, Den Oudsten, & De Vries, 2017). These show the importance of further elucidating psychobiological mechanisms underlying the development and maintenance of PTSD.

The hypothalamus-pituitary-adrenal (HPA)-axis constitutes the body's major neuroendocrine stress response system. When exposed to stress, stress hormones in the brain and periphery are released with glucocorticoid hormones (among them cortisol, CORT, in humans) produced in the adrenal cortex activating a negative feedback cycle shutting down the stress response (de

Kloet, Joëls, & Holsboer, 2005). Dysregulations of the stress system, mostly marked by altered stress hormone levels either basal or under pharmacological (e.g., dexamethasone suppression test, DST, Menke et al., 2012) or psychological challenge tests (e.g., Trier Social Stress Test, TSST, Kirschbaum, Pirke, & Hellhammer, 1993), were proposed as candidate premorbid, diagnostic, and treatment response biomarkers of TE and/or PTSD (Bandelow et al., 2017; Schmidt et al., 2015). Hitherto, research remains inconclusive on the specific direction of HPA-axis dysregulations since both hypo- as well as hyper-activity of HPA-axis were found to be associated with either TE or both TE and PTSD. However, a tendency of an elevate proportion of reports showing lower basal CORT outputs as well as a stress-induced HPA-axis blunting in PTSD was found (Daskalakis et al., 2013; de Kloet et al., 2006; Morris, Hellman, Abelson, & Rao, 2016b; Pan, Wang, Wu, Wen, & Liu, 2018).

Recent research proposed that these inconsistencies may be grounded in a non-linear, two-staged timeline following TE: first, TE may provoke upregulation in CORT secretion and second, each additional TE may contribute to a dose-dependent downregulation of the overall activity of the HPA-axis resulting in hypo-cortisolism in the long-term (e.g., Miller, Chen, & Zhou, 2007; Steudte-Schmiedgen, Kirschbaum, Alexander, & Stalder, 2016). Although this conceptualization adds significantly to possible explanations of inconsistent findings on HPA-axis activity in PTSD, it leaves the trajectory of PTSD-associated phenomena, such as dissociative symptomatology and psychiatric comorbidity, especially with depression and anxiety, unexplained.

Moreover, distinct factors may contribute to long-term, tonic CORT levels (as usually assessed in hair samples, hCORT) than those accounting for stress-induced, phasic CORT fluctuations (as usually assessed in saliva or plasma samples). Whereas hCORT levels were found to be associated more reliably with TE independent from the presence of PTSD symptoms (e.g., Steudte et al., 2013), no reliable correlates of phasic/reactive CORT have been found (e.g., Miller et al., 2007). The parallel assessment of CORT levels from different body samples (e.g., saliva and hair) offers a promising approach to disentangle short- and long-term effects associated with TE and PTSD. However, the few studies that applied multi-method assessments revealed mixed findings as well. For example, paradox associations, such as low phasic saliva CORT (sCORT) levels and high tonic hCORT, were found to be related to sexual early life trauma (ELT) in female PTSD patients (Schalinski, Elbert, Steudte-Schmiedgen, & Kirschbaum, 2015). On the contrary, low levels of both short-term reactive sCORT and long-term hCORT were predictive of PTSD symptom development in German soldiers (Steudte-

Schmiedgen et al., 2015). In conclusion, more multi-method research is needed till general conclusions can be made (see also: Herane-Vives et al., 2018; Zhang et al., 2018).

Another perspective was presented in my recent work (Zaba et al., 2015). We proposed that inconsistent findings on HPA-axis dysregulations associated with TE and PTSD may result from comparisons of calculated group means instead of concentrating on individual response rates and based on them on HPA-axis reactivity subgroup identification and characterization (Zaba et al., 2015). In female PTSD patients, stress-induced (via the Trier Social Stress Test, TSST, Kirschbaum et al., 1993) plasma CORT (pCORT) levels were found to be lower than those of non-traumatized healthy controls (ntHC). However, a careful consideration of the response rates resulted in a more detailed and intriguing picture. In detail, applying a measure of 15.5% stress-related CORT increase, as a definition of a response rate (Miller, Plessow, Kirschbaum, & Stalder, 2013), two different PTSD endophenotypes of HPA-axis reactivity were identified: HPA-axis responders (43.48%) and non-responders (56.52%). Interestingly, the PTSD responders (PTSD-R) and non-responders (PTSD-NR) did not differ in their PTSD symptom severity but PTSD-NR showed higher trauma load (in terms of higher number of traumatic events and combined ELT and adult trauma, ELT+AT), as well as more trauma-related dissociative symptoms and psychiatric comorbidity. Notably, recently, Wichmann and colleagues (2017) repeated these findings by showing pCORT stress response to be at 43.5% in an independent PTSD female group by using the same methodology. Additionally, also in this PTSD sample, CORT response to the TSST was negatively related to dissociative symptoms.

These findings suggest that focusing on dissociative reactions as a response to stress specifically and on emotional stress responses generally may contribute to the explanation of conflicting results on HPA-axis dysregulations associated with TE and PTSD. The link between dissociation and stress, especially traumatic stress, has been repeatedly shown (e.g., Carlson, Dalenberg, & McDade-Montez, 2012; Frewen, Brown, Steuwe, & Lanius, 2015; van Dijke, Ford, Frank, & van der Hart, 2015). However, relatively little is known on how dissociation relates to the psychobiological stress response mechanisms. Generally, dissociation was conceptualized as a neural emotional undermodulation (Lanius et al., 2010) along with psychophysiological shut-down reactions (Schauer & Elbert, 2010). Specifically, evidence on the link between dissociative symptoms and HPA-axis activity is scarce (Simeon, Yehuda, Knutelska, & Schmeidler, 2008; Wichmann, Kirschbaum, Böhme, & Petrowski, 2017; Zaba et al., 2015). Mostly, researches focused on studying trauma exposed individuals and/or PTSD patients but

they set assessments of dissociative symptoms aside. Only a few studies concentrated on dissociative symptomatology in relation to CORT response. Briefly, in these studies, in HC, depersonalization and derealization were found to relate positively whereas absorption negatively to sCORT levels following the TSST (Giesbrecht, Smeets, Merckelbach, & Jelicic, 2007). In TE and PTSD, a negative relationship between reactive pCORT and dissociation was demonstrated (Simeon et al., 2008; Wichmann et al., 2017; Zaba et al., 2015). In line with Simeon and colleagues (2008), it may be concluded that dissociation might depict a missing piece in a puzzle of complex interrelations between TE, PTSD, and HPA-axis functionality. Moreover, it may account for some of the unexplained variance in the mixed findings on HPA-axis dysregulations found in individuals with TE and/or PTSD.

Furthermore, dissociation has been conceptualized as a trauma-specific coping strategy to deal with overwhelming trauma memories through avoidance and self-distance (e.g., Dutra & Wolf, 2017; Ehlers, 1999; Holmes et al., 2005). For this reason, studying dissociative responses in the broader context of stress coping offers a promising perspective on the link between the endocrine and emotional stress response. So far, the PTSD development was found to be associated with employment of avoidant as well as self-regulatory, such as denial or substance use, coping strategies, whereas resilience following TE seemed to be related to active, adaptive coping styles (Lehrner & Yehuda, 2018; Mattson, James, & Engdahl, 2018; Timshel, Montgomery, & Dalgaard, 2017). How these coping strategies correspond with the HPA-axis activity in the context of TE and/or PTSD has not been systematically studied yet (for a review in animal studies see: Radley & Johnson, 2018).

Based on the reviewed literature, the first study of this dissertation focused on the regulation of HPA-axis reactivity in response to a standardized psychosocial stressor (TSST) in female PTSD patients as compared to both female traumatized (tHC) and ntHC. Endocrine stress reactivity assessment in plasma samples was accompanied by measurement of psychological stress reactivity (subjective stress, acute dissociation, and mood state). Moreover, baseline assessments of pCORT levels and general stress coping strategies (e.g., Thomson & Jaque, 2017) as well as dissociation-related phenomena, such as sleeping difficulties (e.g., Selvi et al., 2017), psychological absorption (Giesbrecht, Lynn, Lilienfeld, & Merckelbach, 2008) and fear of death and dying (e.g., Gershuny, Cloitre, & Otto, 2003) were performed. The aims of this study were: first, to repeat the finding of distinct HPA-axis reactivity patterns in an independent sample of PTSD patients; second, by including a tHC sample, to explore the role of TE *per se* for the

stress response; and third, by comprehensive assessment of dissociation and dissociation-related phenomena (i.e., stress coping, sleep difficulties, psychological absorption, and fear of death and dying), to elucidate their contribution to the HPA-axis blunting. This study was conducted at the former trauma outpatient unit of the Max Planck Institute of Psychiatry, Munich, Germany and is presented in **Paper 1**: *"Dissociative symptoms but not trauma exposure or PTSD symptoms are decisive for HPA-axis blunting in female PTSD patients"*.

Although focusing on dissociative symptoms as an emotional stress response, **Paper 1** did not account for analyses of the dissociative subtype of PTSD (DS-PTSD). The DS-PTSD was introduced into the DSM-5 (American Psychiatric Association, 2013) as a novel diagnostic entity that is characterized by depersonalization (e.g., feelings of detachment from self or body) and derealization (e.g., feelings of unreality of surroundings) symptoms. Recent research conceptualized the DS-PTSD as an emotional overmodulation reflected in prefrontal inhibitory activity on limbic regions (Lanius et al., 2010) and as a type of avoidant coping with trauma memories (Dutra & Wolf, 2017). In **Paper 1**, several measures of dissociative symptoms were applied. Unfortunately, none of them allowed to distinguish between dissociative and non-dissociative PTSD. Also, given the relatively small study sample, PTSD patients were not divided into further subtype categories (for a similar approach see: Wolf et al., 2014).
For this reason, the second study concentrated on the identification and characterization of the DS-PTSD in an independent sample of individuals who have been exposed to severe traumata. Since the majority of DS-PTSD studies have been conducted in Western populations (Hansen et al., 2017) and so far only one study collected data on the DS-PTSD across different cultures (Stein et al., 2013), assessments were chosen to be conducted in a non-Western population. The study site was in the refugee camp Nakivale, Uganda, and the results are presented in two papers of this dissertation (**Paper 2**: *"Cross-cultural validity of the dissociative subtype of PTSD: evidence from refugees settled in Uganda"*, **Paper 3**: *"Sexual trauma and dissociation-related stress coping predict blunted cortisol levels as a response to a diagnostic interview in East African refugees"*).
In the Ugandan study, semi-structured interviews on trauma history, PTSD, dissociation as well as other psychopathological measures were conducted. Moreover, the HPA-axis activity was assessed in three saliva samples collected during the interview, namely at the beginning, immediately after TE, PTSD, and dissociation assessments as well as at the end of the study procedure. If possible, hair samples as a measure of long-term HPA-axis function were collected as well.

The aims of **Paper 2** were: first, to identify the DS-PTSD in the total sample by employing a methodology of latent profile analysis (LPA); second, to provide evidence on the DS-PTSD cross-cultural validity, in terms of its relationships with measures of TE, psychopathology, and stress coping. Moreover, a newly developed clinician-based interview, the Dissociative Subtype of PTSD Interview (DSP-I) for DSM-5 (Eidhof et al., *accepted*), was employed and **Paper 2** reports on its psychometric properties in the studied sample.

The LPA strives for the identification of classes or profiles of individuals showing the same symptom pattern thereby enabling their further characterization by subsequent group comparison analyses (Muthén & Muthén, 2006). In a recent review of all so far conducted DS-PTSD LPA studies (n = 11), all but one studies found at least one DS-PTSD profile that was characterized by a high intensity of both PTSD and dissociative symptoms. The other study identified two DS-PTSD profiles, i.e., one with moderate and one with severe DS-PTSD. The prevalence of the DS-PTSD in these studies ranged between 6 and 44.6% (M = 20.35%). In general, sexual TE as well as high levels of psychopathology (severe PTSD and high prevalence of psychiatric comorbidity) were identified as the strongest covariates of the DS-PTSD (e.g., Hansen et al., 2017).

For the assessment of the cross-cultural validity of DS-PTSD, demographic and clinical data (TE, stress coping, depressivity, suicidality, and spirit possession phenomena) were collected. It was expected that the DS-PTSD would be highly related to sexual TE, high intensity of psychopathology (i.e., high severity of PTSD and depressivity), high functional impairment as well as avoidant stress coping.

Paper 3 deals with interrelations between the endocrine and the psychological stress response parameters. The aims of this paper were first, analogue to Zaba et al. (2015) and **Paper 1**, to analyze HPA-axis reactivity to TE, PTSD, and dissociative symptom assessments and to identify HPA-axis reactivity subtypes by stratifying phasic sCORT levels; second; to measure tonic, long-term HPA-axis function by analyzing CORT, cortisone, and dehydroepiandrosterone (DHEA) concentrations in hair samples and relate them to phasic sCORT levels; third, to explore the association of psychological stress-related factors (i.e., TE, PTSD, and dissociative symptoms) with both phasic (as measured in saliva samples) and tonic (as measured in hair samples) HPA-axis activity.

DHEA, another hormone released in response to stress, so far has received relatively little attention regarding the analysis of its altered levels being potentially associated with TE and

PTSD (Kroboth, Salek, Pittenger, Fabian, & Frye, 1999). Recent meta-analytic findings revealed higher DHEA levels in tHC compared to ntHC as well as trendwise higher DHEA levels in PTSD compared to ntHC (van Zuiden et al., 2017). Along with Walker and colleagues (2017), it may be concluded that in-parallel assessment of several stress response markers (sCORT and hCORT as well as cortisone and DHEA hair levels) could provide a more detailed picture on the relationship between TE, PTSD and the HPA-axis function.

In summary, this dissertation aims to further elucidate mechanisms of psychobiological stress processing with a particular focus on endocrine stress reactivity, dissociative symptoms and stress coping. **Paper 1** analyses HPA-axis stress reactivity to a psychological stress challenge test, the TSST, and focuses on dissociative symptomatology as a potential modulator of the stress response in PTSD patients and trauma exposed individuals. The major aim of **Paper 2** is to identify and characterize the DS-PTSD in a non-Western population and to provide evidence of the cross-cultural validity of this relatively novel diagnostic entity. Finally, **Paper 3** analyses several measures of the HPA-axis activity in order to shed light on the relationships between phasic/tonic CORT levels and TE, PTSD, stress coping and dissociative symptomatology.

2. PAPER 1

Dissociative symptoms but not trauma exposure or PTSD symptoms are decisive for HPA-axis blunting in female PTSD patients

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2.1 ABSTRACT

Background: In female PTSD patients, with the Trier Social Stress Test (TSST), we previously identified two hypothalamus-pituitary-adrenal (HPA)-axis reactivity subgroups: PTSD responders (PTSD-R) and non-responders (PTSD-NR). Here, we aimed to replicate the identification of the HPA-axis subgroups in a new PTSD sample, to provide their further clinical characterization, to search for their predictors as well as to elucidate the role of trauma exposure *per se* for psychobiological stress response.

Method: Female PTSD patients (n = 43, from them 23 as published in Zaba et al. (2015) and 20 newly recruited) and age-matched groups of non-traumatized (ntHC, n = 22) and traumatized (tHC, n = 23) female healthy controls were subjected to the TSST. Several psychological (i.e., subjective stress, mood state, and acute dissociation) and endocrine (i.e., blood cortisol and adrenocorticotropin, ACTH) stress reactivity measures were collected. Additionally, the presence and intensity of dissociative symptoms and dissociation-related phenomena (stress coping, sleep difficulties, fear of death and dying, and absorption) were analyzed. Finally, a binary logistic regression analysis was run to predict the HPA-axis subgroup status in female PTSD patients.

Results: We repeatedly identified two HPA-axis reactivity subgroups in female PTSD patients (PTSD-R, n = 19, and PTSD-NR, n = 24). Moreover, we provided further evidence for elevated dissociative symptoms and dissociation-related phenomena (sleep difficulties and fear of death and dying) in PTSD-NR as compared to PTSD-R. In PTSD, high levels of trauma-related dissociative symptoms predicted a blunted HPA-axis reaction in response to the TSST. Moreover, non-pathological forms of dissociation were elevated in tHC as compared to ntHC, although post-TSST cortisol and ACTH blood levels were higher in tHC than in ntHC.

Conclusions: In female PTSD patients, neither trauma exposure nor PTSD symptom severity *per se* may be decisive for the HPA-axis regulation. Instead, our findings suggest that dissociative symptoms may contribute to HPA-axis blunting. In HC, trauma exposure *per se* goes along with dysregulated HPA-axis activity as well as elevation of non-pathological dissociative tendencies (absorption). More studies are needed on the causal link between trauma exposure, dissociation and HPA-axis dysregulations.

2.2 INTRODUCTION

Posttraumatic stress disorder (PTSD) develops following an exposure to a traumatic stressor, i.e. witnessed or direct experience of threatened death, serious injury or sexual violence (American Psychiatric Association, 2013). Although trauma exposure (TE) is common (worldwide over 70%), only a subset of exposed individuals (7-12%) suffers from PTSD (e.g., Breslau, 2009; Kessler et al., 2017). This suggests that for PTSD development psychobiological processing of TE is more important than TE *per se* (Bandelow et al., 2017; Walker et al., 2017). However, in severe traumatized populations, PTSD reaches prevalence of almost 100% suggesting that any individual may develop PTSD once TE is extremely high (Conrad et al., 2017; Kolassa et al., 2010; Neuner et al., 2004). Understanding the way TE affects body and mind may help to improve clinical outcomes of the sufferers and to reduce the large individual and societal burden of PTSD (e.g., Bernardy & Friedman, 2015; Jonas et al., 2013; Visser, Gosens, Den Oudsten, & De Vries, 2017).

Manifestation of PTSD can be seen as a pathological response to extreme stress being outside the range of usual human experience. For this reason, there is a long tradition of studying the hypothalamus-pituitary-adrenal (HPA)-axis, the body's major neuroendocrine stress response system, dysregulations in the context of TE and PTSD research. Under psychological or physiological stress exposure, a cascade of hormones is released in the brain and periphery with glucocorticoid hormones (among them cortisol, CORT, in humans) produced in the adrenal cortex acting through negative feedback on pituitary shutting down the stress response (de Kloet, Joëls, & Holsboer, 2005). Pre-, peri-, and post-trauma measurements of CORT both baseline and under pharmacological (e.g., dexamethasone suppression test, DST, Menke et al., 2012) or psychological challenge tests (e.g., Trier Social Stress Test, TSST, Kirschbaum et al., 1993) have been broadly used as indicators of HPA-axis dysregulations (e.g., Olff & van Zuiden, 2017).

Generally, low baseline levels of CORT as well as HPA-axis blunting following stress exposure resulting from enhanced negative feedback of CORT have been hypothesized to be characteristic for TE and PTSD (Yehuda, 2005). Conform with this hypothesis, some studies were able to find low levels of pre-trauma baseline CORT and low CORT stress reactivity to be predictive for the subsequent PTSD development (Steudte-Schmiedgen et al., 2015b; van Zuiden, Kavelaars, Geuze, Olff, & Heijnen, 2013) as well as low levels of baseline and reactive

CORT in trauma exposed individuals and in those suffering from PTSD (Carpenter et al., 2007; Morris et al., 2012; Pierrehumbert et al., 2009; Pan et al., 2018). Contrary to this hypothesis, many studies, including meta-analyses, have failed to repeat these findings. In detail, they revealed either no differences in basal (Klaassens, Giltay, Cuijpers, van Veen, & Zitman, 2012; Meewisse, Reitsma, de Vries, Gersons, & Olff, 2007) and in reactive CORT levels between PTSD and HC (Roelofs et al., 2009; Simeon et al., 2007), or higher basal CORT concentrations (Inslicht et al., 2006; Lindley, Carlson, & Benoit, 2004) as well as reactive hyper-responsiveness to be related to TE and/or PTSD (Gola et al., 2012; Stoppelbein, Greening, & Fite, 2012).
It has been suggested that these inconsistencies may be grounded in basal demographic variables such age (e.g., Morris, Hellman, Abelson, & Rao, 2016b) and gender (e.g., Meewisse et al., 2007), in characteristics of TE with early life trauma (ELT) being more devastating for HPA-axis functionality than adult trauma (AT) (e.g., Frodl & O'Keane, 2013) as well as in prevalence of PTSD-associated phenomena such as psychiatric comorbidity (e.g., Young & Breslau, 2004) and dissociative symptoms (e.g., Simeon et al., 2008).

In our recent work, we addressed some of these inconsistencies by analyzing individual response rates of studied individuals and providing clinical characterization of identified subgroups (Zaba et al., 2015). In the TSST (Kirschbaum et al., 1993), an established methodology to induce stress in humans (Allen, Kennedy, Cryan, Dinan, & Clarke, 2014), we identified two HPA-axis reactivity subgroups among female PTSD patients: HPA-axis responders and non-responders. Non-responders (defined as response rate lower than 15.5% following stress exposure, Miller et al., 2013) were more frequently represented among PTSD patients than in a studied control group of female non-traumatized healthy controls (ntHC) (56.52% in PTSD vs. 11.11% in ntHC). Moreover, blunted HPA-axis response was associated with high TE, trauma-related dissociative symptoms, and high psychiatric comorbidity, especially with anxiety disorders. Interestingly, supporting our results and using the same methodology, another recent publication showed response rate in female PTSD patients to be at 43.50% and also to negatively correlate with dissociative symptoms (Wichmann et al., 2017). These striking results suggest that considering individual CORT response rates as well as PTSD-associated phenomena such as psychiatric comorbidity and dissociative symptoms may account for some of the unexplained variance in research on psychobiological stress response related to TE and/or PTSD.

A strong link between dissociation and TE (Frewen et al., 2015; van Dijke et al., 2015; Vonderlin et al., 2018), also between non-pathological forms of dissociation, such as absorption (i.e., involvement in mental imaginary) and daydreaming (e.g., Soffer-Dudek, 2017), and TE, has been repeatedly documented. However, little is known how this link relates to the HPA-axis function. Researches usually focused on TE and/or PTSD-related effects on HPA-axis dysregulations but unfortunately they set assessments of dissociative symptomatology aside. Very few reports on dissociation and HPA-axis reactivity showed both hypo- or hyperresponsiveness to stress under high levels of dissociation. In detail, Simeon and colleagues (2008) found high levels of dissociation to be related to low levels of CORT in trauma exposed individuals. On the contrary, Giesbrecht and colleagues (2007) found dissociation subscales to relate to stress response in a different way: trait depersonalization/derealization was found to be related with increased psychological and biological stress response (CORT levels), whereas absorption tendencies were found to be related to lower levels of CORT in healthy undergraduate students (Giesbrecht et al., 2007).

In this study, we aimed to extend our previous results (Zaba et al. 2015): first, by repeating the finding of PTSD responders and non-responders identification in an independent cohort of female PTSD patients; second, by providing further clinical characterization of the HPA-axis hypo-responsiveness and identifying its significant predictor(s) in PTSD; and third, since our previous study was limited by including exclusively ntHC, here we present data on psychobiological stress reactivity, using the same methodology of standardized psychological stress induction via TSST, in three groups: female PTSD patients, ntHC and additionally in tHC without lifetime PTSD history. By doing so we aimed to explain the role of TE *per se* for HPA-axis dysregulations.

Considering the further clinical characterization of the HPA-axis hypo-responsiveness and its prediction in PTSD, we were interested especially in a thorough assessment of dissociative symptomatology and dissociation-related phenomena. Our previous study (Zaba et al., 2015) was limited by measuring dissociation based exclusively on self-report. In this paper, we report on dissociative symptoms as assessed with an additional self-report instrument (full version of the Dissociative Experiences Scale, DES, Spitzer, Stieglitz, & Freyberger, 2005) and also with a clinician-based interview (Structured Clinical Interview for Dissociative Disorder, SCID-D, Gast, Oswald, Zündorf, & Hofmann, 2000). As far as dissociation-related phenomena were concerned, we concentrated on factors being previously described to be associated with dissociation, such

as stress coping (e.g., Thomson & Jaque, 2017), fear of death and dying (Gershuny et al., 2003), sleep difficulties (e.g., Selvi et al., 2017), and psychological absorption (Giesbrecht et al., 2008).

In summary, we hypothesized stress response rates to be the lowest in PTSD patients as compared to both ntHC and tHC. We assumed that CORT non-responders will be most represented among PTSD patients. Furthermore, we expected that stress response rates of tHC will be lower than that of ntHC but higher than that of PTSD patients. Moreover, we hypothesized high levels of dissociation and psychiatric comorbidity as well as high trauma load to be significant predictors of HPA-axis blunting following stress induction.

2.3 METHODS

2.3.1 Participants

PTSD patients. As described in Zaba et al. (2015), we previously studied 23 female PTSD patients (TSST1). In this paper, we present data from 20 newly recruited female PTSD patients (TSST2) as well as from the fused sample (TSST1+TSST2). All individuals were recruited at the former outpatient trauma unit of the Max Planck Institute of Psychiatry in Munich, Germany. Inclusion and exclusion criteria, as described in detail in Zaba et al. (2015), were applied. In summary, we excluded patients with acute suicidality, past or acute psychotic symptoms, acute substance disorders, being pregnant or breastfeeding. For the inclusion to the study, patients needed to score above 45 on the Clinician Administrated PTSD-Scale (CAPS, Schnyder & Moergeli, 2005). TSST1 sample was described in detail in Zaba et al. (2015). In the TSST2 sample, the PTSD severity was on average at 78.90 (SD = 22.21) indicating severe PTSD symptoms. Five patients (25%) received no medication, six (30%) were treated with antidepressants, four (20%) were given antidepressants and neuroleptics, five (25%) underwent a combined pharmacotherapy. The sample was characterized by high psychiatric comorbidity: on average, PTSD patients reported M = 2.50 (SD = 2.12) comorbid and M = 3.78 (SD = 2.60) lifetime psychiatric disorders. The most frequent diagnoses were from anxiety (11 patients suffering from comorbid and 1 from lifetime anxiety disorders) and affective (10 patients suffering from comorbid and 4 from lifetime episode of MD) spectra of psychiatric disorders; six patients met DSM-IV criteria for a lifetime substance disorder. In contrast to our previous study, we included five (11.63%) participants taking hormonal contraceptives and controlled for their usage in the statistical analyses. For details on demographic and clinical data of TSST2 sample, see **Table 2.1**.

Healthy controls. Moreover, we studied 45 female, medically healthy, free from any medication, and any type of psychopathology in their lifetime, controls. 22 were not traumatized and 23 had a history of trauma. HC were recruited in Munich by advertisement; pregnancy and breastfeeding were considered as exclusion criteria. Fifteen (34.88%) participants used hormonal contraceptives. For details see **Table 2.1**.

2.3.2 Clinical interviews and self-report measures

Clinical interviews. In all participants, TE as well as comorbid and lifetime psychiatric disorders according to DSM-IV criteria (American Psychiatric Association, 2000) were assessed with a standardized interview, the Munich Composite International Diagnostic Interview (M-CIDI, Wittchen & Pfister, 1997). In PTSD patients and tHC, the severity of PTSD symptoms were measured with a structured interview, the CAPS (Schnyder & Moergeli, 2005). In all HC and in the TSST2 sample, we additionally assessed severity of dissociative symptoms, derealization and depersonalization (American Psychiatric Association, 2013), with the Structured Clinical Interview for Dissociative Disorders (SCID-D, Gast, Oswald, Zündorf, & Hofmann, 2000).

Self-report measures. In all participants, based on self-report, we collected data on depressive symptoms employing the Beck Depression Inventory (BDI, Hautzinger, Bailer, Worall, & Keller, 1995), on anxiety trait and state symptoms with the State-Trait Anxiety Inventory (STAI, Laux, Glanzmann, Schaffner, & Spielberger, 1981), on dissociative symptoms with the Dissociative Experience Scale (DES, Spitzer, Stieglitz, & Freyberger, 2005), and on stress coping strategies with the German Stress Coping Questionnaire (SVF-78, Erdmann & Janke, 2008). Additionally, in the TSST2 sample and in all HC, in order to assess phenomena being previously shown to be associated with dissociation: sleep quality, fear of death and dying, and absorption, we employed the Sleep Questionnaire for the last night (SF-A) and the last two weeks (SF-B) (Görtelmeyer, 2011), three subscales (fear of postmortal processes, fear of process of dying, and fear of finiteness of life) from the Fear of Death and Dying Questionnaire (FVTS, Ochsmann, 1993), and the Tellegan Absorption Scale (TAS, Ritz & Dahme, 1995), respectively. Moreover, in PTSD and tHC, we assessed coping with the traumatic event with three subscales (rumination, avoidance, and dissociation) from the Response to Intrusions Questionnaire (RIQ, Ehlers, 1999).

Throughout the TSST, psychological stress perception was assessed with the Visual Analogue Scale (VAS) measuring subjectively perceived stress (e.g., Smyth et al., 1998; Zaba et al., 2015), the Zerssen Mood Scale (Bf-S) assessing mood state (von Zerssen, 1976; von Zerssen & Petermann, 2011), and the Dissociation-Tension-Scale acute (DSS-acute) measuring acute dissociative symptoms (Stiglmayr, Braakmann, Haaf, Stieglitz, & Bohus, 2003).

2.3.3 Laboratory analyses

As previously described in detail in Zaba et al. (2015), quantification of serum CORT and plasma adrenocorticotropin (ACTH) concentrations were performed with an electrochemiluminescence immunoassay.

2.3.4 Study procedures

The study procedures were approved by the local Ethic Committee of the Ludwig Maximilians University in Munich and shown schematically in the **Figure 2.1**. After written informed consent was obtained, participants underwent thorough baseline assessments (Day1): clinical interviews (M-CIDI, CAPS, and SCID-D) were conducted and the morning blood sample (at 9:00am) was collected. Self-report questionnaires (BDI, STAI, DES, SVF-78, SF-A, SF-B, FVTS, TAS, and RIQ) were given to the participants, filled out by them at home, and brought back at the second assessment day (Day2), which was set not later than two weeks following baseline assessments. At the second assessment day, participants were examined between 12:30pm and 5:00pm (note that TSST1 sample was studied between 12:30pm and 3:30pm as published in Zaba et al., (2015), therefore in the fused sample TSST1+TSST2 only the three first measurements are analyzed since they were identical in both samples). At the beginning, sensors were fixed for the psychophysiological measures (heart rate and skin conductance) depressive and state anxiety symptoms were assessed with BDI and STAI, respectively. Blood was collected via a catheter from a cubital vein 30 min before (-30min) as well as 10 (+10min), 35 (+35min) and 180 (+180min) after stress exposure, prior to blood collection heart rate and blood pressure were measured using the hand wrist device Boso Medistar® (Bosch & Sohn, Jungingen, Germany). Note that collected data on psychophysiological measures as well as cardiovascular stress reactivity will be published separately. Subjective stress perception, mood state, and acute dissociative symptoms were assessed with the VAS, Bf-S, and DSS-acute, respectively, either prior or immediately following the blood sampling. Between 2:00pm and 2:15pm participants were subjected to a laboratory psychosocial stressor, the Trier Social Stress Test (TSST, Kirschbaum, Pirke, & Hellhammer, 1993). In the TSST, subjects took part in a simulation of a job interview, had to deliver a speech (5min) and solve an arithmetic task of medium difficulty (5min) in front of a committee of two strangers. This protocol has repeatedly been shown to induce moderate stress levels in humans (e.g., Allen et al., 2014). Before and two times after stress exposure, we conducted short (5min) cognitive assessments; these data will be published elsewhere.

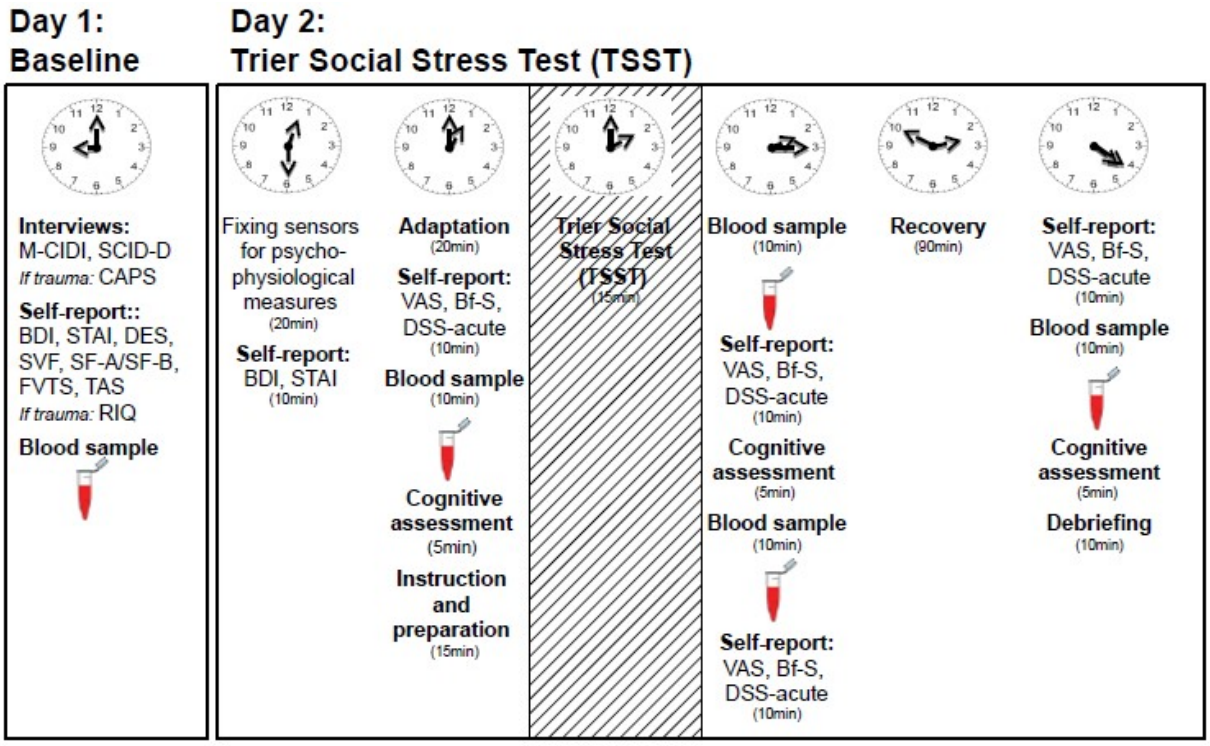


Figure 2.1. *Schematic visualization of the study procedures*

Note. On Day 1, thorough baseline evaluation was conducted. No later than two weeks following the baseline assessments, participants were subjected to the Trier Social Stress Test (TSST), Day 2. For details, see Method section of the paper. Tubes symbolize blood collection as well as heart rate and blood pressure assessment. Abbreviations: M-CIDI, Munich Composite International Diagnostic Interview; SCID-D, Structured Clinical Interview for Dissociative Disorder; CAPS, Clinician Administrated PTSD Scale; BDI, Beck Depression Inventory; STAI, State-Trait Anxiety Inventory; DES, Dissociative Experiences Scale; SVF, German Stress Coping Questionnaire; SF-A, Sleep Questionnaire for the last night; SF-B, Sleep Questionnaire for the last two weeks; FVTS, Fear of Death and Dying Questionnaire; TAS, Tellegan Absorption Scale; RIQ, Response to Intrusions Questionnaire; VAS, Visual Analogue Scale; Bf-S, Zerssen Mood Scale; DSS-acute, Dissociation-Tension-Scale acute; TSST, Trier Social Stress Test.

2.3.5 Statistical analyses

Normal distribution of studied variables was tested with the Kolmogorov-Smirnov test. Outliers were detected with the Grubbs test and removed from subsequent analyses. Group differences were calculated: in continuous, normally distributed variables with one-way ANOVA; in ordinal and/or skewed variables with the Mann-Whitney-U-test (upon analyses of two groups), or with

the Kruskal-Wallis-test (upon analyses of three groups), and in categorical variables with the Chi-squared test two-tailed (**Table 2.1**, **Table 2.2**, **Table 2.3**, **Supplement Table 2.1**). Data on endocrine and psychological stress reactivity throughout the TSST were assessed with the two-way ANOVA with repeated measures followed by Bonferroni corrections (**Figure 2.3**, **Supplement Figure 2.1**). If assumptions of sphericity were violated, Greenhouse-Geisser corrections were applied. The interrelations between variables were calculated with Pearson or in categorical and/or in skewed variables with Spearman correlational coefficients (**Supplement Table 2.2**). Prediction of the HPA-axis response status was performed with a binary logistic regression analysis with backward stepwise elimination method. Metric variables were centered and standardized before entering into the model (**Table 2.4**). If not stated differently, all data are presented as mean ± SEM.

2.4 RESULTS

2.4.1 Demographic and clinical characteristics

First, we describe demographic and clinical characteristics of the newly recruited PTSD patients (TSST2, n = 20) as well as studied ntHC (n = 22) and tHC (n = 23) (**Table 2.1**). Note that demographic and clinical data of TSST1 sample were published in Zaba et al. (2015). No differences in age and ovarian cycle between the groups were found. Trendwise more smokers were represented among PTSD patients. Although the number of traumatic events did not differ between PTSD patients and tHC, PTSD patients experienced more sexual as well as trendwise more early life trauma than tHC. As expected, PTSD patients reported employment of more negative (i.e., escape or rumination) and less positive coping strategies (i.e., downplaying or denial of guilt), more PTSD, depressive, anxiety, and dissociative symptomatology as well as worse sleep characteristics than both HC groups. Interestingly, PTSD patients reported more fear of postmortal processes than both HC groups, whereas no differences in fear of process of dying and in fear of finiteness of life were found. Moreover, ntHC had lower levels of absorption as measured by the TAS than both PTSD and tHC. For statistical details, see **Table 2.1**.

2.4.2 Repeated identification of two HPA-axis reactivity endophenotypes in female PTSD patients

Next, as in Zaba et al. (2015), in order to distinguish between CORT responders and non-responders in the TSST, we applied the method described in Miller, Plessow, Kirschbaum, & Stalder (2013), defining CORT response as 15.5% increase of CORT levels following stress induction. According to this classification, the responder rates were: 45% (*n* = 9) in the newly studied sample of PTSD patients (TSST2), 44.19% (*n* = 19) in the fused PTSD sample (TSST1+TSST2), 77.27% (*n* = 17) in ntHC, and 69.57% (*n* = 16) in tHC. Consequently, the responder rate was lower in PTSD patients than in both HC cohorts (TSST2: $\chi^2(2, n = 65) = 5.15$, $p = .076$; TSST1+TSST2: $\chi^2(2, n = 88) = 8.00$, $p = .018$, **Figure 2.2**).

Table 2.1. *Demographics and clinical characteristics of PTSD patients (TSST2, n = 20), traumatized (tHC, n = 23) and non-traumatized healthy controls (ntHC, n = 22)*

	PTSD patients TSST2 (*n* = 20) Mean ± SD	**Controls without trauma** (*n* = 22) Mean ± SD	**Controls with trauma** (n = 23) Mean ± SD	**Statistical test details**	**Post-hoc analyses**
Age (years)	34.25 ± 12.41	33.18 ± 8.81	36.91 ± 9.98	F(2, 64) = .76, p = .470	-
Number of smokers	7	2	3	**χ^2(2, *n* = 65) = 5.37, p = .068**	-
Medication (no/antidepressants/ antidepressants with neuroleptics/combination therapy)	5/6/4/5	-	-	-	-
Ovarian cycle (follicular/ovulation/luteal/menopause/ hormonal contraceptives)	4/0/9/2/5	3/3/9/0/7	6/1/6/2/8	χ^2(8, *n* = 65) = 7.83, p = .451	-
Number of traumata	2.50 ± 1.20	-	2.48 ± 1.47	U = 197.500, p = .796	-
Trauma age (early life/adulthood/ early life and adulthood)	7/5/8	-	2/12/9	**χ^2(2, *n* = 43) = 5.54, p = .063**	-
Trauma type (sexual/non-sexual/both)	3/2/15	-	0/18/5	**χ^2(2, *n* = 43) = 20.69, p < .001**	-
Coping strategies (*SVF-78 subscales*) :					
Downplaying	5.79 ± 4.49	11.86 ± 3.50	11.96 ± 3.69	**F(2, 62) = 16.45, p < .001**	P/ntHC P/tHC
Denial of guilt	7.95 ± 5.16	12.71 ± 2.63	11.87 ± 2.46	**F(2, 62) = 10.25, p < .001**	P/ntHC P/tHC
Distraction	13.21 ± 3.81	14.33 ± 3.38	14.48 ± 3.62	F(2, 62) = .74, p = .479	-
Substitute gratification	7.53 ± 2.46	10.71 ± 4.21	10.91 ± 5.17	**F(2, 62) = 4.19, p = .021**	P/tHC
Situation control	12.16 ± 5.27	15.95 ± 4.20	17.39 ± 3.73	**F(2, 62) = 7.69, p = .001**	P/ntHC P/tHC
Reaction control	16.42 ± 4.21	14.87 ± 3.34	16.00 ± 4.25	F(2, 62) = .85, p = .431	-
Positive self-instruction	11.05 ± 5.21	17.24 ± 3.43	18.70 ± 3.60	**F(2, 62) = 19.72, p < .001**	P/ntHC P/tHC
Need for social support	10.00 ± 5.68	15.10 ± 5.06	15.70 ± 4.52	**F(2, 62) = 7.90, p = .001**	P/ntHC P/tHC
Avoidance	15.11 ± 6.07	11.48 ± 4.42	11.57 ± 4.63	**F(2, 62) = 3.35, p = .042**	-
Escape	18.11 ± 4.84	7.29 ± 2.92	6.78 ± 2.32	**F(2, 62) = 67.66, p < .001**	P/ntHC P/tHC

Table 2.1. (continued)

	PTSD patients TSST2 (*n* = 20) Mean ± SD	**Controls without trauma** (*n* = 22) Mean ± SD	**Controls with trauma** (n = 23) Mean ± SD	**Statistical test details**	**Post-hoc analyses**
Rumination	17.89 ± 4.36	10.81 ± 4.19	9.78 ± 2.89	**F(2, 62) = 26.77, p < .001**	P/ntHC P/tHC
Resignation	14.11 ± 5.02	5.62 ± 3.31	5.00 ± 2.58	**F(2, 62) = 37.89, p < .001**	P/ntHC P/tHC
Self-blame	15.21 ± 8.10	8.10 ± 4.19	8.13 ± 2.82	**F(2, 62) = 16.25, p < .001**	P/ntHC P/tHC
Depression (BDI)	26.65 ± 9.58	.62 ± .74	2.14 ± 2.62	**χ^2(2, *n* = 63) = 43.07, p < .001**	-
Anxiety Trait (STAI)	59.42 ± 8.09	28.05 ± 4.06	31.48 ± 5.04	**F(2, 62) = 170.70, p < .001**	P/ntHC P/tHC
Anxiety State (STAI)	51.50 ± 11.08	31.41 ± 5.29	33.00 ± 7.47	**F(2, 62) = 38.69, p < .001**	P/ntHC P/tHC
Dissociation (*DES subscales*):					
Amnesia	10.90 ± 11.76	.56 ± .86	1.14 ± 1.44	**χ^2(2, *n* = 60) = 33.25, p < .001**	-
Absorption	32.34 ± 20.69	3.97 ± 2.82	8.03 ± 4.91	**F(2, 60) = 31.84, p < .001**	P/ntHC P/tHC
Derealization	21.93 ± 19.97	.08 ± .37	.83 ± 1.52	**χ^2(2, *n* = 61) = 41.03, p < .001**	-
Conversion	21.40 ± 18.60	.06 ± .25	.86 ± 2.11	**χ^2(2, *n* = 61) = 43.91, p < .001**	-
Sleep characteristics (*SF-A last night*):					
Sleep quality	2.30 ± .88	4.41 ± .40	4.09 ± .47	**F(2, 62) = 70.90, p < .001**	P/ntHC P/tHC
Psychological well-being before sleeping	2.15 ± .82	4.13 ± .54	3.89 ± .55	**F(2, 61) = 56.38, p < .001**	P/ntHC P/tHC
Psychological exhaustion before sleeping	3.22 ± .79	2.46 ± .61	2.85 ± .66	**F(2, 62) = 6.21, p = .004**	P/ntHC
Psychosomatic symptoms during sleep	1.86 ± .47	1.09 ± .17	1.11 ± .18	**χ^2(2, *n* = 63) = 37.93, p < .001**	-
Sleep characteristics (*SF-B last two weeks):*					
Sleep quality	2.29 ± .79	4.06 ± .58	3.58 ± .74	**F(2, 58) = 32.57, p < .001**	P/ntHC P/tHC
Psychological well-being before sleeping	2.11 ± 4.20	4.20 ± .56	3.89 ± .62	**F(2, 62) = 75.81, p < .001**	P/ntHC P/tHC
Psychological exhaustion before sleeping	4.26 ± .55	3.12 ± .87	3.35 ± .68	**F(2, 61) = 13.66, p < .001**	P/ntHC P/tHC
Psychosomatic symptoms during sleep	2.60 ± .62	1.26 ± .32	1.29 ± .30	**χ^2(2, *n* = 62) = 35.94, p < .001**	-
Fear of death and dying (*FVTS subscales*):					
Fear of postmortal processes	14.74 ± 3.36	10.90 ± 2.68	11.18 ± 3.06	**F(2, 61) = 9.76, p < .001**	P/ntHC P/tHC
Fear of process of dying	19.00 ± 5.02	19.38 ± 3.85	18.74 ± 3.17	F(2, 62) = .14, p = .869	-

Table 2.1. (continued)

	PTSD patients TSST2 (*n* = 20) Mean ± SD	**Controls without trauma** (*n* = 22) Mean ± SD	**Controls with trauma** (n = 23) Mean ± SD	**Statistical test details**	**Post-hoc analyses**
Fear of finiteness of life	14.79 ± 3.91	13.43 ± 3.47	13.70 ± 2.62	F(2, 62) = .93, p = .402	-
Absorption (TAS)	46.26 ± 22.15	25.57 ± 15.72	45.30 ± 26.84	**F(2, 62) = 5.78, p = .005**	P/ntHC ntHC/tHC
PTSD severity (CAPS)	78.90 ± 22.21	-	.88 ± 2.00	**U = .000, p < .001**	-
CAPS subscales:					
Re-experiencing	26.80 ± 8.66	-	.00 ± .00	**U = .000, p < .001**	-
Avoidance	30.65 ± 12.39	-	.32 ± 1.25	**U = 1.000, p < .001**	-
Hyperarousal	21.45 ± 7.81	-	.00 ± .00	**U = .000, p < .001**	-
RIQ subscales:					
Rumination	2.29 ± .63	-	1.50 ± .65	**F(1, 40) = 23.52, p < .001**	-
Avoidance	2.41 ± .51	-	1.82 ± .62	**F(1, 40) = 10.77, p = .002**	-
Dissociation	1.95 ± .59	-	1.22 ± .27	**U = 50.000, p < .001**	-
Comorbid and lifetime disorders (*M-CIDI*):					
Comorbid major depression (current/past)	10/4	-	-	-	-
Comorbid anxiety disorders (current/past)	11/1	-	-	-	-
Comorbid substance disorders (current/past)	0/6	-	-	-	-
Comorbid disorders	2.50 ± 2.12	-	-	-	-
Lifetime disorders	3.78 ± 2.60	-	-	-	-

Note. Group differences were calculated with: one-way ANOVA; Mann-Whitney-U-test, Kruskal-Wallis-test or Chi-squared test two-tailed, appropriate to test requirements. Shown are: Fisher test (F), U value (U), or results of Chi-squared test (χ^2), respectively. For details see Methods section. Significant or trendwise significant results are marked in bold. Abbreviations: SD, standard deviation; SVF-78, Stress Coping Questionnaire; BDI, Beck Depression Inventory; STAI, State-Trait Anxiety Inventory; DES, Dissociative Experiences Scale; SF-A, Sleep Questionnaire, Version A for the last night; SF-B, Sleep Questionnaire, Version B for the last two weeks; FVTS, Fear of Death and Dying Questionnaire; TAS, Tellegan Absorption Scale; CAPS, Clinician Administrated PTSD Scale; RIQ, Response to Intrusions Questionnaire; M-CIDI, Munich Composite International Diagnostic Interview; P/ntHC, post-hoc effect PTSD versus (vs.) ntHC; P/tHC, post-hoc effect PTSD vs. tHC; ntHC/tHC, post-hoc effect tHC vs. ntHC. Following outliers were identified: SVF-78: one PTSD; BDI, one ntHC, one tHC; DES amnesia: one PTSD, one ntHC, one tHC; DES absorption: one ntHC, one tHC; DES derealization: one tHC, one

ntHC; DES conversion, one ntHC, one tHC; SF-A, one ntHC; SF-B, one PTSD; CAPS avoidance; one tHC; CAPS hyperarousal: one tHC.

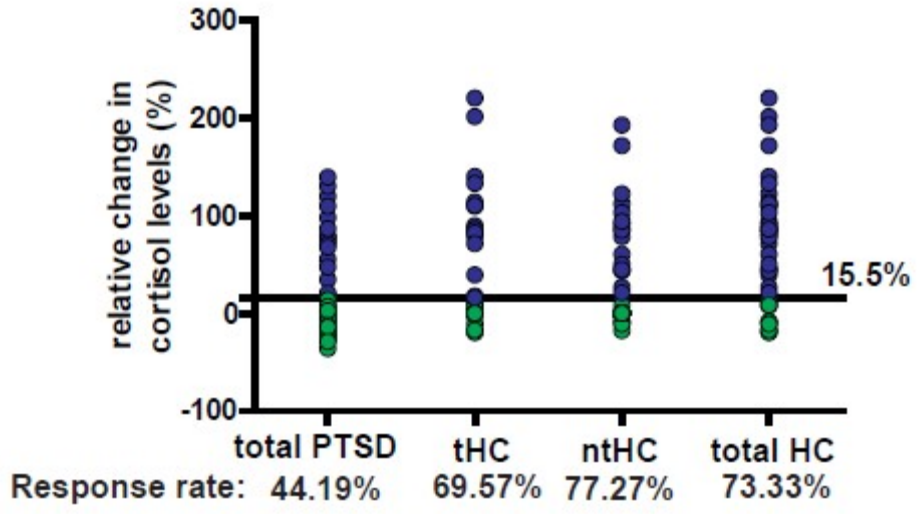


Figure 2.2. *Classification of cortisol responders and non-responders to the TSST*

Note. Cortisol responders (blue) and non-responders (green) were classified based on 15.5% cut-off criterion (Miller et al. 2013; Zaba et al. 2015). Abbreviations: PTSD, posttraumatic stress disorder; tHC, traumatized healthy controls; ntHC, non-traumatized healthy controls. Outliers: one PTSD.

Repeating the results from Zaba et al. (2015), the newly studied PTSD-R and PTSD-NR exhibited no differences in basal morning CORT levels ($F(1, 19) = .845$, $p = .370$, **Supplement Figure 2.1A**) while showing two different endocrine stress reactivity patterns (responders and non-responders) (CORT: Time: $F(1.86, 31.55) = 12.22$, $p < .001$; Time x Group: $F(1.86, 31.55) = 8.95$, $p = .001$, **Supplement Figure 2.1B**; ACTH: Group: $F(1, 15) = 7.12$, $p = .018$; Time: $F(1.66, 24.79) = 10.34$, $p = .001$; Time x Group: $F(1.65, 24.79) = 8.53$, $p = .002$, **Supplement Figure 2.1C**) without any differences in psychological stress reactivity between them (**Supplement Figure 2.1D-F**). Contrary to Zaba et al. (2015), although PTSD-NR showed stress-induced CORT blunting, the general levels of CORT throughout the TSST were not lower than that of PTSD-R (**Supplement Figure 2.1B**). Following, the analyses of basal CORT as well as reactive CORT and ACTH levels were controlled for ovarian cycle and usage of

hormonal contraceptives. The main results did not change but the highest CORT levels, both baseline ($F(1, 20) = 14.47$, $p = .001$) and in the TSST ($F(1, 16) = 6.09$, $p = .025$), were found in PTSD patients using hormonal contraceptives.

2.4.3 Demographic and clinical characteristics of PTSD responders and non-responders

As a next step, we compared demographic and clinical characteristics of PTSD-R and PTSD-NR in the newly studied sample (TSST2) as well as in the fused TSST1+TSST2 sample. In both samples, PTSD-R and PTSD-NR did not differ neither in age, smoking status, ovarian cycle, medication and number of traumata nor in the intensity of PTSD, depressive, and anxiety symptomatology (for statistical details of the TSST2 sample see **Supplement Table 2.1**, for the fused TSST1+TSST2 sample see **Table 2.2**). In the fused sample TSST1+TSST2, PTSD-NR showed higher trauma dose in terms of exposure to both ELT and adulthood trauma (AT). In both samples, PTSD-NR showed higher levels of trauma-related dissociation and avoidance than PTSD-R, as measured by the RIQ. In the M-CIDI, PTSD-NR from the TSST2 sample showed trendwise more comorbid psychiatric disorders, whereas those from the TSST1+TSST2 sample exhibited more comorbid as well as lifetime psychiatric disorders, especially considering anxiety disorders. Additionally, in the TSST2 sample, as measured with the SVF-78, PTSD-NR reported to employ more frequently coping strategies of reaction control and trendwise positive self-instruction than PTSD-R.

Moreover, **Table 2.3** presents further characterization of PTSD-R and PTSD-NR on dissociative symptoms and phenomena associated with dissociation (sleep quality, fear of death and dying, and absorption), which were additionally assessed in the TSST2 sample. PTSD-NR scored higher on depersonalization symptoms as measured with the SCID-D and reported trendwise more conversion symptoms as measured with the DES. Additionally, we found sleep indicators of PTSD-NR to be more disturbed as well as they reported higher fear of process of dying as compared to PTSD-R. No differences in absorption between PTSD-R and PTSD-NR were found (for statistical details see **Table 2.3**).

Table 2.2. *Demographics and clinical characteristics of PTSD responders (PTSD-R, n = 19) and non-responders (PTSD-NR, n = 24) in the fused TSST1+TSST2 sample*

	PTSD Responders (*n* = 19) Mean ± SD	**PTSD Nonresponders** (*n* = 24) Mean ± SD	**Statistical test details**
Age (years)	38.00 ± 13.11	37.58 ± 11.82	F(1, 42) = .012, p = .913
Number of smokers	6	10	χ^2(1, *n* = 43) = .462, p = .497
Medication (antidepressants/antidepressants with neuroleptics/combination therapy/benzodiazepine/no)	7/2/5/1/4	8/2/8/0/6	χ^2(4, *n* = 43) = 1.60, p = .809
Ovarian cycle (follicular/luteal/menopause/hormonal contraceptives)	4/10/3/2	6/10/5/3	χ^2(3, *n* = 43) = .526, p = .913
Number of traumata	2.74 ± 1.79	3.40 ± 1.79	U = 141.000, p = .157
Trauma age (early life/adulthood/ early life and adulthood)	7/9/3	5/6/13	**χ^2(2, *n* = 43) = 6.69, p = .035**
Trauma type (sexual/non-sexual/both)	10/2/7	9/6/9	χ^2(2, *n* = 43) = 1.75, p = .418
Coping strategies (SVF-78):			
Downplaying	6.42 ± 4.71	5.14 ± 4.58	F(1, 40) = .782, p = .382
Denial of guilt	7.74 ± 5.05	6.55 ± 5.31	F(1, 40) = .537, p = .468
Distraction	13.79 ± 4.18	13.77 ± 5.75	F(1, 40) = < .001, p = .992
Substitute gratification	7.74 ± 2.83	6.59 ± 3.62	F(1, 40) = 1.25, p .271
Situation control	12.21 ± 6.89	13.77 ± 3.74	F(1, 40) = .845, p = .364
Reaction control	14.74 ± 5.39	17.05 ± 4.08	F(1, 40) = 2.45, p = .127
Positive self-instruction	11.00 ± 6.12	11.91 ± 5.55	F(1, 40) = .249, p = .621
Need for social support	10.47 ± 6.92	10.64 ± 4.50	F(1, 40) = .008, p = .928
Avoidance	13.74 ± 5.84	15.91 ± 4.51	F(1, 40) = 1.80, p = .187
Escape	15.95 ± 7.06	17.64 ± 5.53	F(1, 40) = .737, p = .396
Rumination	18.16 ± 3.78	17.55 ± 4.36	F(1, 40) = .227, p = .636
Resignation	14.79 ± 6.72	14.18 ± 5.61	F(1, 40) = .100, p = .754
Self-blame	15.42 ± 7.04	15.91 ± 5.39	F(1, 40) = .063, p = .803
Depression (BDI)	21.05 ± 9.94	23.13 ± 9.75	F(1, 42) = .471, p = .496

Table 2.2. *(continued)*

	PTSD Responders (*n* = 19) Mean ± SD	**PTSD Nonresponders** (*n* = 24) Mean ± SD	**Statistical test details**
Anxiety Trait (STAI)	59.53 ± 9.80	57.00 ± 8.90	F(1, 41) = .765, p = .387
Anxiety State (STAI)	49.79 ± 10.98	53.79 ± 10.52	F(1, 42) = 1.48, p = .231
PTSD severity (CAPS)	73.05 ± 19.45	78.88 ± 19.09	F(1, 42) = .970, p = .330
CAPS subscales:			
Reexperiencing	23.89 ± 9.15	26.71 ± 7.17	F(1, 42) = 1.28, p = .264
Avoidance	27.11 ± 11.66	29.50 ± 11.64	F(1, 42) = .448, p = .507
Hyperarousal	21.47 ± 6.02	22.58 ± 8.30	F(1, 42) = .239, p = .627
Response to intrusions *(RIQ subscales):*			
Rumination	2.31 ± .56	2.29 ± .55	F(1, 40) = .012, p = .912
Avoidance	2.19 ± .46	2.50 ± .46	**F(1, 40) = 4.76, p = .035**
Dissociation	1.61 ± .38	2.23 ± .60	**F(1, 40) = 15.34, p < .001**
Comorbid and lifetime disorders (*M-CIDI*):			
Comorbid major depression (current/past)	6/5	11/3	χ^2(2, *n* = 40) = 1.65, p = .437
Comorbid anxiety disorders (current/past)	9/1	18/1	**χ^2(2, *n* = 40) = 4.92, p = .085**
Comorbid substance disorders (current/past)	0/5	0/9	χ^2(1, *n* = 40) = .750 p = .386
Comorbid disorders	1.24 ± 1.09	2.65 ± 1.23	**U = 68.500, p = .002**
Lifetime disorders	2.61 ± 1.69	4.33 ± 2.20	**U = 98.000, p = .009**

Note. Group differences were calculated with: one-way ANOVA; Mann-Whitney-U-test, or Chi-squared test two-tailed, appropriate to test requirements. Shown are: Fisher test (F), U value (U), or results of Chi-squared test (χ^2), respectively. For details see Methods section. Significant or trendwise significant results are marked in bold. Abbreviations: SD, standard deviation; SVF-78, Stress Coping Questionnaire; BDI, Beck Depression Inventory; STAI, State-Trait Anxiety Inventory; CAPS, Clinician Administrated PTSD Scale; RIQ, Response to Intrusions Questionnaire; M-CIDI, Munich Composite International Diagnostic Interview. Following outliers were identified: M-CIDI recent comorbidity: one PTSD-R and one PTSD-NR.

Table 2.3. *Dissociative symptoms and dissociation-related constructs in PTSD responders (PTSD-R, n = 9) and non-responders (PTSD-NR, n = 11) in the TSST2 sample*

	Responders (*n* = 9) Mean ± SD	**Nonresponders** (*n* = 11) Mean ± SD	**Statistical test details**
DES subscales:			
Amnesia	8.91 ± 5.96	8.19 ± 6.85	F(1, 16) = .052, p = .823
Absorption	33.70 ± 18.38	31.11 ± 23.50	F(1, 18) = .071, p = .794
Derealization	14.81 ± 14.10	28.33 ± 22.91	F(1, 18) = 2.33, p = .145
Conversion	13.95 ± 7.66	28.11 ± 23.11	**F(1, 18) = 3.06, p = .098**
SCID-D:			
Depersonalization (severity)	1.11 ± 1.05	2.20 ± 1.03	**F(1, 18) = 2.33, p = .036**
Derealization (severity)	0.44 ± 0.88	1.00 ± 1.15	U = 32.500, p = .233
SF-A (last night):			
Sleep quality	2.58 ± .85	2.06 ± .87	F(1, 18) = 1.74, p = .204
Psychological well-being before sleeping	2.62 ± .78	1.72 ± .62	**F(1, 18) = 7.91, p = .012**
Psychological exhaustion before sleeping	3.20 ± .84	3.24 ± .79	F(1, 18) = .011, p .916
Psychosomatic symptoms during sleep	1.84 ± .47	1.88 ± .49	F(1, 18) = .026, p = .874
SF-B (two weeks):			
Sleep quality	2.48 ± .57	2.13 ± .93	F(1, 17) = .889, p = .360
Psychological well-being before sleeping	2.20 ± .45	2.02 ± .62	F(1, 18) = .556, p .466
Psychological exhaustion before sleeping	3.83 ± .83	4.43 ± .55	**F(1, 18) = 3.41, p = .082**
Psychosomatic symptoms during sleep	2.28 ± .51	2.92 ± .57	**F(1, 17) = 6.28, p = .023**
FVTS subscales:			
Fear of postmortal processes	14.11 ± 3.82	15.30 ± 2.98	F(1, 18) = .578, p = .458
Fear of process of dying	16.33 ± 5.39	21.40 ± 3.34	**F(1, 18) = 6.22, p = .023**
Fear of finiteness of life	14.44 ± 5.10	15.10 ± 2.69	F(1, 18) = .127, p = .726
Absorption (TAS)	44.11 ± 23.80	48.20 ± 21.64	F(1, 18) = .154, p = .700

Note. Group differences were calculated with: one-way ANOVA, or Mann-Whitney-U-test, appropriate to test requirements. Shown are: Fisher test (F), or U value (U), respectively. For details see Methods section. Significant or trendwise significant results are marked in bold. Abbreviations: SD, standard deviation; DES, Dissociative Experiences Scale; SF-A, Sleep

Questionnaire, Version A for the last night; SF-B, Sleep Questionnaire, Version B for the last two weeks; FVTS, Fear of Death and Dying Questionnaire; TAS, Tellegan Absorption Scale. Following outliers were identified: DES amnesia, one PTSD-R and PTSD-NR.

2.4.4 Elevated CORT levels following stress in traumatized HC as compared to both PTSD patients and non-traumatized HC

Endocrine and psychological stress reactivity parameters were compared between the newly subjected ntHC and tHC with PTSD-R and PTSD-NR from the fused TSST1+TSST2 sample. Whereas we did not find any differences between the groups in the basal CORT levels collected in the morning (9:00am, $F(3, 85) = 1.23$, $p = .304$, **Figure 2.3A**), differences in the stress-induced CORT (Time: $F(1.46, 116.98) = 47.42$, $p < .001$; Group: $F(3, 80) = 9.37$, $p < .001$; Time x Group: $F(4.39, 116.98) = 13.26$, $p < .001$, **Figure 2.3B**) and ACTH (Time: $F(1.27, 99.98) = 75.28$, $p < .001$; Group: $F(3, 79) = 6.53$, $p = .001$; Time x Group: $F(3.80, 99.98) = 9.79$, $p < .001$, **Figure 2.3C**) levels were exhibited. As expected, in PTSD-NR, both the stress induced CORT and ACTH responses were missing, whereas interestingly tHC exhibited higher CORT response as compared to both groups of PTSD patients (PTSD-R and PTSD-NR) and ntHC. Controlling for hormonal contraceptives did not influence the group differences in CORT and ACTH levels. However, significant main effects of hormonal contraceptives were found upon the analysis of basal ($F(1, 86) = 19.63$, $p < .001$) as well as stress-induced $F(1, 79) = 6.36$, $p = .014$) CORT levels, in such a way that participants using hormonal contraceptives showed higher levels of CORT. In their psychological stress response, PTSD-R and PTSD-NR scored higher than both ntHC and tHC (subjective stress perception: Time: $F(2, 162) = 227.58$, $p < .001$; Group: $F(3, 81) = 15.73$, $p < .001$; Time x Group: $F(6, 162) = 2.38$, $p = .031$, **Figure 2.3D**; mood state: Time: $F(2, 166) = 23.16$, $p < .001$; Group: $F(3, 83) = 39.04$, $p < .001$, **Figure 2.3E**; acute dissociation: Time: $F(1,65, 130.37) = 41.30$, $p < .001$; Group: $F(3, 79) = 20.57$, $p < .001$; Time x Group: $F(4.95, 130.37) = 5.08$, $p < .001$, **Figure 2.3F**).

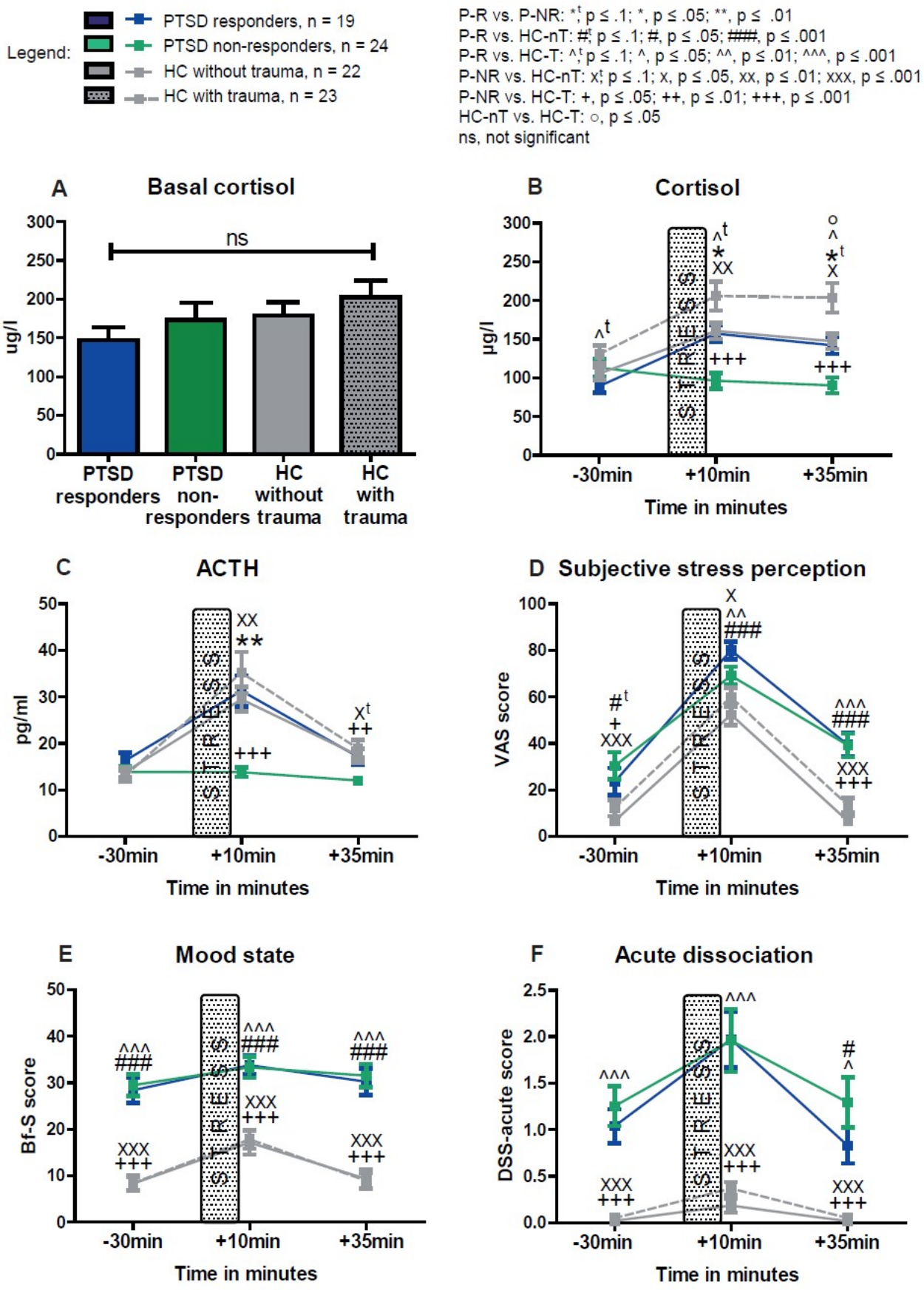

Legend:
PTSD responders, n = 19
PTSD non-responders, n = 24
HC without trauma, n = 22
HC with trauma, n = 23
P-R vs. P-NR: *t p ≤ .1; *, p ≤ .05; **, p ≤ .01
P-R vs. HC-nT: #t p ≤ .1; #, p ≤ .05; ###, p ≤ .001
P-R vs. HC-T: ^t p ≤ .1; ^, p ≤ .05; ^^, p ≤ .01; ^^^, p ≤ .001
P-NR vs. HC-nT: xt p ≤ .1; x, p ≤ .05, xx, p ≤ .01; xxx, p ≤ .001
P-NR vs. HC-T: +, p ≤ .05; ++, p ≤ .01; +++, p ≤ .001
HC-nT vs. HC-T: ○, p ≤ .05
ns, not significant
A
Basal cortisol
ug/l
ns
PTSD responders
PTSD non-responders
HC without trauma
HC with trauma
B
Cortisol
µg/l
-30min
+10min
+35min
Time in minutes
C
ACTH
pg/ml
-30min
+10min
+35min
Time in minutes
D
Subjective stress perception
VAS score
-30min
+10min
+35min
Time in minutes
E
Mood state
Bf-S score
-30min
+10min
+35min
Time in minutes
F
Acute dissociation
DSS-acute score
-30min
+10min
+35min
Time in minutes

Figure 2.3. *Basal cortisol levels and stress reactivity parameters in the TSST of PTSD responders (PTSD-R, n = 19) vs. PTSD non-responders (PTSD-NR, n = 24) vs. traumatized healthy controls (tHC, n = 23) vs. non-traumatized healthy controls (ntHC, n = 22)*

Note. Basal cortisol levels (A) were calculated with one-way ANOVA. The protocol of the TSST is shown in detail in Fig.1. Stress hormones, cortisol (B) and ACTH (C), changes due to stress exposure as well as psychological stress response, subjective stress perception (D), mood state (E), acute dissociation (F), were calculated with two-way ANOVA with repeated measures followed by Bonferroni corrections. Excluded outliers: (A) one ntHC; (B) one PTSD-R, one PTSD-NR, one ntHC; (C) one PTSD-R, one PTSD-NR., one ntHC; (D) one PTSD-R, one ntHC; (F) one PTSD-R, one PTSD-NR, one ntHC, one tHC. Significant post-hoc analyses are as follows: (B) group effects: at +10min: between PTSD-R and tHC, p = .051; betw. PTSD-R and PTSD-NR, p = .017; betw. PTSD-R and tHC, p = .095; betw. PTSD-NR and ntHC, p = .005; betw. PTSD-NR and tHC, p < .001; at +35min: betw. PTSD-R and PTSD-NR, p = .068; betw. PTSD-R and tHC, p = .017; betw. PTSD-NR and ntHC, p = .02; betw. PTSD-NR and tHC, p < .001; betw. ntHC and tHC, p = .023; time effects: PTSD-R: betw. -30min and +10min, p < .001; ntHC: betw. -30min and +10min: p < .001; tHC: betw. -30min and +10min, p < .001; (C) group effects: at +10min: betw. PTSD-R and PTSD-NR, p = .002; betw. PTSD-NR and ntHC, p = .004; betw. PTSD-NR and tHC, p < .001; at +35min, betw. PTSD-NR and ntHC, p = .084; betw. PTSD-NR and tHC, p = .008; time effects: PTSD-R: betw. -30min and +10min, p < .001; betw. +10 min and +35min, p < .001; ntHC: betw. -30min and +10min, p < .001; betw. +10min and +35min, p < .001; tHC: betw. -30min and +10min, p < .001; betw. +10min and +35min, p < .001; (D) group effects: at -30min: betw. PTSD-R and ntHC, p = .086; betw. PTSD-NR and ntHC, p = .001; betw. PTSD-NR and ntHC, p = .02; at +10min, betw. PTSD-R and ntHC, p < .001; betw. PTSD-R and tHC, p = .008; betw. PTSD-NR and ntHC, p = .024; at +35min, betw. PTSD-R and ntHC, p < .001; betw. PTSD-R and tHC., p < .001; betw. PTSD-NR and ntHC, p < .001; betw. PTSD-NR and tHC, p < .001; time effects: PTSD-R: betw. -30min and +10min, p < .001; betw. +10min and +35min, p < .001; PTSD-NR: betw. -30min and +10min, p < .001; betw. +10min and +35min, p < .001; ntHC, betw. -30min and +10min, p < .001; betw. +10min and +35min, p < .001; tHC, betw. -30min and +10min, p < .001; betw. +10min and +35min, p < .001; (E) group effects: at -30min: betw. PTSD-R and ntHC, p < .001; betw. PTSD-R and tHC, p < .001; betw. PTSD-NR and ntHC, p < .001; betw. PTSD-NR and tHC, p < .001; at +10min: betw. PTSD-R and ntHC, p < .001; betw. PTSD-R and tHC, p < .001; betw. PTSD-NR and ntHC, p < .001; betw. PTSD-NR and tHC, p < .001; at +35min: betw. PTSD-R and ntHC, p < .001; betw. PTSD-R and tHC, p < .001; betw. PTSD-NR and ntHC, p < .001; betw. PTSD-NR and tHC, p < .001; time effects: ntHC: betw. -30min and +10min, p = .001; betw. +10min and +35min, p < .001; tHC: betw. -30min and +10min, p < .001; betw. +10min and +35min, p < .001; (F) group effects: at -30min: betw. PTSD-R and ntHC, p < .001; betw. PTSD-R and tHC, p < .001; betw. PTSD-NR and ntHC, p < .001; betw. PTSD-NR and tHC, p < .001; +10min: betw. PTSD-R and ntHC, p < .001; betw. PTSD-R and tHC, p < .001; betw. PTSD-NR and ntHC, p < .001; betw. PTSD-NR and tHC, p < .001; at +35min: betw. PTSD-R and ntHC, p = .011; betw. PTSD-R and tHC, p = .015; betw. PTSD-NR and ntHC, p < .001; betw. PTSD-NR and tHC, p < .001; time effects: PTSD-R: betw. -30min and +10min, p < .001; betw. +10min and +35min, p < .001; PTSD-NR: betw. -30min and +10min, p < .001; betw. +10min and +35min, p < .001; tHC: betw. +10min and +35min, p = .069.

2.4.5 Dissociative symptoms predict blunted HPA-axis response to the TSST

Next, we selected factors that were found to be reliably associated with non-responding to the TSST in female PTSD patients in TSST1 (Zaba et al., 2015) and TSST2 (**Table 2.2**, **Supplement Table 2.1**) samples, i.e., trauma age (ELT, AT, ELT+AT), number of comorbid and lifetime psychiatric disorders as well as trauma-related dissociation as measured by the RIQ. **Supplement Table 2.2** presents a correlational matrix of the mentioned variables with CORT levels at three assessment times as well as a percentage stress-induced CORT response. CORT levels following stress exposure were negatively correlated with the number of comorbid psychiatric disorders. Interestingly, percentage CORT response was negatively associated with both comorbid and lifetime psychiatric disorders as well as with trauma-related dissociation. Moreover, psychiatric comorbidity was positively associated with dissociation severity. For statistical details, see **Supplement Table 2.2**. Next, to answer the question, which of the factors will be the strongest predictor of the HPA-axis non-responder group status, we ran a binary logistic regression analysis with backward stepwise elimination method. Note that to reduce the multicollinearity, we added the number of comorbid disorders but removed lifetime disorders from the statistical model.

The model with the best fit indices was statistically significant ($\chi^2(4) = 19.28$, p = 001), explained 55.3% (Nagelkerke R^2) of the variance in CORT non-responding, and correctly classified 77.8% of cases (76.5% responders and 78.9% non-responders). High levels of dissociation (ß = 1.46, Exp(ß) = 4.29, p = .027) predicted CORT non-responding to the TSST in PTSD. The other predictors did not reach statistical significance in the final model. However, the result of significance test of recent comorbidity was on a trend level (ß = .899, Exp(ß) = 2.46, p = .092). The model characteristics are presented in **Table 2.4**.

Table 2.4. *Prediction of stress response status in PTSD (n = 43)*

	Model characteristics			Variables in the equation			
	χ^2	p	R^2	ß	Exp(ß)	df	p
Step 1	19.276	.001	.553				
Trauma age ELT+AT						2	.271
Trauma age ELT				-2.013	.134	1	.117
Trauma age AT				-.596	.551	1	.618
Recent comorbidity				.910	2.48	1	.163
Dissociation (RIQ)				**1.456**	**4.290**	**1**	**.027**
Step 2	16.261	.001	.485				
Recent comorbidity				**.899**	**2.456**	**1**	**.092**
Dissociation (RIQ)				**1.301**	**3.674**	**1**	**.044**

Note. Binary logistic regression analysis with backward stepwise elimination method was ran in PTSD patients from the fused TSST1+TSST2 sample. Trauma age and comorbidity as assessed with the M-CIDI. Responding to the TSST was defined as 15.5% CORT increase after stress induction (Miller et al., 2013; Zaba et al., 2015; **Figure 2**). Bold numbers indicate significant ($p \leq .05$) or trendwise significant ($p \leq .1$) results. Abbreviations: ELT, early life trauma; AT, adult trauma; RIQ, Response to Intrusions Questionnaire.

2.5 DISCUSSION

As hypothesized, we replicated the finding of Zaba et al. (2015) by showing CORT stress response to a laboratory standardized psychosocial stressor, the TSST, in an independent sample of female PTSD patients to be the lowest as compared with both female ntHC and tHC. Moreover, based on the analysis of individual response rates, applying an established criterion of CORT stress response (Miller et al., 2013), we repeatedly were able to identify and to further characterize two HPA-axis endophenotypes in PTSD: PTSD-R and PTSD-NR. However, contrary to Zaba et al. (2015), PTSD-NR in the TSST2 sample exhibited stress-induced CORT blunting while not showing general CORT levels to be lower than those of PTSD-R. Since measures of psychological stress reactivity demonstrated the peak of subjective stress perception following but not prior to the stressor (the TSST) in both groups, we possibly may rule out the effect of anticipatory anxiety being more pronounced in PTSD-NR than in PTSD-R (see also: Engert et al., 2013). Additionally, among all studied individuals, hormonal contraceptive users showed the highest CORT levels. Since these participants were represented in the TSST2 but not in the TSST1 sample, we speculate that the usage of hormonal contraceptives was the reason for elevated CORT levels in PTSD-NR in the TSST2 relatively to the TSST1 sample. This conclusion is supported by high variation in CORT levels of PTSD-NR in the TSST2 sample.

Moreover, we replicated the finding of higher levels of self-report dissociative symptoms (RIQ) in PTSD-NR as compared to PTSD-R and provided its further validation by showing PTSD-NR to score higher than PTSD-R on other self-report (DES) as well as clinician-based (SCID-D) measurements of dissociative symptoms. Furthermore, PTSD-NR were characterized by high trauma dose (ELT+AT), high comorbidity especially with anxiety disorders, fear of process of dying, sleep difficulties, avoidant trauma-coping as well as reaction control and positive self-instruction as general coping strategies. Most importantly, among factors associated with the HPA-axis blunting in PTSD, dissociative symptoms were shown to be the strongest predictor of CORT levels following stress exposure.

The strong link between dissociative symptoms and the HPA-axis blunted response suggests that, at least in female PTSD patients, neither TE nor PTSD symptom severity may be decisive for HPA-axis dysregulated reactivity. We speculate that accounting for individual response rates

as well as for dissociative symptom severity in future studies on HPA-axis function in PTSD would enable to explain at least some of the inconsistent results in the field.
Furthermore, our results show that factors contributing to basal levels of CORT may be distinct from those associated with phasic regulatory processes. Whereas high trauma load was related to generally low CORT levels in PTSD, it was not a significant predictor of the HPA-axis stress response. On the contrary, dissociative symptom severity was prognostic for the blunting of the HPA-axis but did not correlate with general CORT levels. Interestingly, stress-related blunting of the HPA-axis was not necessarily related to generally lower levels of CORT.

Contrary to the hypothesis, in tHC a different pattern of results was found: whereas the levels of non-pathological dissociation (absorption) were higher than in ntHC and not differing from that of PTSD patients, CORT levels following stress exposure were higher as compared to both PTSD and ntHC. These results support and add to the non-linear model of the link between TE, PTSD and CORT secretion (Steudte-Schmiedgen et al., 2016). We speculate that, as a response to TE, CORT and non-pathological dissociation raise as a part of a psychobiological coping mechanism. A strong relationship between TE and dissociative phenomena has been frequently shown (Frewen et al., 2015; Soffer-Dudek, 2017; Vonderlin et al., 2018). Interestingly, both high dissociation (Gandubert et al., 2016; Orr et al., 2012) and low CORT levels following TE (Mouthaan et al., 2014) were found independently as significant predictors for the PTSD development. It may be possible that with each additional trauma dissociative symptoms may turn into their pathological manifestations and that this process may be accompanied by downregulation of CORT. This suggests that accounting for dissociative symptom development may depict one of the missing pieces of the puzzle of the complex link between TE, PTSD and CORT secretion. Definitely, more research is needed to provide empirical support for this reasoning.

Furthermore, understanding this complexity may help to improve treatment and prevention options for PTSD. This may be especially of interest considering glucocorticoid administration for either PTSD treatment or PTSD prevention following TE (Carmi, Fostick, Burshtein, Cwikel-Hamzany, & Zohar, 2016; Dunlop & Wong, 2019; Yoon & Kim, 2019). Whereas promising results were shown in trauma survivors treated with glucocorticoids shortly after TE (Birur, Math, & Fargason, 2017), this kind of treatment has not been proven successful in full-blown PTSD (Graebener, Michael, Holz, & Lass-Hennemann, 2017; Ludäscher et al., 2015). This suggests that for glucocorticoid treatment to be successful, it needs to be applied in a critical period of

time (“golden hours” or “window of opportunity”), whereas raise of baseline levels of CORT alone presumably may not have a therapeutical effect. We speculate that in PTSD pharmacological manipulation of HPA-axis reactivity may be a more promising approach.

Moreover, future studies should explore how CORT administration corresponds with dissociative phenomena manifestations, especially in the light of “state” and “trait” assessment. Interestingly, in our studies, the blunted HPA-axis response was associated with trauma-related dissociative symptoms (“trait”), but no differences in acute dissociative reactions to stress (“state”) were found between PTSD-R and PTSD-NR (Zaba et al., 2015; *results at hand*). Since PTSD itself may be considered a dissociative disorder (Dorahy & van der Hart, 2015), it is possible that both PTSD-R and PTSD-NR exhibit dissociative phenomena in a response to stress but PTSD-NR tend to show more persistent forms of dissociation (“trait”). Especially, a usual dissociative response to trauma-related memories/material (as assessed with the RIQ) may go along with the blunted HPA-axis reactivity. A follow-up study concentrating on direct provocation of dissociative symptoms, for example using mirror-gazing (Brewin & Mersaditabari, 2013; Schäflein, Sattel, Schmidt, & Sack, 2018), rubber hand illusion (Rabellino et al., 2018, 2016), or trauma script exposure (Lanius et al., 2010; Sack et al., 2017), and parallel assessment of the HPA-axis function is urgently needed. Furthermore, long-term multiple measurements of CORT levels both basal and as a stress reactivity, especially in the course of therapy, would give more insights into the “state” vs. “trait” distinction.

Additionally, future studies in PTSD populations need to account for the diagnosis of the dissociative subtype of PTSD (DS-PTSD). The DS-PTSD was introduced to the latest, fifth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, (American Psychiatric Association, 2013) as a novel diagnostic entity. It has been proposed that the DS-PTSD shows unique biopsychological mechanisms and that accounting for them will broaden the understanding of different trauma symptom trajectories (Lanius et al., 2018; Lanius, Brand, Vermetten, Frewen, & Spiegel, 2012; van Huijstee & Vermetten, 2017). In our study, we applied several measures of dissociative symptoms. In fact, none of them gave a qualified possibility to distinguish between dissociative and non-dissociative PTSD. Also, given the small study sample, we decided not to divide PTSD patients into further subtype categories (for a similar approach see: Wolf et al., 2014). However, the identified PTSD-NR were found to be characterized with variables being previously associated with the DS-PTSD, such as: high comorbidity, high trauma load and combined ELT+AT (Armour, Elklit, Lauterbach, & Elhai, 2014; Hansen et al.,

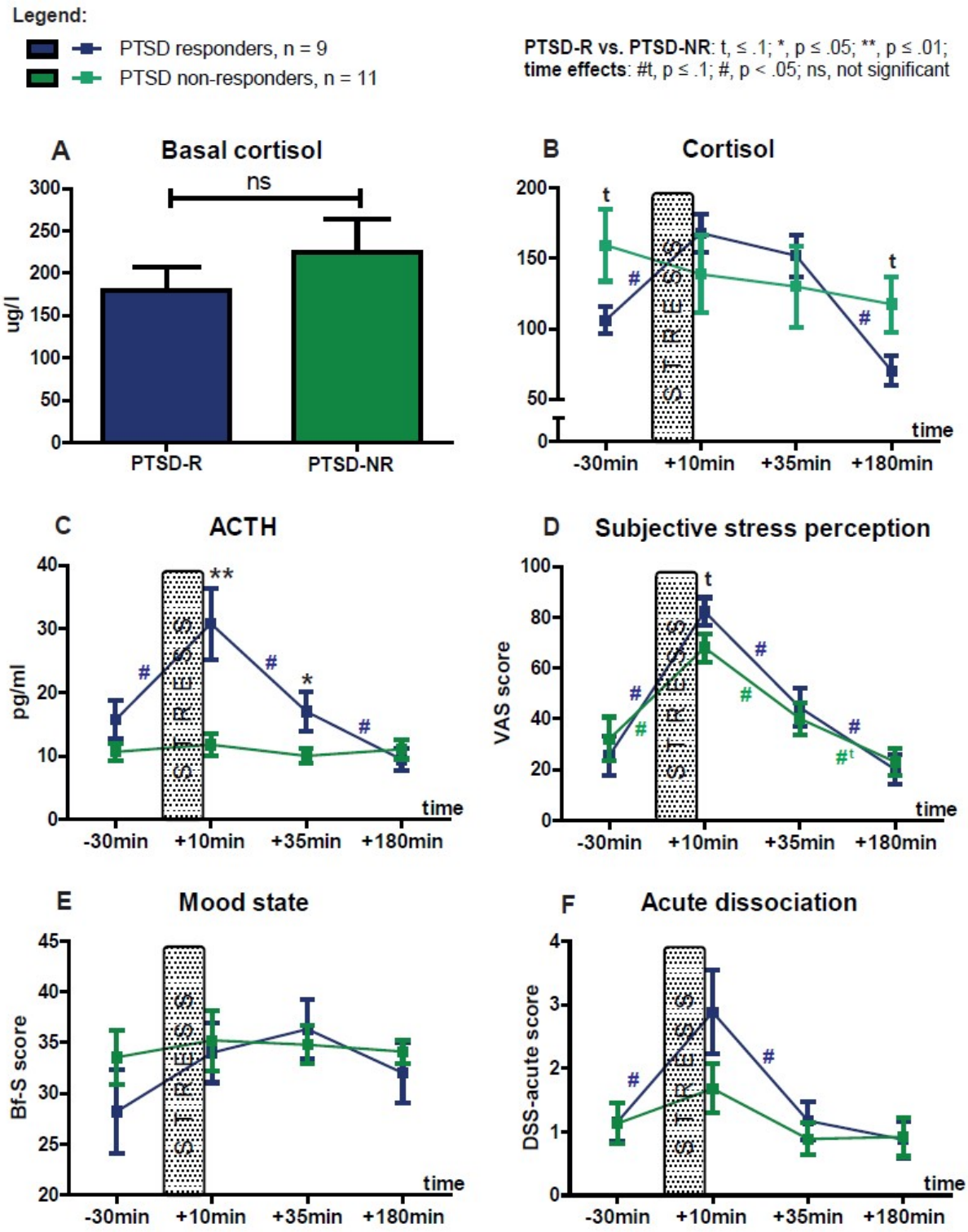
2017; McKinnon et al., 2016). Contrary to previous results on the DS-PTSD, first, we did not find higher PTSD severity in PTSD-NR (Műllerová, Hansen, Contractor, Elhai, & Armour, 2016; Ross, Baník, Dědová, Mikulášková, & Armour, 2017; Wolf et al., 2017), and second the prevalence of PTSD-NR was found to be at around 50%. For the DS-PTSD, prevalence around 15-30% was found (McKinnon et al., 2016). However, in our study, the subjected patients were all female with relatively high levels of sexual and childhood trauma, both factors being previously associated with the DS-PTSD (Frewen et al., 2015; van Dijke et al., 2015; Vonderlin et al., 2018). Also in the PTSD sample as reported by Wichmann and colleagues (2017), female PTSD patients with high levels of sexual and childhood adversity were studied that can also contribute to the similar finding of a response rate of around 50%. Future studies are needed to answer the question, whether the HPA-axis non-responding can be seen as a biological hallmark of the DS-PTSD. Since new validated instruments enabling a precise diagnosis of the DS-PTSD are currently available, they should be used for the measurement (via self-report: Wolf et al., 2017; clinician-based interview: Eidhof et al., *accepted*).

Our results are interesting beyond trauma and PTSD research. Dissociative symptoms are transdiagnostically associated with a greater illness burden and reduced treatment outcomes (Lyssenko et al., 2018; McKinnon et al., 2016). Moreover, dissociation as well as high psychiatric comorbidity are the factors associated with non-response to therapy (Bae, Kim, & Park, 2016). For these reasons, elucidating the link between TE, the HPA-axis function, dissociation and the subsequent psychopathology development offers a promising field of research. Furthermore, given high psychiatric comorbidity in our studied population and its link with low CORT levels, it is also worth discussing that HPA-axis blunting may be considered a hallmark of chronic stress due to TE early in life and long persistent psychopathology. A similar line of reasoning was presented in the context of panic disorder (PD) research. This disorder was also characterized with long symptom persistence and a tendency of lower reactive CORT levels (Petrowski, Herold, Joraschky, Wittchen, & Kirschbaum, 2010; Petrowski, Wintermann, Schaarschmidt, Bornstein, & Kirschbaum, 2013). On the other side, given a recent promising research on genetic background of the DS-PTSD (Wolf et al., 2014), future studies need to clarify if the HPA-axis blunted response may be characterized as a risk factor (“trait”) being present prior to TE and subsequent symptom development.

This study is limited by a relatively small number of participants, inclusion of medicated PTSD

patients, absence of male individuals as well as by a cross-sectional design not allowing to make causal conclusions.

2.6 SUPPLEMENT PAPER 1



Supplement Figure 2.1. *Basal cortisol levels and stress reactivity parameteres in the TSST in PTSD responders (PTSD-R, n = 9) vs. PTSD non-responders (PTSD-NR, n = 11) from the TSST2 sample*

Note. Basal cortisol levels (A) were calculated with one-way ANOVA. Stress hormones, cortisol (B) and ACTH (C) as well as psychological stress reactivity:(D) subjective stress perception, (E) mood state, (F) acute dissociation were analyzed during the Trier Social Stress Test, TSST, with two-way ANOVA with repeated measures followed by Bonferroni corrections. The protocol of the TSST is shown in detail in Fig.1. Excluded outliers: (E) one PTSD-NR, (F) one PTSD-NR. Significant post-hoc analyses are as follows: (B) group effects: at -30min: $p = .080$; at +180min: $p = .055$; time effects: in PTSD-R: -30min vs. +10min, $p < .001$; +35min vs. +180min, $p = .003$; (C) group effects: at +10min: $p = .004$; at +35min: $p = .042$; time effects: in PTSD-R: -30min vs. +10min, $p = .005$; +10min vs. +35min, $p = .004$; +35min vs. +180min, $p = .016$; (D) group effects: at +10min: .086; time effects: in PTSD-R: -30min vs. +10min, $p < .001$; +10min vs. +35min, $p = .001$; +35min vs. +180min, $p = .010$; in PTSD-NR: -30min vs. +10min, $p = .006$;+10min vs. +35min, $p = .006$; +35min vs. +180min, $p = .087$; (F) time effects: in PTSD-R: -30min vs.+10min, $p = .024$; +10min vs. +35min, $p = .002$. Abbreviations: PTSD, posttraumatic stress disorder; R, responder; NR, non-responder; ns, not significant; ACTH, adrenocrticotropin.

Supplement Table 2.1. *Demographics and clinical characteristics of PTSD responders (PTSD-R, n= 9) and PTSD non-responders (PTSD-NR, n = 11) in the TSST2 sample*

	PTSD responders (*n* = 9) Mean ± SD	**PTSD non-responders** (*n* = 11) Mean ± SD	**Statistical test details**
Age (years)	34.22 ± 14.19	34.27 ± 11.47	F(1, 19) = <.001; p = .993
Number of smokers	2	5	χ^2(1, *n* = 20) = 1.17, p = .279
Medication (no/antidepressants/antidepressants with neuroleptics/combination therapy)	2/2/2/3	3/4/2/2	χ^2(3, *n* = 20) = .875, p = .831
Ovarian cycle (follicular/luteal/menopause/ hormonal contraceptives)	1/5/1/2	3/4/1/3	χ^2(3, *n* = 20) = 1.12, p = .772
Number of traumata	2.44 ± 1.24	2.56 ± 1.24	U = 39.500, p = .926
Trauma age (early life/adulthood/ early life and adulthood)	4/3/2	3/2/6	χ^2(2, *n* = 20) = 2.17, p = .339
Trauma type (sexual/non-sexual/both)	1/1/7	2/1/8	χ^2(2, *n* = 20) = .202, p = .904
Coping strategies (SVF-78):			
Downplaying	4.56 ± 3.57	6.90 ± 5.11	F(1, 18) = 1.31, p = .268
Denial of guilt	8.33 ± 5.50	6.22 ± 2.82	F(1, 17) = 1.05, p = .321
Distraction	12.11 ± 2.89	14.20 ± 4.39	F(1, 18) = 1.46, p = .243
Substitute gratification	8.11 ± 2.26	7.00 ± 2.62	F(1, 18) = .966, p = .339
Situation control	11.44 ± 6.73	12.80 ± 3.79	F(1, 18) = .301, p = .590
Reaction control	14.44 ± 4.07	18.20 ± 3.65	**F(1, 18) = 4.51, p = .049**
Positive self-instruction	8.89 ± 4.51	13.00 ± 5.23	**F(1, 18) = 3.33, p = .086**
Need for social support	10.56 ± 7.23	9.50 ± 4.06	F(1, 18) = .156, p = .698
Avoidance	13.78 ± 7.48	16.30 ± 4.55	F(1, 18) = .808, p = .381
Escape	18.63 ± 3.96	17.70 ± 5.62	F(1, 17) = .154, p = .700
Rumination	18.67 ± 3.91	17.20 ± 4.83	F(1, 18) = .522, p = .480
Resignation	14.89 ± 6.05	12.33 ± 2.45	F(1, 17) = 1.38, p = .257
Self-blame	15.67 ± 6.75	14.80 ± 6.14	F(1, 18) = .086, p = .773
Depression (BDI)	24.22 ± 10.34	28.64 ± 8.90	F(1, 19) = 1.05, p = .318

Supplement Table 2.1. *(continued)*

	PTSD responders (*n* = 9) Mean ± SD	**PTSD non-responders** (*n* = 11) Mean ± SD	**Statistical test details**
Anxiety Trait (STAI)	60.89 ± 9.92	58.10 ± 6.26	F(1, 18) = .550, p = .469
Anxiety State (STAI)	48.33 ± 11.93	54.09 ± 10.14	F(1, 19) = 1.36, p = .258
PTSD severity (CAPS)	70.00 ± 21.41	86.18 ± 30.00	F(1, 19) = 2.89, p = .106
CAPS subscales:			
Re-experiencing	23.44 ± 9.45	29.55 ± 7.26	F(1, 19) = 2.67, p = .119
Avoidance	27.00 ± 13.62	33.64 ± 11.03	F(1, 19) = 1.45, p = .244
Hyperarousal	19.56 ± 7.07	23.00 ± 8.37	F(1, 19) = .961, p = .340
Response to Intrusions *(RIQ subscales)*:			
Rumination	2.29 ± .70	2.29 ± .60	F(1, 18) = < .001, p = 1.00
Avoidance	2.17 ± .50	2.61 ± .45	**F(1, 18) = 4.07, p = .060**
Dissociation	1.67 ± .35	2.20 ± .65	**F(1, 18) = 4.72, p = .044**
Comorbid and lifetime disorders (*M-CIDI*):			
Comorbid major depression (current/past)	4/3	5/1	$\chi^2(2, n = 17) = 2.06$, p = .357
Comorbid anxiety disorders (current/past)	4/0	6/1	$\chi^2(2, n = 17) = 2.02$, p = .365
Comorbid substance disorders (current/past)	0/2	0/4	$\chi^2(1, n = 17) = .701$, p = .402
Comorbid disorders	1.38 ± 1.30	3.22 ± 2.33	**U = 17.000, p = .062**
Lifetime disorders	2.50 ± 1.31	4.78 ± 3.15	U = 22.000, p = .171

Note. Group differences were calculated with: one-way ANOVA, Chi-squared test two-tailed, or, Mann-Whitney-U-test. Appropriate to test requirements, shown are results of: Fisher test (F), Chi-squared test (χ^2), or U value (U), respectively. Significant results are marked in bold. Symbol: *, p ≤ .05. Abbreviations: SD, standard deviation; SVF-78, Stress Coping Questionnaire; BDI, Beck Depression Inventory; STAI, State-Trait Anxiety Inventory; CAPS, Clinician Administrated PTSD Scale; RIQ, Response to Intrusions Questionnaire. Comorbid and lifetime disorders as well as traumatic events were assessed with the Munich Composite International Diagnostic Interview (M-CIDI). Excluded outliers: SVF: one PTSD-R, two PTSD-NR.

Supplement Table 2.2. *Correlational analyses of variables associated with the HPA-axis response in PTSD from the fused TSST1+TSST2 sample (n = 43)*

	Recent comorbidity	Lifetime comorbidity	Dissociation (RIQ)	CORT -30min	CORT +10min	CORT +35min	Cortisol response (%)
Trauma age	***.276***^{t}	*.268*	*.140*	*-.011*	*-.219*	*-.199*	*-.243*
Recent comorbidity	-	***.759******	***.558*****	*.108*	***-.463****	***-.547*****	***-.571****
Lifetime comorbidity		-	***.558*****	*.223*	*-.232*	*-.268*	***-.387****
Dissociation (RIQ)			-	.203	-.092	-.084	**-.439****

Note. The interrelations between variables were calculated with Pearson or in ordinal data with Spearman (indicated in italics). Trauma age and comorbidity as assessed with the M-CIDI. Symbols: t, ≤ .1; *, p ≤ .05; **, p ≤ .01; ***, p ≤ .001. Significant results are shown in bold. Abbreviations: RIQ, Response to Intrusions Questionnaire; CORT, cortisol. Excluded outliers: recent comorbidity: one PTSD-R, one PTSD-NR; cortisol response: one PTSD-R.

3. PAPER 2

Cross-cultural validity of the dissociative subtype of PTSD: evidence from refugees settled in Uganda

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3.1 ABSTRACT

Background: A dissociative subtype of posttraumatic stress disorder (DS-PTSD) was introduced to the latest version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5, APA 2013). Hitherto, numerous studies employing Latent Profile Analyses (LPA) provided statistical evidence for this construct. However, none of these studies were conducted in a non-Western population. Concluding, data on the cross-validity of the construct are largely missing.

Method: East African refugees (n = 214, 49.1% female) settled in the Uganda's Nakivale refugee camp were studied in semi-structured interviews for trauma exposure, PTSD, stress coping, dissociative and depressive symptoms as well as for suicidality and general functionality. A LPA was performed to identify the DS-PTSD. The DS-PTSD Interview (DSP-I, Eidhof et al., *accepted*) was applied to provide its psychometric properties.

Results: The best LPA fit indices were found for a 4-class solution. Among the classes, one class without PTSD symptoms as well as 3 PTSD classes were identified: mild (mPTSD), severe (sPTSD) and severe dissociative PTSD (DS-PTSD). The DS-PTSD comprised 14% of the total sample and 26% of all identified PTSD cases. The cross-cultural validity of the DS-PTSD was given since the DS-PTSD was, similarly to Western populations, characterized by high trauma load, especially family and sexual trauma, high psychopathology in terms of high depressive symptoms, suicidality and low functionality. Although DS-PTSD exhibited the highest prevalence of maladaptive coping strategies among all classes, no differences in coping strategies were found between the DS-PTSD and sPTSD. Furthermore, we found DSP-I to have excellent psychometric properties (i.e., reliability, convergent and discriminant validity).

Conclusions: The DS-PTSD is not limited to Western samples. Some correlates/risk factors of the DS-PTSD, such as sexual trauma, high trauma load and high psychopathology, seem to be general across different populations. The DSP-I was proven to be a cultural-sensitive instrument for the DS-PTSD assessment.

3.2 INTRODUCTION

Posttraumatic stress disorder (PTSD), a disorder developing in a sequelae of a stressor outside the range of usual human experience, was first added to international psychiatric diagnostic classifications in 1980, specifically to the third edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-III, American Psychiatric Association, 1980). Based on a current, global definition of dissociation describing it as “an experienced loss of information or control over mental processes that, under normal circumstances, are available to conscious awareness, self-attribution, or control, in relation to the individual’s age and cognitive development” (Cardeña & Carlson, 2011, p. 251), PTSD has been conceptualized as a dissociative disorder (Dorahy & van der Hart, 2015). Although some of the dissociative symptoms, such as re-experiencing or memory loss for details of the traumatic event, were included into the core PTSD symptoms, others, such as absorption, depersonalization, derealization or “out of body” experiences, have been assessed only as common, side phenomena of PTSD (e.g., Carlson et al., 2012).

The presence of severe dissociative symptomatology has been found to manifest in distinct psychobiological mechanisms (e.g., Lanius et al., 2010) as well as to go along with reduced therapeutical outcomes (e.g., Bae et al., 2016; Kleindienst et al., 2016) than PTSD without them. For this reason, both clinicians and researchers pleaded for adding further dissociative symptoms into the core assessment of PTSD. Following, thirty-three years after publication of DSM-III, in the latest, fifth edition of the DSM (DSM-5), the dissociative subtype (DS-PTSD) was introduced into the official PTSD diagnosis. The DS-PTSD was defined by the occurrence of depersonalization (e.g., feelings of detachment from self or body) and/or derealization (e.g., feelings of unreality of surroundings) symptoms (American Psychiatric Association, 2013).
The decision to identify the DS-PTSD was rationalized with the expected boost of the empirically driven research on dissociative phenomena in PTSD as well as with the improvement of diagnosis and treatment strategies for patients of concern (e.g., Dutra & Wolf, 2017; Lanius et al., 2012). However, critiques of the concept arose discussing that patients not being diagnosed with the DS-PTSD belong to a *non*-dissociative subtype, which is in conflict when PTSD itself is conceptualized as a dissociative disorder (Dorahy & van der Hart, 2015). Moreover, dividing PTSD patients into two groups may neglect a dimensional structure of dissociative symptoms postulated in some reports (Dalenberg & Carlson, 2012).

Hitherto, across the statistical models established to understand the nature of the relationship between TE, PTSD, and dissociative symptoms, the component or subtype model received empirical support (Dalenberg & Carlson, 2012). Specifically, dissociative symptoms of clinical relevance do not show a dimensional structure in PTSD patients but rather manifest in some of them changing the clinical picture of PTSD.

The empirical evidence for that was provided in studies on trauma exposed individuals and/or on PTSD sufferers using statistical analyses enabling clustering of studied participants accordingly to their manifestation of PTSD and dissociative symptoms. Taxometric analyses determine whether the variables show a typological (i.e., taxonic) or a dimensional structure, whereas latent profile analyses (LPA) allow identification of distinct relationship patterns between variables (Muthén & Muthén, 2006). Both kinds of analyses provided evidence for the DS-PTSD. See for example: taxometric analyses in trauma exposed Vietnam veterans (Waelde, Silvern, & Fairbank, 2005) as well as LPA in PTSD sufferers stemming from a community sample (Frewen et al., 2015) and victims of sexual violence (Armour et al., 2014). Whereas taxometric investigation is limited because it enables only two groups (i.e., taxons) to be identified, LPA defines many classes to fit the best potential heterogeneity of manifested symptoms. Moreover, it assesses, for each studied individual, the degree of probability of assignment to a particular class/profile (see also: Dalenberg, Glaser, & Alhassoon, 2012; Galatzer-Levy & Bryant, 2013).

So far, 11 LPA studies were conducted in trauma exposed individuals and/or PTSD sufferers. In all but one study at least one DS-PTSD profile was identified as being characterized with high PTSD severity accompanied by the presence of dissociative symptoms (Hansen et al., 2017). The other study identified two dissociative PTSD profiles: one with severe and one with moderate levels of PTSD (Frewen et al., 2015). Prevalence of the DS-PTSD in these studies ranged between 6% and 44.6% (M = 20.35%). Generally, sexual and childhood trauma, high severity of PTSD as well as high levels of psychopathology (such as comorbid anxiety and depressive disorders, high suicidality and low general functioning) were identified to be the strongest covariates/risk factors of the DS-PTSD (e.g., Dorahy & van der Hart, 2015; Hansen et al., 2017; Lanius et al., 2012; Stein et al., 2013).

Moreover, in order to understand general psychological mechanisms of dissociative tendencies, some studies focused on coping styles as DS-PTSD correlate/risk factor. It was proposed that

trauma-related dissociation can be conceptualized as a stress coping strategy to deal with overwhelming trauma memories through cognitive avoidance and self-distance (e.g., Dutra & Wolf, 2017; Ehlers, 1999; Holmes et al., 2005). Whereas in two samples emotion-focused coping was found to be associated with the DS-PTSD (Hansen, Műllerová, Elklit, & Armour, 2016), a recent study demonstrated no differences in avoidant coping between DS-PTSD and non-DS-PTSD patients (Haagen, van Rijn, Knipscheer, van der Aa, & Kleber, 2018). These inconsistent results show the need of more studies on general psychological variables, such as stress coping strategies, differentiating between the DS and non-DS-PTSD.

Furthermore, note that all mentioned LPA studies were conducted in Western populations. Although significant evidence for the cross-cultural validity of PTSD is given and the presence of dissociative symptoms was shown to be associated with TE and PTSD across different cultures and populations worldwide (e.g., Jong & Reis, 2013; Schalinski, Elbert, & Schauer, 2011; Van Ommeren et al., 2001), little is known about the applicability of the DS-PTSD cross-culturally (Hinton & Lewis-Fernández, 2011). Additionally, correlates/risk factors of the DS-PTSD across different populations/cultures are generally unknown. So far, one study conducted an analysis on dissociative symptoms belonging to the DS-PTSD in 16 countries, including non-Western populations. In this report, the link between the presence of dissociative symptoms and childhood trauma, severe PTSD symptomatology and high role impairment and suicidality was shown (Stein et al., 2013). This report provided first evidence for the cross-cultural validity of the DS-PTSD construct. However, it was limited by poor methodology since it analyzed dissociative symptoms post-hoc using a checklist of non-specific psychological distress. Still, this study depicts an important step forward by showing the global relevance of research on the DS-PTSD. More evidence on correlates/risk factors of the DS-PTSD in different populations may help to explore general mechanisms of the subtype that are not specific for a given population (see also: Galatzer-Levy & Bryant, 2013; Hansen et al., 2017).

Furthermore, still little is known about the psychometric measures of tools assessing dissociative symptoms across different cultures and so to say across different languages. Verbal expression of dissociative symptoms may vary worldwide. For this reason, cultural adaptation of assessment tools, as those assessing the DS-PTSD (e.g., Eidhof et al., *accepted*; Wolf et al., 2017), should address any possible translation challenges (see also: Lewis-Fernández, Martínez-Taboas, Sar, Patel, & Boatin, 2007).

Based on the literature reviewed above, the goals of this study were: first, to assess PTSD together with dissociative symptoms in a low-income, non-Western population highly exposed to trauma and to identify a subset of individuals belonging to the DS-PTSD in order to provide evidence for the cross-cultural utility of the construct; second, to explore its relationships with TE, stress coping, and measures of psychopathology (PTSD and depressive symptoms, suicidality and general functioning) in order to prove the cross-cultural validity of the DS-PTSD; third, to employ a newly developed clinician-based interview for the assessment of the DS-PTSD (Dissociative Subtype of PTSD Interview, DSP-I, Eidhof et al., *accepted*) in order to prove its cultural sensitivity as well as to provide its psychometric measures in an independent non-Western population.

Specifically, we hypothesized that a proportion of PTSD sufferers will be identified as belonging to the DS-PTSD and that those individuals will report high levels of childhood adversity as well as experiences of sexual violence. Furthermore, they will exhibit high levels of psychopathology (i.e., more severe PTSD accompanied by higher depressive symptoms, higher suicidality and lower general functionality) than PTSD without dissociative symptoms, and that the DS-PTSD will be associated with avoidant and maladaptive coping strategies (according to the TE/avoidance model of dissociation: Dutra & Wolf, 2017).

3.3 METHODS

3.3.1 Participants

East African citizens settled in the refugee camp Nakivale, Uganda, who were between 18 and 70 years old, were studied. Since we collected biological samples (hair and saliva, results are presented in **Paper 3**), participants needed to be medically healthy without any psychotic or addictive (drugs/alcohol) symptoms currently or in the past as well as were not pregnant or nursing for female participants (for more details on inclusion and exclusion criteria see **Supplement Table 3.1**). In total, into the study, we included 214 refugees (105 females, 49.1%). Nine individuals were excluded from further analyses: eight due to missing data, one because no relevant trauma exposure was reported. 205 interviewees (48.8% female) remaining for the analyses were on average 31.06 years old (SD=10.41, min=18, max=65). The majority came originally from the Democratic Republic of Congo (DRC) (158, 77.1%), followed by Burundians (33, 16.1%), and Rwandese (14, 6.8%) (**Table 3.1**).

3.3.2 Assessment tools

Semi-structured interviews to collect psychological data from study participants were applied. We worked with local interpreters who were assisted with an interview manual translated into the local language (Kiswahili). Stress coping strategies were assessed with the Brief COPE Questionnaire (Carver, 1997). Trauma exposure, such as war events, sexual and family violence, was determined with the Checklist for Traumatic Experiences (CTE) (Ertl et al., 2010), which has been culturally adopted to study populations in East Africa. PTSD symptoms were assessed with the PTSD Symptom Scale Interview (PSSI) (Foa, Riggs, Dancu, & Rothbaum, 1993), supplemented by two items measuring the dissociative subtype of PTSD according to the DSM-5 (American Psychiatric Association, 2013). In accordance with the PSSI algorithm, a PTSD diagnosis was made when at least one re-experiencing, three avoidance and two hyperarousal symptoms were present in asked individuals over the last month (Foa et al., 1993). Furthermore, interviewers assessed observed dissociative symptoms with an adapted version of the Clinician-Administrated Dissociative States Scale (CADSS) (Bremner et al., 1998). Functionality, depressive symptoms and suicidality were measured with the Work and Social Adjustment Scale (WSAS) (Mundt, Marks, Shear, & Greist, 2002), the Patient Health Questionnaire (PHQ-9) (Kroenke, Spitzer, & Williams, 2001), and the screening section of the

Mini International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998), respectively. Moreover, we assessed experience of spirit possession with the Spirit Possession Questionnaire (SPQ) (Neuner et al., 2012; van Duijl, Nijenhuis, Komproe, Gernaat, & de Jong, 2010), a research tool that was developed to study culturally specific dissociative phenomena in East Africa. During the first assessment period (n = 51) we applied the Structured Clinical Interview for DSM-IV Dissociative Disorders (SCID-D, Steinberg, 1994) and in the second assessment period (n = 154) a newly developed interview for dissociative subtype of PTSD (DSP-I, Eidhof et al, *accepted*). Note that to improve readability we do not show the results of SCID-D and the results of SPQ will be published elsewhere. The 10-item, DSP-I draft version, was employed, containing 5 items for the depersonalization and 5 for the derealization assessment. Note that the final DSP-I version consists of 9 items (Eidhof et al., *accepted*).

3.3.3 Study procedures

Study procedures were approved by the local Ethic Committee of the Mbarara University of Science and Technology in Uganda as well as by the German Ethic Committee of the University of Konstanz. Interviews were conducted twice within a three-month period in 2014 and 2015. Interviewers were mental health experts who have been either clinical psychologists, psychosocial workers or psychologists in training. Interpreters were trained on the interview manual within a comprehensive 4-day group training. Participants were selected randomly according to the principle of approaching one out of four houses by the research team. After examination of the inclusion and exclusion criteria (see **Supplement Table 3.1**), study procedures were explained and written informed consents obtained from participants (in case of illiteracy, thumb print was provided). To avoid variability in hormonal assessment due to the circadian rhythm of stress hormone secretion, all interviews began at 12am (± 15 minutes). On average, an interview lasted 184 minutes (m) (min = 91m; max = 365m; SD = 42m, **Figure 3.1**). First, two saliva samples were collected (one for epigenetic and the first for hormonal analyses). Second, stress coping (COPE), trauma exposure (CTE), and PTSD symptoms (PSSI) were assessed. Third, second saliva sample (for hormonal analyses) was collected and third-party assessment of dissociative symptoms was performed by interviewers (CADSS). Fourth, depressive symptoms (PHQ-9), functionality (WSAS), suicidality (M.I.N.I.), spirit possession (SPQ), and dissociative symptoms (SCID-D or DSP-I) were measured. Fifth, third saliva sample (for hormonal analyses) was taken as well as, if possible (hair length ≥ 3cm), a hair sample was collected. Data on saliva and hair samples are shown in **Paper 3**. **Figure 3.1** visualizes the

study protocol. Participants with severe symptomatology were transferred for treatment to the Psychiatric Outpatient Unit at the Mbarara University of Science and Technology or were advised to utilize mental health services based in the Nakivale refugee camp.

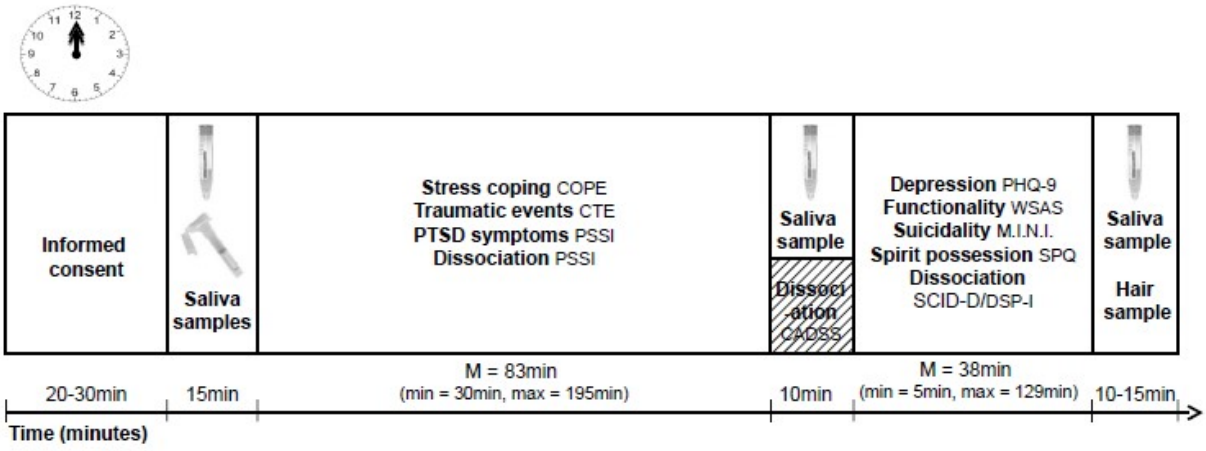

Figure 3.1. *Schematic visualization of the study protocol*

Note. For detailed description, see Methods section of the paper. Tubes symbolize saliva collection. Abbreviations: COPE, Brief Stress Coping Questionnaire; CTE, Checklist for Traumatic Experiences; PSSI, PTSD Symptom Scale; CADSS, Clinician-Administrated Dissociative States Scale; PHQ-9, Patient Health Questionnaire; WSAS, Work and Social Adjustment Scale; M.I.N.I., Mini International Neuropsychiatric Interview; SPQ, Spirit Possession Questionnaire; SCID-D, Structured Clinical Interview for Dissociative Disorders; DSPI, Dissociative Subtype of PTSD Interview.

3.3.4 Statistical analyses

Normal distribution of the data was proven with the Kolmogorov-Smirnov test. Significant outliers were identified with the Grubbs test and removed from the subsequent analyses. Group differences were calculated: in normal distributed, metric variables with one-way ANOVA; in skewed and ordinal data with the Kruskal-Wallis (in analyses of four groups) or the Mann-Whitney-U test (in analyses of two groups), in categorical variables with the Chi-squared test two-tailed (**Table 3.3**, **Table 3.4**, **Supplement Table 3.2**). Correlational analyses between PTSD and dissociative symptoms were performed using the Spearman coefficient for skewed data (**Figure 3.2**). Identification of classes underlying the structure of the PTSD and dissociative symptom data was done with a Latent Profile Analysis (LPA) (**Figure 3.3**), which was performed with the MPlus Version 4.2 (Muthén & Muthén, 2006). Following fit indices for the identified

class solutions were applied: Akaike Information Criterion, AIC; Bayesian Information Criterion, BIC; sample-size adjusted Bayesian Criterion, ssBIC (**Table 3.2**). To prove psychometric qualities of the DSP-I, Cronbach's α coefficient was used to assess internal consistency as a measure of reliability, whereas a correlational matrix between studied variables (non-parametric Spearman coefficient for skewed data) was applied to provide evidence on construct, convergent, and discriminant validity (**Supplement Table 3.3**). All statistical analyses excluding the LPA calculations were conducted with the SPSS Version 18 (PASW Statistics for Windows, Version 18.0, 2009).

3.4 RESULTS

3.4.1 Demographics and clinical characteristics

The studied individuals have spent on average 7.67 (SD = 4.90) years in educational institutions and have been living on average 4.97 (SD = 4.67) years in the refugee camp. As assessed with the CTE, the interviewees experienced on average 21.75 trauma events (SD = 10.98, median = 22) and accordingly to the PSSI scores, the severity of PTSD symptoms was on average 15.65 (SD = 12.55, min = 0, max = 46). The COPE revealed that the most frequent employed coping strategies were religion (e.g., “You have been praying or meditating”) and planning (e.g., “You have been thinking hard about what steps to take”), whereas the most infrequent were substance use (e.g., “You have been using alcohol or other drugs to help you get through it”) and humor (e.g., “You have been making jokes about it”). More detailed information on demographics and clinical characteristics of the whole sample is presented in **Table 3.1**.

To provide an overview of the relationship between PTSD and dissociative symptoms, we conducted correlational analyses between them. **Figure 3.2** outlines the results in (**A**) the whole sample and (**B**) individuals fulfilling the diagnosis criteria for the current PTSD according to the PSSI algorithm (Foa et al., 1993). Whereas dissociative symptoms were skewed in both samples, PTSD symptom data were skewed when studied in trauma exposed individuals (**A**) but followed normal distribution in the PTSD subsample (**B**). In both samples, strong positive relationship between PTSD and dissociative symptoms was found. For statistical details, see **Figure 3.2**.

Table 3.1. *Demographic and clinical characteristics of studied individuals (n = 205)*

Refugees settled in Uganda (n = 205) Mean ± SD	
Age (years)	31.06 ± 10.41
Sex (male/female)	105/100
In female subjects: Contraceptives (yes/no)	4/96
Country of origin (DRC/Burundi/Rwanda)	158/33/14
Years of education	7.67 ± 4.90
Years of stay in the refugee camp	4.97 ± 4.67
Traumatic events (CTE):	
Number of traumata	21.75 ± 10.98
General traumata	2.83 ± 1.59
War traumata	12.28 ± 6.79
Family and community traumata	6.26 ± 4.55
Sexual traumata	.46 ± .81
Childhood traumata	6.22 ± 7.58
Adult traumata	14.12 ± 10.97
PTSD symptoms (PSSI):	
PTSD general score	15.65 ± 12.55
Re-experience	5.03 ± 4.48
Avoidance	6.25 ± 5.04
Hyperarousal	4.37 ± 4.19
Dissociation	.86 ± 1.58
Clinician observed dissociation (CADSS)	1.47 ± 2.50
Stress coping (COPE) :	
Self-distraction	5.45 ± 1.72
Active coping	5.49 ± 1.82
Denial	4.78 ± 1.95
Substance use	2.38 ± 1.07
Emotional support	5.13 ± 1.98
Instrumental support	5.24 ± 1.99
Behavioral disengagement	4.40 ± 1.83
Venting	4.62 ± 1.88
Positive reframing	4.80 ± 2.02
Planning	6.22 ± 1.74
Humor	3.18 ± 1.73
Acceptance	5.77 ± 1.81
Religion	6.85 ± 1.59
Self-blame	4.64 ± 2.04
Depressive symptoms (PHQ-9)	6.18 ± 6.83
Functionality (WSAS)	3.29 ± 5.26
Suicidality (M.I.N.I.)	1.00 ± 3.04

Note. Abbreviations and symbols: SD, standard deviation; DRC, Democratic Republic of Congo; CTE, Checklist for Traumatic Experiences; PSSI, PTSD Symptom Scale; PTSD, posttraumatic stress disorder; CADSS, Clinician-Administrated Dissociative States Scale; COPE, Brief Stress Coping Questionnaire; PHQ-9, Patient Health Questionnaire; WSAS, Work and Social Adjustment Scale; M.I.N.I., Mini International Neuropsychiatric Interview. Excluded outliers: years of stay in the refugee camp: one; sexual trauma: one; CADSS: one; COPE substance use: one; M.I.N.I.: one.

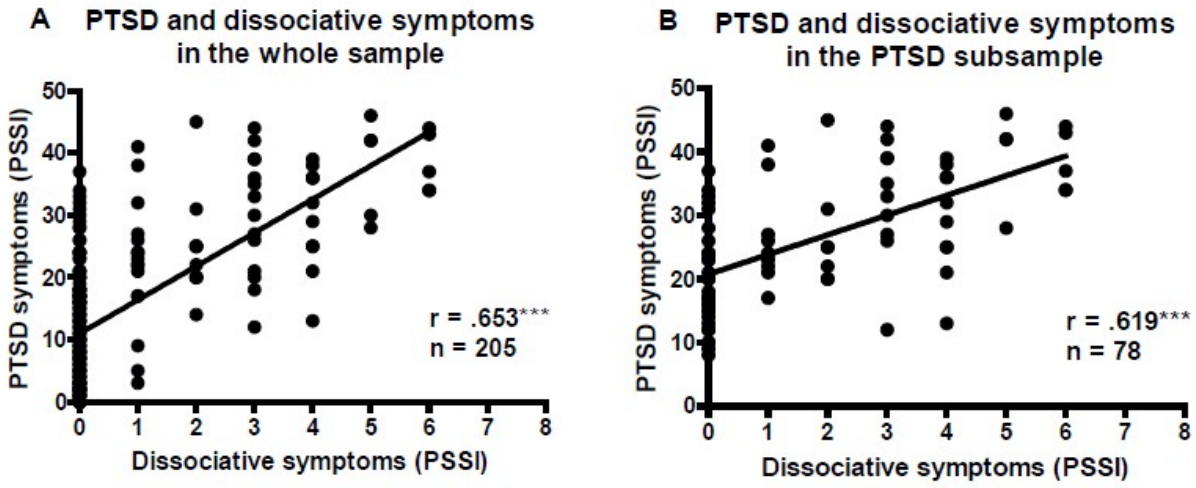

Figure 3.2. *Correlational analyses between PTSD and dissociative symptoms as measured in (A) the whole sample and (B) the PTSD subsample*

Note. Mean values of the PSSI were correlated with two items measuring dissociative symptoms using the Spearman correlational coefficient for skewed data. Abbreviations: PTSD, posttraumatic stress disorder; PSSI, PTSD Symptom Scale Interview. Symbols: r, correlation coefficient; ***, $p < .001$; n, number of studied individuals.

3.4.2 Identification of the Dissociative Subtype of PTSD

Next, we ran a LPA on 19 items from the PSSI corresponding with the 17 PTSD symptoms according to the DSM-IV classification (American Psychiatric Association, 2000) as well as two additional items assessing depersonalization and derealization symptoms. We evaluated 2- through 6-class models. All models converged but the log-likelihood was not replicated in the 5- and 6-class solution suggesting that these models attempted to extract too many classes (Lo, Mendell, & Rubin, 2001). In the 2-, 3-, and 4-class models the best log-likelihood was replicated. Fit indices of all models are presented in **Table 3.2**.

Table 3.2. *Fit indices across all models of the Latent Profile Analysis*

Model	AIC	BIC	ssBIC	Entropy
2	10367.214	10559.948	10376.184	0.973
3	9959.562	10218.757	9971.626	0.972
4	**9820.762**	**10146.417**	**9835.919**	**0.945**
5	9748.251	10140.367	9766.502	0.952
6	9700.557	10159.132	9721.901	0.957

Note. Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; ssBIC, sample-size adjusted Bayesian Information Criterion. Selected class solution is presented in bold.

The best fit indices (AIC, BIC, and ssBIC) among the models with the replicated best values of the log-likelihood were given for the 4-class solution. Moreover, the entropy value for this solution over 0.9 indicates a clear delineation of classes (Celeux & Soromenho, 1996). This can also be supported by high latent class probabilities for most likely latent class membership (class 1 = 0.97; class 2 = 0.96; class 3 = 0.96; class 4 = 0.99). Class 1 was represented by 97 subjects (46.6%), class 2 by 23 subjects (11.3%), class 3 by 57 subjects (28.6%), and class 4 by 28 subjects (13.6%). **Figure 3.3** presents the 4-class solution and **Supplement Table 3.2** shows the demographic and clinical characteristics of the identified classes.

Based on the PTSD and dissociative symptom levels, we reasoned that class 1 represents individuals without clinical symptoms (no symptoms, NS), class 2 individuals with severe PTSD symptoms without dissociative symptoms (sPTSD), class 3 individuals with mild PTSD symptoms without dissociative symptoms (mPTSD), and class 4 individuals showing both high severity of PTSD and high dissociative symptoms (DS-PTSD).

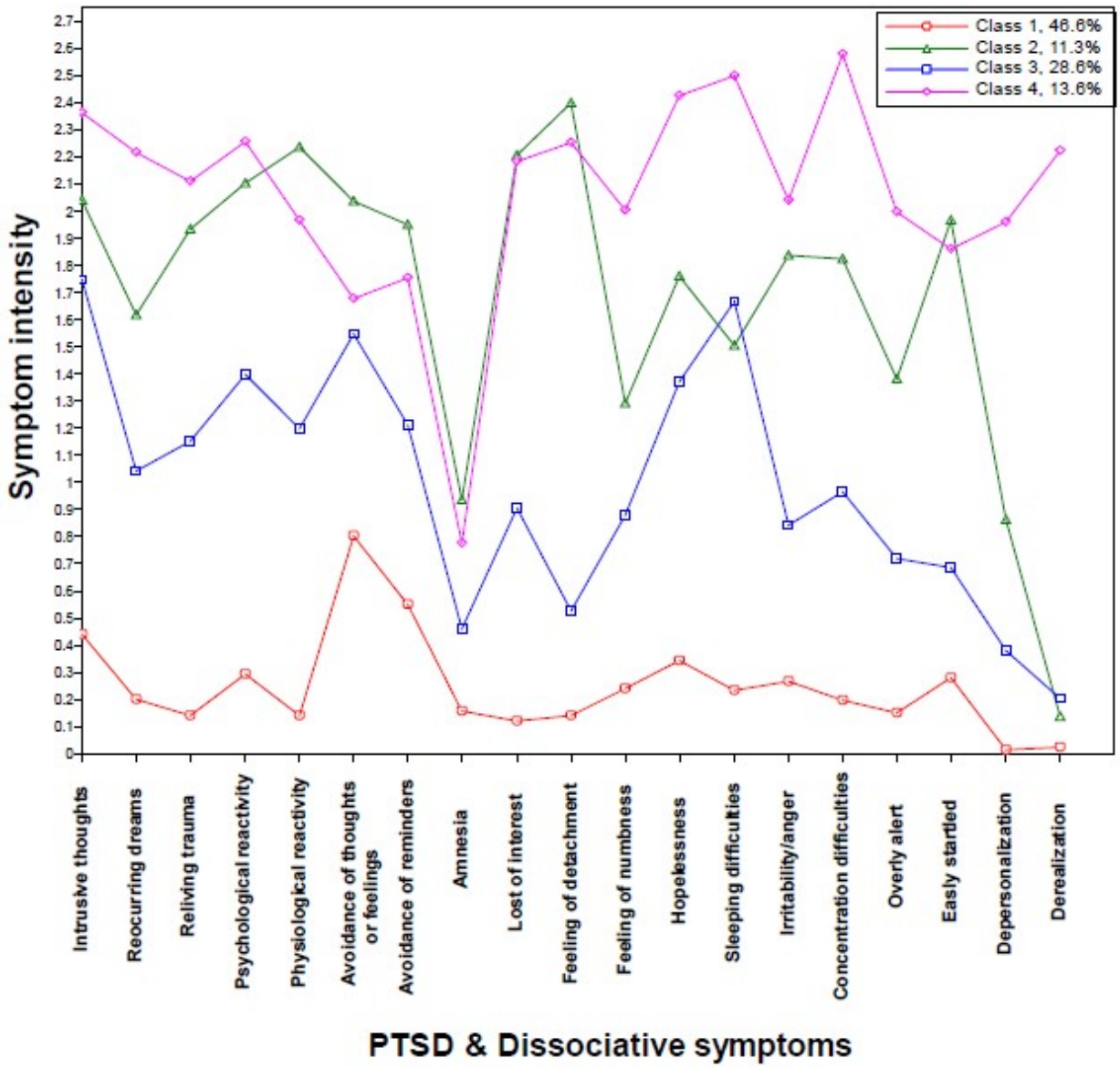

Figure 3.3. *Plot of the Latent Profile Analysis solution with the best fit indices: four classes*

Note. Mean values of PTSD symptoms as assessed with the Symptom Scale Interview (PSSI) supplemented by two items measuring the dissociative subtype of PTSD are shown. Abbreviation: PTSD, posttraumatic stress disorder.

3.4.3 Demographic and clinical characterization of the dissociative subtype of PTSD

Following, no significant differences between DS-PTSD and other classes in demographic variables (age, gender, education years, and the length of stay in the refugee camp) were found. Interestingly, among the studied groups, DS-PTSD showed the highest trauma exposure (CTE), especially considering the amount of family, community and sexual violence as well as the highest levels of psychopathology, in terms of the highest PTSD (PSSI), dissociative (PSSI, CADSS), depressive (PHQ-9) levels, the highest suicidality (M.I.N.I.) and the lowest general functionality (WSAS). Considering coping strategies as measured with the COPE, DS-PTSD scored the highest on both behavioral disengagement and self-blame. Moreover, sPTSD scored trendwise higher on acceptance than DS-PTSD. For statistical details see **Supplement Table 3.2**. Next, to explore, which characteristics are typical for DS-PTSD and can distinguish between DS-PTSD and sPTSD, we compared these two groups concerning the above mentioned variables. DS-PTSD experienced more traumata, specifically family, community, sexual, and trendwise childhood trauma than sPTSD. Moreover, they exhibited higher levels of PTSD, especially hyperarousal symptoms as well as higher depressivity and suicidality. Since high levels of hyperarousal rather than re-experiencing and/or avoidance are contradictory to the theoretical models of DS-PTSD (Lanius et al., 2010), we conducted a post-hoc analysis of mean differences between single items belonging to the hyperarousal cluster. One-way ANOVAs revealed that DS-PTSD scored higher on sleeping ($F(1, 50) = 13.86$, $p = .001$) and concentration difficulties ($F(1, 50) = 10.69$, $p = .002$) as well as trendwise on over-alertness ($F(1, 50) = 3.30$, $p = .075$) than sPTSD. Finally, DS-PTSD was characterized by higher clinician observed dissociation than sPTSD on a trend level. For statistical details see **Table 3.3**.

Table 3.3. *Demographic and clinical characteristics in severe (sPTSD, n = 23) and dissociative PTSD (DS-PTSD, n = 28)*

	Severe PTSD (class 2) n = 23 mean ± SD	**Dissociative subtype of PTSD** (class 4) n= 28 mean ± SD	**Statistical test details**
Age (years)	30.78 ± 8.69	32.11 ± 10.21	F(1, 50) = .24, p = .625
Sex (male/female)	13/10	13/15	$\chi^2(1, n = 51) = .515$, p = .473
Country of origin (DRC/Burundi/Rwanda)	18/4/1	14/12/2	$\chi^2(2, n = 51) = 4.39$, p = .112
Years of education	9.00 ± 5.16	7.18 ± 5.27	F(1, 50) = 1.54, p = .221
Years of stay in the refugee camp	3.42 ± 3.06	3.90 ± 3.26	F(1, 50) = .30, p = .587
Traumatic events (CTE):			
Number of traumata	25.13 ± 6.81	30.75 ± 9.74	**U = 192.000, p = .014**
General traumata	2.96 ± 1.40	3.50 ± 1.43	U = 252.500, p = .178
War traumata	14.61 ± 4.76	16.43 ± 5.48	U = 252.500, p = .187
Family and community traumata	7.04 ± 4.45	10.43 ± 4.43	**U = 188.000, p = .011**
Sexual traumata	.36 ± .79	1.18 ± 1.09	**U = 172.000, p = .004**
Childhood traumata	4.86 ± 6.37	9.54 ± 8.71	**U = 233.500, p = .092**
Adult traumata	16.39 ± 10.04	19.75 ± 11.63	U = 272.500, p = .348
PTSD symptoms (PSSI):			
PTSD general score	30.96 ± 5.55	34.93 ± 6.94	**F(1, 50) = 4.94, p =.031**
Re-experience	9.96 ± 3.56	10.89 ± 2.50	F(1, 50) = 1.21, p = .276
Avoidance	12.52 ± 3.55	13.07 ± 3.31	F(1, 50) = .33, p = .571
Hyperarousal	8.48 ± 2.87	10.96 ± 2.59	**F(1, 50) = 10.54, p = .002**
Dissociation	1.00 ± 1.13	4.18 ± 1.19	**F(1, 50) = 94.56, p < .001**
Clinician observed dissociation (CADSS)	3.14 ± 3.01	4.86 ± 3.61	**F(1, 49) = 3.23, p = .079**
Stress coping (COPE) :			
Self-distraction	5.48 ± 1.75	5.82 ± 1.72	F(1, 50) = .49, p = .486
Active coping	5.65 ± 1.67	5.29 ± 2.07	F(1, 50) = .47, p = .496
Denial	5.57 ± 2.31	4.96 ± 2.01	F(1, 50) = .99, p .326
Substance use	2.59 ± 1.26	2.36 ± .73	U = 297.000, p = .766
Emotional support	4.87 ± 2.01	4.46 ± 2.41	F(1, 50) = .41, p = .523
Instrumental support	5.52 ± 1.88	4.75 ± 2.34	F(1, 50) = 1.64, p = .207
Behavioral disengagement	4.70 ± 2.03	5.57 ± 1.99	F(1, 50) = 2.40, p = .128
Venting	5.13 ± 2.20	4.79 ± 2.22	F(1, 50) = .307, p = .582
Positive reframing	4.43 ± 2.09	4.54 ± 2.01	F(1, 50) = .031, p = .861
Planning	6.52 ± 1.56	6.32 ± 1.81	F(1, 50) = .175, p = .678
Humor	3.09 ± 1.78	3.07 ± 1.92	U = 300.000, p = .619
Acceptance	6.48 ± 1.70	5.71 ± 1.98	F(1, 50) = 2.13, p = .151
Religion	7.35 ± 1.30	6.68 ± 1.79	U = 268.000, p =.222
Self-blame	5.04 ± 2.16	5.50 ± 2.19	F(1, 50) = .556, p = .459
Depressive symptoms (PHQ-9)	10.14 ± 5.95	16.64 ± 6.12	**F(1, 49) = 14.27, p < .001**
Functionality (WSAS)	5.77 ± 5.44	8.54 ± 7.27	F(1, 49) = 2.20, p = .144

Table 3.3. *(continued)*

	Severe PTSD (class 2) n = 23 mean ± SD	**Dissociative subtype of PTSD** (class 4) n= 28 mean ± SD	**Statistical test details**
Suicidality (M.I.N.I.)	1.68 ± 3.73	3.78 ± 5.69	**U = 200.500, p = .041**

Note. Group differences were calculated with: one-way ANOVA, Mann-Whitney-U-test, or Chi-squared test two-tailed. Appropriate to test requirements, shown are: Fisher test (F), U value (U), or results of Chi-squared test two-tailed (χ^2). Significant or trendwise significant results are shown in bold. Abbreviations and symbols: SD, standard deviation; DRC, Democratic Republic of Congo; CTE, Checklist for Traumatic Experiences; PSSI, PTSD Symptom Scale; PTSD, posttraumatic stress disorder; CADSS, Clinician-Administrated Dissociative States Scale; COPE, Brief Stress Coping Questionnaire; PHQ-9, Patient Health Questionnaire; WSAS, Work and Social Adjustment Scale; M.I.N.I., Mini International Neuropsychiatric Interview. Excluded outliers: CTE, one sPTSD; COPE, one sPTSD; M.I.N.I., one DS-PTSD.

3.4.4 Dissociative Subtype of PTSD Interview (DSP-I): psychometrics and evidence for its cross-cultural sensitivity

Data on the DSP-I were available for 154 study participants (48.1% female). General Cronbach's α = .815 indicates high internal consistency in the studied sample. High intercorrelation between depersonalization and derealization subscales (r = .779, p < .001) as well as their relatively lower internal consistencies (depersonalization: α = .675; derealization: α = .656) suggest that depersonalization and derealization items tend to capture co-existing phenomena. **Supplement Table 3.3** presents a correlational matrix between DSP-I measures and other study variables. Positive relationships between DSP-I scores and dissociative symptom severity as measured with the PSSI and CADSS provide evidence on the construct validity. Since positive interrelations between DSP-I measures and high TE as well as high psychopathology (i.e., high PTSD and depressive symptoms, high suicidality, low functionality as well as high behavioral disengagement and substance use as a coping strategies) were found, the convergent validity was given. Negative relationships between DSP-I measures and active coping provide evidence on the discriminant validity.

Finally, we analyzed the DSP-I scores with respect to four identified LPA classes, as described above. As expected, DS-PTSD showed the highest values of DSP-I scores as compared to NS, mPTSD, and sPTSD. For statistical details see **Table 3.4**. When analyzed separately, sPTSD

and DS-PTSD differed in all dissociation measures (DSPI total: F(2, 35) = 3.15, p = .056; depersonalization: U = 80.500, p = .030; derealization: F(2, 34) = 4.94, p = .014).

Table 3.4. *DSP-I measures with respect to the identified LPA classes*

	No symptoms (class 1) n = 73 mean ± SD	**Severe PTSD** (class 2) n = 16 mean ± SD	**Mild PTSD** (class 3) n = 46 mean ± SD	**Dissociative subtype of PTSD** (class 4) n= 19 mean ± SD	**Statistical test details**
DSP-I total	.04 ± .26	3.00 ± 4.77	.49 ± 1.39	7.32 ± 5.78	**χ^2(3, *n* = 152) = .66.88, p < .001**
DSP-I depersonalization	.00 ± .00	1.00 ± 1.93	.24 ± .88	3.32 ± 3.25	**χ^2(3, *n* = 151) = .63.53, p < .001**
DSP-I derealization	.01 ± .12	1.07 ± 1.75	.24 ± .61	4.00 ± 3.33	**χ^2(3, *n* = 151) = 70.12, p < .001**

Note. Group differences were calculated with the Kruskal-Wallis-test (shown are results of the Chi-squared test). Significant results are shown in bold. Abbreviations: SD, standard deviation; DSP-I, Dissociative Subtype of PTSD Interview. Excluded outliers: DSP-I total, one NS, one mPTSD; DSP-I depersonalization, one NS, one sPTSD, one mPTSD; DSP-I derealization, one NS, one sPTSD; one mPTSD.

3.5 DISCUSSION

To the best of our knowledge, this is the first study providing data on the cross-cultural validity of the DS-PTSD construct that was conducted in a non-Western population employing expert-based interviews rather than analyzing self-report data. Moreover, this is the first LPA study in a non-Western population that, similarly to previous results in Western countries (Hansen et al., 2017), identified two PTSD classes exhibiting high PTSD with one of them showing high dissociative symptomatology. Consequently, the DS-PTSD was characterized by more dissociative symptoms as assessed by expert-based interviews (PSSI and DSP-I) as well as by expert-based observation (CADSS) as compared to sPTSD. Other constructs that were present in DS-PTSD and not in sPTSD, such as high trauma dose (i.e., number of experienced traumata), exposure to community, family, and sexual TE as well as high depressivity provide additional evidence for its cross-cultural validity. Interestingly, DS-PTSD showed more behavioral disengagement as a general coping strategy, lower functionality, and higher suicidality as compared to mPTSD and HC but not to sPTSD. Note that in the studied sample no differences between DS-PTSD and other groups on demographic variables such as gender or age were demonstrated. Additionally, we demonstrated that the newly developed interview, the DSP-I (Eidhof et al., *accepted*), shows excellent psychometric properties, in terms of reliability and validity measures. This instrument was proven to capture the symptoms of depersonalization and derealization phenomena in a culturally sensitive way.

The DS-PTSD was found in 14% of all studied individuals and in 26% of all study participants identified to belong to one of three PTSD classes (mPTSD, sPTSD or DS-PTSD). This proportion is within the range of hitherto conducted studies (e.g., Ginzburg et al., 2006; Hansen et al., 2017; Stein et al., 2013). This finding, similarly to Stein and coworkers (2013), but employing more reliable methodology, provides clear evidence that the presence of the DS-PTSD is not limited to Western countries and that further cross-cultural studies on the DS-PTSD applicability are needed.

Similarly to previous reports (e.g., Hansen et al., 2017), in our study, PTSD levels were higher in DS-PTSD than in sPTSD. However, the difference between the mean values was relatively small (DS-PTSD: M=34.93, SD=6.94; sPTSD: M=30.96, SD=5.55). Morever, this effect was mainly driven by higher levels of hyperarousal symptoms in DS-PTSD as compared to sPTSD. The fact that DS-PTSD was characterized by higher hyperarousal symptoms than sPTSD is surprising, since according to the theoretical models, DS-PTSD should rather score higher on

re-experiencing and/or avoidance symptom clusters (Dutra & Wolf, 2017; Lanius et al., 2010). Intrigued by this finding, we conducted a post-hoc analysis of mean differences between single items belonging to the hyperarousal cluster in DS-PTSD and sPTSD according to the PSSI measurement. DS-PTSD scored higher on sleeping and concentration difficulties as well as trendwise on over-alertness. These findings may actually not conflict with the theoretical models of the DS-PTSD but even support the evidence of its higher general impairment (stronger sleeping and concentration difficulties) (e.g., Selvi et al., 2017; Stein et al., 2013) as well as feeling of unsafety/insecurity (over-alertness), characteristic for dissociation (e.g., Ehlers, 1999; Fiedler, 2013).

Furthermore, considering general psychological factors associated with dissociative states, we hypothesized the DS-PTSD to be connected with avoidant and maladaptive coping strategies, such as denial and behavioral disengagement (see also: Dutra & Wolf, 2017). Interestingly, similarly to Haagen et al. (2018) and contrary to Hansen et al. (2016), no differences between DS-PTSD and sPTSD with respect to general stress coping strategies were found. However, DS-PTSD scored the highest on behavioral disengagement among all studied groups and these differences reached statistical significance when compared to NS and mPTSD. It may be suggested that this general coping strategy may constitute a correlate/risk factor for the development of dissociative symptoms as a consequence of TE. Moreover, behavioral disengagement was operationalized by two items: “I’ve been giving up trying to deal with it” and “I’ve been giving up the attempt to cope”. This kind of coping has been repeatedly found in relation to sexual TE (e.g., Schauer & Elbert, 2010), which was indeed most frequent reported by DS-PTSD in comparison to other studied groups. Furthermore, a positive correlation between DSP-I measures and substance use as a coping strategy was found. This result is conformed with the previous report in U.S. veterans suffering from DS-PTSD showing more alcohol use problems than those with non-DS-PTSD (Tsai, Armour, Southwick, & Pietrzak, 2015). Future, prospective research should clarify if general coping strategies, such as behavioral disengagement or substance use, constitute pre-, peri-, or post-TE correlates/risk factors of PTSD and dissociation.

The similarity of correlates found in the Ugandan population to previously studied Western populations (e.g., Hansen et al., 2017), suggests that clinicians may expect the clinical picture of the DS-PTSD to be similar worldwide. This offers compelling opportunities of adopting treatment strategies that target dissociative symptomatology and testing their effectiveness in different

cultural contexts (e.g., Carpenter et al., 2007; Haagen et al., 2018; Wolf, Lunney, & Schnurr, 2016).

The results at hand and their interpretation need to be discussed in light of several limitations of this study. First, the cross-over design is limited by the absence of prospective data and does not allow causal interpretations to be made. Second, for the assessment of PTSD symptoms, DSM-IV criteria (American Psychiatric Association, 2000) were used. However, the DS-PTSD was conceptualized to be assessed together with DSM-5 criteria (American Psychiatric Association, 2013). Similar to our study, previous reports used the same methodology and suggested that the DS-PTSD can also be identified in relation to three symptoms clusters of the DSM-IV PTSD criteria (see also: Hansen et al., 2017). Third, we assessed PTSD symptoms considering their severity in the last four weeks and by doing so we did not consider lifetime PTSD symptomatology. In this highly traumatized population there is a high possibility that a significant proportion of identified NS fulfilled the PTSD as well as DS-PTSD diagnostic criteria across the lifespan. Fourth, the interviews were conducted by mental health experts accompanied by local lay-interpreters. Although they had undergone a comprehensive training on studied constructs, a presence of more or less systematic translation biases during data collection cannot be ruled out. Fifth, as other dissociative phenomena, such as trance and possessive states, have been found in different non-Western samples including Ugandan population to be associated with TE and PTSD symptomatology (e.g., Hecker, Barnewitz, Stenmark, & Iversen, 2016; Hecker, Braitmayer, & van Duijl, 2015; van Duijl, Kleijn, & de Jong, 2014; van Duijl et al., 2010), future reports should explore how these phenomena relate to the DS-PTSD. Indeed, as stated in the Methods section of this paper, we employed a measure of spirit possession phenomena (SPQ) in this sample but its results will be presented separately. Sixth, as for LPA studies, the sample size was relatively small.

Acknowledging the above mentioned limitations, the strengths of this study were: first, assessment of studied variables based on semi-structured interviews conducted by trained mental health experts; second, dissociative symptomatology was captured with several measurements including a newly developed interview for the DS-PTSD (DSP-I, Eidhof et al., *accepted*); third, an equal proportion of female and male individuals included into the sample rule out a possibility of a gender bias; fourth, to the best of our knowledge, this is the very first study using LPA methodology in a non-Western population providing extensive data on the cross-cultural validity of the DS-PTSD.

3.6 SUPPLEMENT PAPER 2

Supplement Table 3.1. *Study inclusion and exclusion criteria*

Inclusion criteria	Age between 18 and 70 years
Exclusion criteria	Psychotic symptoms (current and in the past) Drugs/alcohol consumption/ acute intoxication Chronic diseases (e.g., cancer, diabetes, tuberculosis) Chronic infection diseases (e.g., HIV, hepatitis) Acute infections in the last week (including symptoms like: fever, cough, sore throat, headache, skin rash) Gastro-intestinal complaints in the last week (e.g., diarrhea, blood in stool, abdominal pain) Visible wounds Shift work Traveling to Guinea, Sierra Leone, and Liberia in the past months* *In women*: pregnancy or nursing

* Due to the Ebola outbreak in West Africa during the data collection in 2014 and 2015.

Supplement Table 3.2. *Demographic and clinical characteristics of four classes identified with the Latent Profile Analysis*

	No symptoms (class 1) n = 97 mean ± SD	**Severe PTSD** (class 2) n = 23 mean ± SD	**Mild PTSD** (class 3) n = 57 mean ± SD	**Dissociative subtype of PTSD** (class 4) n= 28 mean ± SD	**Statistical test details**
Age (years)	30.08 ± 11.07	30.78 ± 8.69	31.73 ± 9.13	32.11 ± 10.21	$\chi^2(3, n = 203) = 3.50$, p = .321
Sex (male/female)	42/55	13/10	37/20	13/15	**$\chi^2(3, n = 203) = 7.23$, p = .065**
In female subjects: Contraceptives (yes/no)	0/55	0/10	4/16	0/15	**$\chi^2(3, n = 100) = 16.67$, p = .001**
Country of origin (DRC/Burundi/Rwanda)	84/2/11	18/4/1	42/15/0	14/12/2	**$\chi^2(3, n = 205) = 38.94$, p < .001**
Years of education	7.21 ± 4.78	9.00 ± 5.16	8.18 ± 4.78	7.18 ± 5.27	$\chi^2(3, n = 204) = 3.69$, p = .297
Years of stay in the refugee camp	6.39 ± 5.93	3.42 ± 3.06	3.75 ± 2.61	3.90 ± 3.26	**$\chi^2(3, n = 199) = 7.58$, p = .055**
Traumatic events (CTE):					
Number of traumata	15.69 ± 9.58	25.13 ± 6.81	26.26 ± 9.42	30.75 ± 9.74	**$\chi^2(3, n = 205) = 59.09$, p < .001**
General traumata	2.33 ± 1.54	2.96 ± 1.40	3.32 ± 1.59	3.50 ± 1.43	**$\chi^2(3, n = 205) = 19.35$, p < .001**
War traumata	8.94 ± 6.94	14.61 ± 4.76	14.98 ± 4.94	16.43 ± 5.48	**$\chi^2(3, n = 205) = 42.06$, p < .001**
Family and community traumata	4.10 ± 3.19	7.04 ± 4.45	7.58 ± 4.69	10.43 ± 4.43	**$\chi^2(3, n = 205) = 48.21$, p < .001**
Sexual traumata	.24 ± .58	.36 ± .79	.46 ± .68	1.18 ± 1.09	**$\chi^2(3, n = 203) = 27.79$, p < .001**
Childhood traumata	4.73 ± 6.11	4.86 ± 6.37	7.65 ± 8.95	9.54 ± 8.71	**$\chi^2(3, n = 204) = 9.93$, p = .019**
Adult traumata	10.12 ± 9.43	16.39 ± 10.04	17.25 ± 11.19	19.75 ± 11.63	**$\chi^2(3, n = 205) = 25.55$, p < .001**
PTSD symptoms (PSSI):					
PTSD general score	4.78 ± 4.13	30.96 ± 5.55	18.49 ± 3.73	34.93 ± 6.94	**$\chi^2(3, n = 205) = 172.55$, p < .001**
Re-experience	1.16 ± 1.51	9.96 ± 3.56	6.65 ± 2.34	10.89 ± 2.50	**$\chi^2(3, n = 204) = 156.47$, p < .001**
Avoidance	2.28 ± 2.08	12.52 ± 3.55	6.96 ± 2.71	13.07 ± 3.31	**$F(3, 203) = 178.90$, p < .001**
Hyperarousal	1.19 ± 1.69	8.48 ± 2.87	4.88 ± 2.49	10.96 ± 2.59	**$\chi^2(3, n = 205) = 142.88$, p < .001**
Dissociation	.02 ± .14	1.00 ± 1.13	.54 ± .95	4.18 ± 1.19	**$\chi^2(3, n = 203) = 131.41$, p < .001**
Clinician observed dissociation (CADSS)	.47 ± 1.20	3.14 ± 3.01	.79 ± 1.33	4.86 ± 3.61	**$\chi^2(3, n = 202) = 71.30$, p < .001**
Stress coping (COPE) :					
Self-distraction	5.29 ± 1.81	5.48 ± 1.75	5.53 ± 1.54	5.82 ± 1.72	$\chi^2(3, n = 205) = 2.23$, p = .527

Supplement Table 3.2. *(continued)*

	No symptoms (class 1) n = 97 mean ± SD	**Severe PTSD** (class 2) n = 23 mean ± SD	**Mild PTSD** (class 3) n = 57 mean ± SD	**Dissociative subtype of PTSD** (class 4) n= 28 mean ± SD	**Statistical test details**
Active coping	5.54 ± 1.85	5.65 ± 1.67	5.46 ± 1.75	5.29 ± 2.07	$\chi^2(3, n = 205) = .45$, p = .929
Denial	4.43 ± 1.78	5.57 ± 2.31	4.96 ± 1.97	4.96 ± 2.01	**$\chi^2(3, n = 205) = 6.69$, p = .082**
Substance use	2.19 ± .74	2.59 ± 1.26	2.46 ± 1.17	2.36 ± .73	$\chi^2(3, n = 202) = 5.50$, p = .139
Emotional support	5.31 ± 1.99	4.87 ± 2.01	5.25 ± 1.67	4.46 ± 2.41	$\chi^2(3, n = 205) = 4.60$, p = .203
Instrumental support	5.49 ± 2.04	5.52 ± 1.88	4.93 ± 1.72	4.75 ± 2.34	$\chi^2(3, n = 205) = 5.07$, p = .167
Behavioral disengagement	3.95 ± 1.60	4.70 ± 2.03	4.47 ± 1.80	5.57 ± 1.99	**$\chi^2(3, n = 205) = 15.79$, p = .001**
Venting	4.42 ± 1.75	5.13 ± 2.20	4.67 ± 1.80	4.79 ± 2.22	$\chi^2(3, n = 205) = 2.43$, p = .488
Positive reframing	5.10 ± 2.03	4.43 ± 2.09	4.54 ± 1.96	4.54 ± 2.01	$\chi^2(3, n = 205) = 4.09$, p = .252
Planning	6.24 ± 1.78	6.52 ± 1.56	6.04 ± 1.72	6.32 ± 1.81	$\chi^2(3, n = 205) = 1.62$, p = .655
Humor	3.14 ± 1.65	3.09 ± 1.78	3.33 ± 1.79	3.07 ± 1.92	$\chi^2(3, n = 205) = 1.70$, p = .638
Acceptance	5.46 ± 1.84	6.48 ± 1.70	6.02 ±1.65	5.71 ± 1.98	**$\chi^2(3, n = 205) = 7.35$, p = .061**
Religion	6.92 ± 1.58	7.35 ± 1.30	6.63 ± 1.60	6.68 ± 1.79	$\chi^2(3, n = 205) = 5.90$, p = .117
Self-blame	4.35 ± 1.90	5.04 ± 2.16	4.54 ± 2.04	5.50 ± 2.19	**$F(3, 204) = 2.73$, p = .045**
Depressive symptoms (PHQ-9)	1.73 ± 3.05	10.14 ± 5.95	6.74 ± 4.77	16.64 ± 6.12	**$\chi^2(3, n = 203) = 112.16$, p < .001**
Functionality (WSAS)	.90 ± 2.14	5.77 ± 5.44	3.22 ± 4.61	8.54 ± 7.27	**$\chi^2(3, n = 201) = 61.30$, p < .001**
Suicidality (M.I.N.I.)	.09 ± .29	1.68 ± 3.73	.46 ± 1.06	3.78 ± 5.69	**$\chi^2(3, n = 201) = 60.40$, p < .001**

Note. Group differences were calculated with: one-way ANOVA, Chi-squared test two-tailed, or Kruskal-Wallis test, appropriate to test requirements, shown are: Fisher test (F) or results of Chi-squared test (χ^2), respectively. Significant or trendwise significant results are shown in bold. Abbreviations and symbols: SD, standard deviation; DRC, Democratic Republic of Congo; CTE, Checklist for Traumatic Experiences; PSSI, PTSD Symptom Scale; PTSD, posttraumatic stress disorder; CADSS, Clinician-Administrated Dissociative States Scale; COPE, Brief Stress Coping Questionnaire; PHQ-9, Patient Health Questionnaire; WSAS, Work and Social Adjustment Scale; M.I.N.I., Mini International Neuropsychiatric Interview. Excluded outliers: age, one mPTSD; years of stay in the refugee camp, one mPTSD; CTE, one NS, one sPTSD; PSSI, two NS; CADSS, one NS, one mPTSD; COPE, one NS, one sPTSD, one mPTSD; PHQ-9, one NS; WSAS, one NS, one mPTSD; M.I.N.I., one NS, one sPTSD, one mPTSD, one DS-PTSD.

Supplement Table 3.3. *Correlational matrix: validity measures of the Dissociative Subtype of PTSD Interview (DSP-I)*

	DSP-I total score	DSP-I depersonalization	DSP-I derealization
Age (years)	**.205***	**.219****	**.204***
Years of education	-.122	-.032	-.125
Years of stay in the refugee camp	.039	-.031	-.001
Traumatic events (CTE):			
Number of traumata	**.394*****	**.356*****	**.353*****
General traumata	**.175***	.133	**.155**^{t}**
War traumata	**.278*****	**.269*****	**.244****
Family and community traumata	**.448*****	**.383*****	**.406*****
Sexual traumata	**.211****	**.185***	**.241****
Childhood traumata	**.143**^{t}**	.089	**.140**^{t}**
Adult traumata	**.228****	**.217****	**.202***
PTSD symptoms (PSSI):			
PTSD general score	**.548*****	**.500*****	**.544*****
Re-experience	**.508*****	**.455*****	**.507*****
Avoidance	**.470*****	**.451*****	**.456*****
Hyperarousal	**.547*****	**.484*****	**.547*****
Dissociation	**.571*****	**.539*****	**.584*****
Clinician observed dissociation (CADSS)	**.515*****	**.534*****	**.529*****
Stress coping (COPE):			
Self-distraction	.072	.013	.095
Active coping	**-.184***	**-.194***	**-.167***
Denial	.069	.004	.106
Substance use	**.186***	.110	**.174***
Emotional support	-.092	**-.137**^{t}**	-.054
Instrumental support	-.104	-.095	-.087
Behavioral disengagement	**.178***	**.185***	**.188***
Venting	-.076	-.075	-.083
Positive reframing	-.131	**-.152**^{t}**	-.127
Planning	.016	-.009	.006
Humor	-.018	-.112	-.035
Acceptance	-.017	.022	.017
Religion	-.070	-.018	-.078
Self-blame	.086	.099	.105
Depressive symptoms (PHQ-9)	**.463*****	**.466*****	**.435*****
Functionality (WSAS)	**.375*****	**.382*****	**.368*****
Suicidality (M.I.N.I.)	**.467*****	**.407*****	**.474*****

Note. Due to skewed distribution of the DSP-I data, the interrelations between variables were calculated with the Spearman coefficient. Symbols: t, ≤ .1; *, p ≤ .05; **, p ≤ .01; ***, p ≤ .001. Significant or trendwise significant results are shown in bold. Abbreviations: DSP-I, Dissociative Subtype of PTSD Interview; CTE, Checklist for Traumatic Experiences; PSSI, PTSD Symptom

Scale; PTSD, posttraumatic stress disorder; CADSS, Clinician-Administrated Dissociative States Scale; COPE, Brief Stress Coping Questionnaire; PHQ-9, Patient Health Questionnaire; WSAS, Work and Social Adjustment Scale; M.I.N.I., Mini International Neuropsychiatric Interview. Excluded outliers: CTE, one sPTSD; PSSI, one DS-PTSD; CADSS, one DS-PTSD; COPE, one mPTSD; PHQ-9, one DS-PTSD; WSAS, one DS-PTSD; M.I.N.I., one DS-PTSD; DSP-I, one DS-PTSD.

4. PAPER 3

Sexual trauma and dissociation-related stress coping predict blunted cortisol levels as a response to a diagnostic interview in East African refugees

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4.1 ABSTRACT

Background: Inconsistent results were found whether PTSD diagnostic procedures evoke endocrine stress response in traumatized individuals. Moreover, little is known how biological stress response corresponds with various psychobiological variables, such as trauma characteristics (e.g., early life trauma vs. adult trauma), psychopathology (e.g., comorbidity), psychological stress coping, or long-term, non-reactive endocrine stress parameters.

Method: Participants who underwent semi-structured interviews assessing TE, PTSD, and associated psychopathology and provided sufficient amounts of body material for subsequent analyses, were selected from a bigger sample as described in **Paper 2**. Saliva cortisol (sCORT) stress response rates and their relations with various psychological variables (trauma exposure, PTSD, depressive, dissociative symptoms, stress coping, and suicidality) were analyzed in 153 mixed-sex participants. In 52 female individuals, long-term endocrine parameters (i.e., CORT, cortisone, and dehydroepiandrosteron (DHEA)) and their relations with psychological variables were analyzed in hair samples. The relationship between phasic saliva and tonic hair hormone levels was analyzed in 37 female interviewees.

Results: Within the whole sample, the interview procedures did not evoke a significant stress hormone response. However, a subset of CORT responders (29% of all participants) showed higher PTSD, especially re-experiencing, and depressive symptomatology as well as lower acceptance, lower emotional and instrumental support as compared to CORT non-responders. Elevated CORT response was best predicted by low emotional support, whereas low saliva CORT levels by sexual trauma as well as dissociation-related stress coping (defined as high levels of denial and behavioral disengagement). Interestingly, high concentration of stress hormone levels in hair samples was positively correlated with traumatization and several measures of psychopathology (e.g., PTSD and dissociative symptoms). Hair and saliva hormone levels related inversely with each other.

Conclusions: Generally, diagnostic procedures in trauma exposed individuals, at least not at the assessment time tested in this study, may not evoke endocrine stress response in a systematic way. However, a significant response cannot be excluded under high levels of PTSD re-experiencing and depressive symptomatology. Beyond trauma exposure and psychopathology, type of stress coping may contribute to phasic/reactive as well as to tonic/long-term CORT levels.

4.2 INTRODUCTION

An exposure to extreme, traumatic stress has been found to be strongly associated with psychopathology (e.g., Sayed, Iacoviello, & Charney, 2015; Walker et al., 2017), especially with a subsequent development of posttraumatic stress disorder (PTSD) in a proportion of exposed individuals (Breslau, 2009; Kessler et al., 2017). Identifying pre-, peri-, and post-trauma indicators associated with disease intensity may help to understand its psychobiological mechanisms (Bandelow et al., 2017; Schmidt et al., 2015) as well as to optimize still insufficient diagnosis and treatment strategies (Bernardy & Friedman, 2015; Jonas et al., 2013; Visser et al., 2017).

Alterations of the hypothalamus-pituitary-adrenal (HPA)-axis, the body's main stress response system, have been found to be associated pre-trauma with subsequent PTSD development (Steudte-Schmiedgen et al., 2015b; van Zuiden et al., 2013) as well as with trauma exposure (TE) itself and/or PTSD (Klaassens et al., 2012; Morris et al., 2012). The HPA-axis function is regulated by negative feedback processes. Briefly, upon stress exposure, corticotropin-releasing hormone (CRH) is produced by the hypothalamus and acts on the pituitary that in turn releases adrenocorticotropic hormone (ACTH) activating glucocorticoid (among others cortisol, CORT, in humans) production in the adrenal cortex. Peripheral CORT travels back to the hypothalamus and the pituitary suppressing their activation and shutting down the stress response (de Kloet et al., 2005; Smith & Vale, 2006). Both phasic/tonic as well as static/dynamic measurements of CORT, an end-point indicator of the HPA-axis activity being detected in saliva, plasma, urine, fingernail or hair samples, have been applied in past research (Yeo, Babic, Hannoush, & Weiss, 2000), with recommendations of using more than one measurement to increase validity (de Kloet et al., 2006; Walker et al., 2017).

Static, overall lower CORT outputs (as assessed in urine, saliva, and plasma samples) were shown to be associated with TE and/or PTSD (Morris et al., 2012; Pan et al., 2018), a finding conform with the hypothesis of enhanced negative HPA-axis feedback in PTSD (Yehuda, 2005). However, numerous studies were not able to repeat these results and showed either higher basal levels of CORT to be associated with TE/PTSD (Inslicht et al., 2006; Lindley et al., 2004) or no differences between non-traumatized healthy controls (ntHC) as well traumatized healthy controls (tHC) and PTSD (Klaassens et al., 2012; Meewisse et al., 2007; Zaba et al., 2015; **Paper 1**). Considering static, tonic levels, reflecting the accumulation of CORT over the last

months (Gao et al., 2013), the hitherto studies revealed a mixed picture as well, by showing both high and low hair CORT concentrations (hCORT) to be associated with TE and/or PTSD (Steudte-Schmiedgen et al., 2016).

Dynamic assessments of the HPA-axis function have been performed with both pharmacological and psychological challenge tests. The low-dose dexamethasone suppression test (DST) represents the common pharmacological challenge test (McFarlane, Barton, Yehuda, & Wittert, 2011; Yehuda et al., 1993) that revealed enhanced CORT suppression following dexamethasone administration in tHC/PTSD (de Kloet et al., 2006; Klaassens et al., 2012). Although this finding has been consistent across different samples, a correlation between CORT suppression and PTSD symptom severity was not found (de Kloet et al., 2006). Moreover, recent findings demonstrated that significant improvement in PTSD symptoms did not affect DST outcomes as measured pre-post treatment (Schubert et al., 2019). This finding was found in panic disorder (PD) patients, too (Wichmann, Bornstein, Lorenz, & Petrowski, 2018). These data question the clinical relevance of the test itself.

Furthermore, various protocols, such as exposure to trauma reminders (Elzinga, Schmahl, Vermetten, van Dyck, & Bremner, 2003; Gola et al., 2012), cognitive challenge (Bremner et al., 2003), standardized laboratory (Pierrehumbert et al., 2009; Wichmann et al., 2017; Zaba et al., 2015) or non-laboratory stressors (Stoppelbein et al., 2012), were used to induce psychological stress in TE/PTSD. These studies produced conflicting results as well. While some suggested that TE *per se* is decisive for HPA-axis blunting (Elzinga et al., 2008; Lovallo, Farag, Sorocco, Cohoon, & Vincent, 2012; Pierrehumbert et al., 2009; Zaba et al., 2015), hyper-responsiveness related to TE has been observed too (Alexander et al., 2018; Rao, Hammen, Ortiz, Chen, & Poland, 2008; **Paper 1**). Adding to this complexity, both elevated (e.g., Elzinga et al., 2003; Gola et al., 2012), and flattened (e.g., Pierrehumbert et al., 2009) CORT responses were found in PTSD as well as no differences between PTSD and HC (Roelofs et al., 2009; Simeon et al., 2007).

To resolve these inconsistencies, several approaches were proposed. First, it has been hypothesized that after TE, CORT follows a non-linear trajectory responsible for detecting both lower and higher levels of CORT related to TE/PTSD (Miller et al., 2007; Steudte-Schmiedgen et al., 2016). Second, focusing on individual response rates in studied individuals instead of analyzing group means may help to identify HPA-axis reactivity subgroups characterized by

distinct clinical features (Wichmann et al., 2017; Zaba et al., 2015; **Paper 1**). Third, several confounding factors, such as age (Morris et al., 2016), gender (Meewisse et al., 2007), psychiatric comorbidity (Young & Breslau, 2004), trauma characteristics (Frodl & O'Keane, 2013; Miller et al., 2007), or psychological stress reactions, especially with the focus on dissociative phenomena (Simeon et al., 2008; Zaba et al., 2015; **Paper 1**) may account for some of the unexplained variance in the findings. Fourth, a combination of distinct parameters of the HPA-axis activity, such as joint assessment of phasic, dynamic (e.g., in the DST or TSST) and tonic CORT (e.g., hair samples) levels may shed light on the complex relationships between TE, PTSD and alterations of the psychobiological stress system (e.g., Hinkelmann et al., 2013; Schalinski et al., 2015). Fifth, the majority of research concentrated on CORT as a measure of the HPA-axis activity, whereas assessing other HPA-axis related steroid hormone parameters such as cortisone and dehydroepiandrosteron (DHEA) (Gao et al., 2013; Kroboth et al., 1999; Usta et al., 2018; van Zuiden et al., 2017) may give a clearer picture of the HPA-axis activity.

The study at hand aimed to enhance an understanding of these inconsistent results by addressing some of the aspects listed above. In a subset of individuals, as described in **Paper 2**, we measured phasic salivary CORT levels (sCORT) as a stress response to an interview on TE, PTSD, and associated symptomatology, and correlated it with tonic hCORT, cortisone, and DHEA levels. Consistent with Gola et al. (2012), we hypothesized the interview procedures to evoke a significant psychobiological stress response. Accordingly to **Paper 1**, we expected individuals high on dissociation to exhibit lower reactive sCORT as compared to these showing low dissociative symptomatology. Furthermore, to shed more light on the complexity between TE, PTSD, associated psychopathology and the HPA-axis activity, we explored correlations between phasic/tonic HPA-axis measures and general stress coping, TE, PTSD, dissociative and depressive symptoms, general functionality, and suicidality. As a next step, the identified significant correlates were studied as possible predictors of the HPA-axis activity measures. Finally, we compared the HPA-axis activity parameters between groups (no symptoms, mild, severe, and dissociative PTSD) identified with the Latent Profile Analysis (LPA) as described in **Paper 2**.

4.3 METHODS

4.3.1 Participants

The studied participants were East African citizens settled in the refugee camp Nakivale, Uganda, who represent a subset of a bigger study population as described in **Paper 2**. They were between 18 and 70 years old, medically healthy without any psychotic or addictive (drugs/alcohol) symptoms currently or in the past. Female individuals were not pregnant or nursing (for details on inclusion and exclusion see supplement material of **Paper 2**). For study analyses, we selected individuals in which a sufficient amount (≥ 50µl) of saliva in all three samples was given (for details on study procedures see a subsequent paragraph of the Methods section as well as **Paper 2**). As a result, we selected 459 samples from 153 subjects (46.41% female). Hair samples with sufficient study material (hair length ≥ 3cm) were available for 52 female participants. In 37 female participants, joint analyses of both saliva and hair samples were possible. For demographic and clinical characteristics of the studied samples see **Supplement Table 4.1**. In each analysis, we, first, studied the whole sample, and second, applying the LPA classification as described in **Paper 2** analyzed group differences between the identified classes.

4.3.2 Psychological assessment tools

As described in detail in **Paper 2**, psychological data were assessed with semi-structured interviews. Briefly, for TE measurement, the Checklist for Traumatic Experiences (Ertl et al., 2010) was applied. Levels of psychopathology such as PTSD symptoms, depressivity, suicidality and general functioning were assessed with the PTSD Symptom Scale Interview (PSSI) (Foa et al., 1993), the Patient Health Questionnaire (PHQ-9) (Kroenke et al., 2001), the Mini International Neuropsychiatric Interview (M.I.N.I.) (Sheehan et al., 1998), and the Work and Social Adjustment Scale (WSAS) (Mundt et al., 2002), respectively. Moreover, dissociative symptoms were assessed with two items measuring the DS-PTSD, supplementing the PSSI, as well as with a clinician-based interview, the Dissociative Subtype of PTSD Interview (DSP-I) (Eidhof et al., *accepted*), and estimated by interviewers with the adapted version of the Clinician Administrated Dissociative States Scale (CADSS) (Bremner et al., 1998). General coping strategies were measured with the Brief Stress Coping Questionnaire (COPE) (Carver, 1997).

4.3.3 Analyses of body samples

sCORT samples were collected using Salivette® (Sarstedt, Nümbrecht, Germany) tubes provided with cotton swabs for chewing. The first sample was collected at 12am (± 15 minutes), the second in the middle, and the third at the end of the interview. Assessment procedures lasted between two and three hours. During the interview, tubes were stored in cooling boxes (4 °C) and centrifuged (hand driven centrifuge, Hettich, Bäch, Switzerland) for 5 minutes the same day in room temperature. The recovered saliva was stored at 4 °C until assayed with the Cortisol Enzyme Immunoassay Kit (Salimetrics, Carlsbad, the United States) according to the manufacturer's instructions.

Hair steroid hormones (hCORT, cortisone, and DHEA) were analyzed with the mass spectrometry method as described in detail by Gao and coworkers (Gao et al., 2013).

4.3.4 Study procedures

For details on the study procedures and their schematic visualization see Method section of **Paper 2**. Briefly, ethical approvements were given by the ethic institutions of the Mbarara University of Science and Technology in Uganda and the University of Konstanz in Germany. Interviews were conducted by trained professionals assisted by local interpreters. Random selection (one out of four houses) was used to identify participants. Upon agreement to take part in the study, they needed to sign a written informed consent (in case of illiteracy, thumb print was provided). Interviews began at 12am (± 15 minutes) to avoid variability in hormonal assessment due to the circadian rhythm of CORT secretion. Saliva samples were collected: first, at the beginning of an interview; second, following assessments of stress coping (COPE), TE (CTE), PTSD and dissociative symptoms (PSSI); third, at the end of the interview, after assessments of depressive symptoms (PHQ-9), functionality (WSAS), suicidality (M.I.N.I.), and dissociative symptoms (DSP-I). During the second saliva collection, third-party assessment of dissociative symptoms was performed by interviewers (CADSS). At the end of the study procedures, if possible, hair sample was collected.

4.3.5 Statistical analyses

The Kolmogorov-Smirnov test was applied to test for normal distribution, whereas the Grubbs test to detect outliers, which were removed from subsequent analyses. Group differences were calculated: in continuous, normally distributed variables with one-way ANOVA; in ordinal or in

skewed variables with the Kruskal-Wallis-test (upon comparison of 3 groups) or Mann-Whitney-U test (upon comparison of 2 groups), and in categorical variables with the Chi-squared test two-tailed (**Supplement Table 4.1**, **Supplement Table 4.2**). sCORT throughout the study procedures was analyzed with two-way ANOVA with repeated measures (**Figure 4.1**). Greenhouse-Geisser corrections were applied, if assumptions of sphericity were violated. The LPA was conducted as described in detail in **Paper 2**. Correlational analyses were performed with Pearson coefficient, in case of not normal distribution or ordinal data, Spearman coefficients were applied (**Table 4.1**, **Figure 4.2**, **Figure 4.3**, **Supplement Table 4.3**, **Supplement Table 4.4**). Subsequently, Bonferroni corrected for multiple testing results were reported. Based on correlational analyses, variables of interest were selected and subsequently regressed on saliva and hair endocrine parameters using linear regression model. Predictors were centered before entering into the model (**Table 4.1**, **Supplement Table 4.5**). Statistical analyses were calculated with the SPSS Version 18 (PASW Statistics for Windows, Version 18.0, 2009).

4.4 RESULTS

4.4.1 Demographic and clinical characteristics

First, we present demographic and clinical characteristics of the three studied subsamples according to the amounts of body material available for the analyses (saliva, n = 153, hair, n = 52, saliva+hair, n = 37). Apart from gender, educational years as well as behavioral disengagement as a coping strategy, the subsamples did not differ in their demographic and clinical characteristics. The fact that in the second and third samples only female individuals were studied, may explain the reason for more years of education as well as, interestingly, for lower levels of behavioral disengagement as a coping strategy in the first mixed-sex sample. For statistical details see **Supplement Table 4.1**.

4.4.2 Phasic CORT levels: HPA-axis response to trauma exposure, PTSD and dissociative symptom assessment in saliva samples

Figure 4.1A presents measures of CORT assessments at the three assessment times (AT), within the whole sample. Based on the LPA classification as presented in **Paper 2**, among the studied participants we identified 73 individuals with no symptoms (NS, 47.7%), 43 with mild PTSD (mPTSD, 28.1%), 19 with severe PTSD and dissociative symptoms (DS-PTSD, 12.4%), and 18 with severe PTSD (sPTSD, 11.8%). In order to analyze a comparable number of individuals in each group, we randomly selected 19 NS and 19 mPTSD and compared them to 19 DS-PTSD and 18 sPTSD cases (**Figure 4.1B**). In both analyses, two-way ANOVA with repeated measures revealed significant effects of Time (**A**: $F(1.58, 236.98) = 25.49$, $p < .001$: **B**: $F(1.65, 115.41) = 6.70$, $p = .003$), indicating a significant decrease of sCORT following assessment of trauma, PTSD, and dissociative symptoms. In all subjects as well as in the studied LPA groups gender was a significant control variable (**A**: $F(1, 149) = 5.46$, $p = .021$; **B**: $F(1, 69) = 9.01$, $p = .004$), with female participants showing lower levels of CORT at all ATs. Additionally, in LPA groups a trend of a Group effect ($F(1, 70) = 3.34$, $p = .081$) was found, with sPTSD showing a trend towards higher sCORT than the other studied groups.

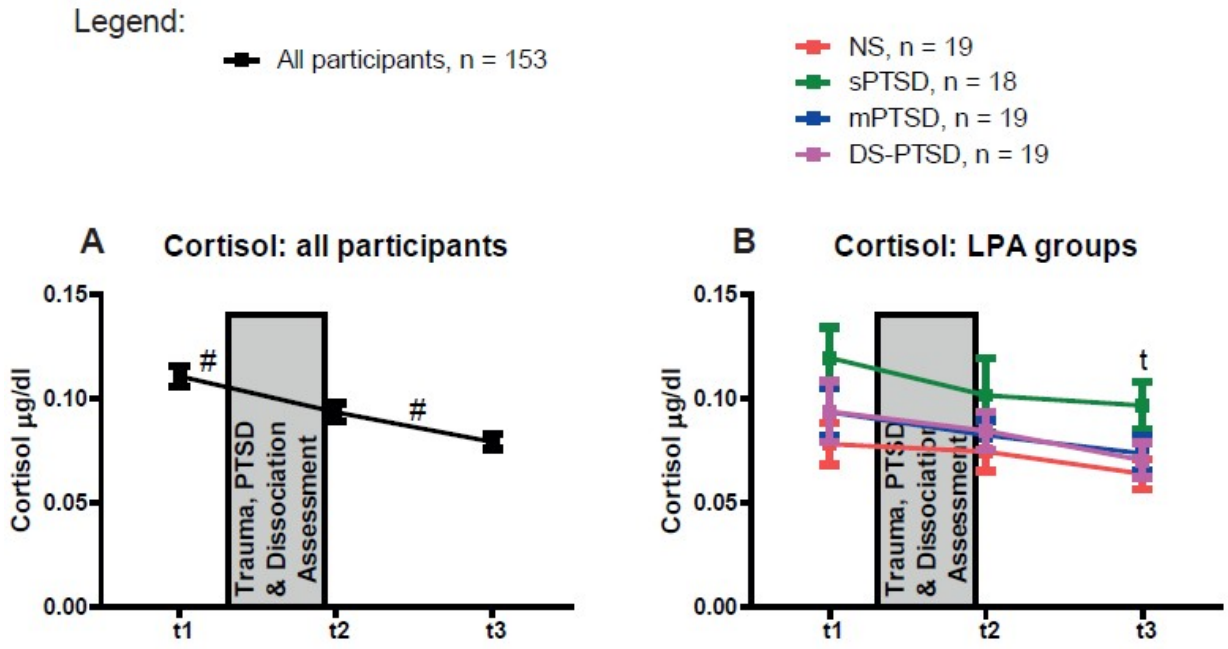

Figure 4.1. *Phasic cortisol levels: response to trauma, PTSD, and dissociation assessment in (A) all participants, and (B) in identified LPA groups*

Note. Cortisol levels were calculated with two-way ANOVA with repeated measures followed by Bonferroni corrections. The study protocol is described in detail in **Paper 2**. Symbols and abbreviations: PTSD, posttraumatic stress disorder; NS, no symptoms; sPTSD, severe PTSD; mPTSD, mild PTSD; DS-PTSD, Dissociative Subtype of PTSD; LPA, Latent Profile Analysis; t1, first assessment; t2, second assessment; t3, third assessment; #, significant time effect; t, trendwise group effect. Significant post-hoc analyses are as follows: (A) time effects: between (betw.) t1 and t2: p = .002; betw. t2 and t3: p < .001: (B) group effects: at t3, betw. HC and sPTSD, p = .071. Excluded outliers: (A) two; (B) one mPTSD.

Following, we applied the 15.5% cut-off of CORT response to a psychosocial stressor (Miller et al., 2013; Zaba et al., 2015), considering the first and the second AT. In the whole sample we identified 45 (29.4%) CORT responders (CORT-R) and 108 (70.6%) non-responders (CORT-NR). According to the LPA classification as described in **Paper 2**, the distribution of CORT-R across the groups was as follows: NS: 5 (26.32%), mPTSD: 8 (42.11%), sPTSD: 5 (27.78%), and DS-PTSD: 8 (42.11%). Contrary to our hypothesis, CORT response did not differ between the groups ($\chi^2(3, n = 75) = 1.89$, p = .595).

Next, explorative, we conducted between-group comparisons between CORT-R and CORT-NR in all studied variables. Interestingly, CORT-R exhibited higher scores of PTSD symptoms, especially re-experiencing symptoms as well as depressive symptoms. Also, they did show

lower levels of emotional and instrumental support as well as lower acceptance as coping strategies as compared to CORT-NR. For statistical details, see **Supplement Table 4.2**.

4.4.3 Relationship between phasic CORT levels and clinical characteristics

Next, within the whole sample, we present a correlational matrix of sCORT at all three AT as well as the percentage of CORT response between the first and the second as well as the first and the last AT with clinical characteristics such as TE, PTSD, dissociative and depressive symptoms, general functionality and suicidality. Lower sCORT levels were related to higher number of general and sexual trauma. Clinician observed dissociation as measured with the CADSS was negatively related to sCORT at the second AT. Coping strategies, denial and behavioral disengagement, were negatively correlated with the two last AT as well as with the CORT response, whereas emotional support only negatively with the CORT response. For statistical details see **Supplement Table 4.3**. Note that following Bonferroni correction for multiple testing, all results expecting the negative relationship between denial as a coping strategy and sCORT at the second AT would not remain significant. **Figure 4.2** visualizes the correlational analyses between single-point as well as reactive CORT levels and following variables of interest: sexual trauma, PTSD and depressive symptoms, dissociation-related stress coping (a variable created as a mean score of coping strategies: denial and behavioral disengagement[1]) as well as emotional support.

[1] To avoid multicollinearity in the subsequent analysis, we created a mean score of two highly related coping strategies (in this sample: $r = .347^{***}$, $p < .001$), denial and behavioral disengagement. The new variable was named: “dissociation-related stress coping”.

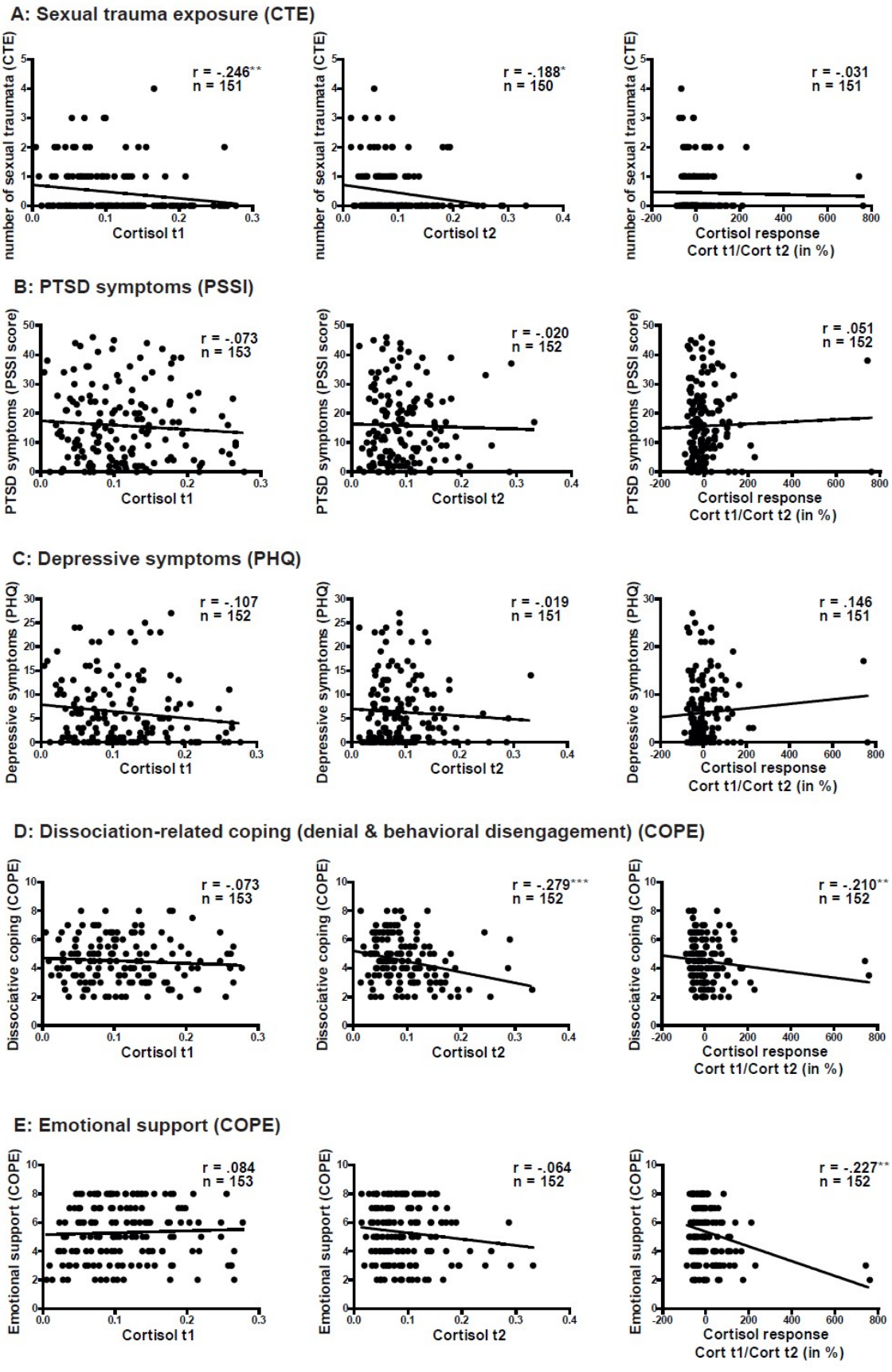
A: Sexual trauma exposure (CTE)
number of sexual traumata (CTE)
r = -.246**
n = 151
Cortisol t1
r = -.188*
n = 150
Cortisol t2
r = -.031
n = 151
Cortisol response
Cort t1/Cort t2 (in %)
B: PTSD symptoms (PSSI)
PTSD symptoms (PSSI score)
r = -.073
n = 153
Cortisol t1
r = -.020
n = 152
Cortisol t2
r = .051
n = 152
Cortisol response
Cort t1/Cort t2 (in %)
C: Depressive symptoms (PHQ)
Depressive symptoms (PHQ)
r = -.107
n = 152
Cortisol t1
r = -.019
n = 151
Cortisol t2
r = .146
n = 151
Cortisol response
Cort t1/Cort t2 (in %)
D: Dissociation-related coping (denial & behavioral disengagement) (COPE)
Dissociative coping (COPE)
r = -.073
n = 153
Cortisol t1
r = -.279***
n = 152
Cortisol t2
r = -.210**
n = 152
Cortisol response
Cort t1/Cort t2 (in %)
E: Emotional support (COPE)
Emotional support (COPE)
r = .084
n = 153
Cortisol t1
r = -.064
n = 152
Cortisol t2
r = -.227**
n = 152
Cortisol response
Cort t1/Cort t2 (in %)

Figure 4.2. *Visualization of correlational analyses between single-point and reactive cortisol levels with variables of interest: (A) sexual trauma exposure, (B) PTSD symptoms, (C) depressive symptoms, (D) dissociation-related stress coping, (E) emotional support as a coping strategy*

Note. Correlational analyses were performed with Pearson coefficient, in case of not normal distribution, Spearman coefficients were calculated. Abbreviations: r, correlational coefficient; t1, first assessment; t2, second assessment; t3, third assessment; Cort t1/Cort t2, percentage of Cortisol change between t1 and t2; CTE, Checklist for Traumatic Experiences; PTSD, Posttraumatic stress disorder; PSSI, PTSD Symptom Scale; PHQ, Patient Health Questionnaire; COPE, Brief Stress Coping Questionnaire. Symbols: *, $p \leq .05$; **, $p \leq .01$; ***, $p \leq .001$.

Following, we conducted linear regression analyses for sCORT levels at the three AT as well as reactive (Cort1/Cort2) CORT levels. High exposure of sexual trauma as well as dissociation-related stress coping predicted lower levels of sCORT levels following assessment of trauma exposure, PTSD and dissociative symptoms. CORT stress response was best predicted by emotional support as a coping strategy: the more emotional support as a coping strategy was reported by the participants, the lower was their percentage CORT response to diagnostic procedures. Statistical details are presented in **Table 4.1**.

4.4.4 Tonic CORT, cortisone and DHEA levels: analyses of hair samples

Hair samples were available from 52 female participants. We employed correlational analyses between hCORT, cortisone, quotient of hCORT to cortisone as well as DHEA levels and clinical characteristics: TE, coping strategies, PTSD, dissociative and depressive symptomatology, general functionality and suicidality. Interestingly, a relatively constant picture of relationships was found. Whereas positive correlations between hCORT, cortisone and DHEA levels with measures of TE, PTSD, dissociation and depressive symptomatology, functionality and suicidality were found, negative correlations between them and the hCORT/cortisone quotient were exhibited. Measures of coping strategies revealed mixed findings with only two coping strategies, namely substance use and behavioral disengagement, revealing the same pattern of relationships as for the above mentioned measures of TE and psychopathology. Note that following Bonferroni correction for multiple testing all results would not remain significant. For more detailed results see **Supplement Table 4.4**.

Table 4.1. *Linear regression analyses for saliva cortisol (CORT) measures (n = 153)*

	Model characteristics			Variables in the equation		
	R	F	p	ß	T	p
Cortisol t1	.196	1.162	.331			
Sexual trauma (CTE)				**-.156**	**-1.691**	**.093**
PTSD symptoms (PSSI)				.073	.576	.566
Depressive symptoms (PHQ)				-.105	-.865	.389
Dissociation-related coping (COPE)				-.024	-.271	.787
Emotional support (COPE)				.046	.555	.580
Cortisol t2	.345	3.888	.002			
Sexual trauma (CTE)				**-.177**	**-1.999**	**.047**
PTSD symptoms (PSSI)				.179	1.480	.141
Depressive symptoms (PHQ)				-.093	-.797	.427
Dissociation-related coping (COPE)				**-.250**	**-3.001**	**.003**
Emotional support (COPE)				-.130	-1.636	.104
Cortisol t3	.314	3.156	.010			
Sexual trauma (CTE)				-.131	-1.457	.147
PTSD symptoms (PSSI)				**.207**	**1.682**	**.095**
Depressive symptoms (PHQ)				-.112	-.949	.344
Dissociation-related coping (COPE)				**-.272**	**-3.219**	**.002**
Emotional support (COPE)				-.029	-.356	.722
CORT response (Cort1/Cort2)	.325	3.411	.006			
Sexual trauma (CTE)				-.051	-.579	.564
PTSD symptoms (PSSI)				.020	.167	.868
Depressive symptoms (PHQ)				.066	.567	.571
Dissociation-related coping (COPE)				-.118	-1.411	.160
Emotional support (COPE)				**-.282**	**-3.531**	**.001**

Note. Linear regression analyses were run applying following variables as a predicted criterion: CORT at the beginning, in the middle and at the end of the diagnostic procedures, and CORT response. CORT response was defined as 15.5% CORT increase between the first and the second assessment time (Miller et al., 2013; Zaba et al., 2015). Bold numbers indicate significant ($p \leq .05$) or trendwise significant results ($p \leq .1$). Abbreviations: t1, first assessment; t2, second assessment; t3, third assessment; Cort1/Cort2, percentage of CORT change between t1 and t2; CTE, Checklist for Traumatic Experiences; PTSD, Posttraumatic stress disorder; PSSI, PTSD Symptom Scale; PHQ, Patient Health Questionnaire; COPE, Brief Stress Coping Questionnaire.

Correlational analyses between hCORT, cortisone, hCORT/cortisone, and DHEA levels with the variables of interest: number of traumata, PTSD, dissociative symptoms, and behavioral disengagement as a coping strategy, are visualized in **Figure 4.3**.

According to the LPA classification, the participants available for the analyses belonged to the following classes: NS, 31 (59.6%), mPTSD, 7 (13.5%), sPTSD, 6 (11.5%), DS-PTSD, 8 (15.4%). Since the groups were small, we decided to restrain from further between-group analyses.

As a next step, we conducted regression analyses of hCORT, cortisone, hCORT/cortisone and DHEA levels with variables of interest: number of traumata, PTSD, dissociative symptoms, and behavioral disengagement as a coping strategy. Interestingly, despite significant interrelations between the studied variables, none of the predictors survived the significance test. Statistical results are shown in **Supplement Table 4.5**.

4.4.5 Phasic and tonic measures of HPA-axis function: joint analysis of saliva and hair samples

Finally, we analyzed the above mentioned measures of the HPA-axis function in 37 female participants from whom saliva and hair samples were available. We conducted correlational analyses between phasic and tonic measures of the HPA-axis parameters. The results show a strong tendency towards a negative relationship between tonic measures of the HPA-axis function and phasic measures of sCORT with one result showing a significant negative relationship between hCORT and sCORT at the first AT. Note that this pattern of results was not observed for the relationship between hair stress hormone levels and sCORT response. The significant result would not be present after applying Bonferroni correction for multiple testing. **Table 4.2** presents the results.

According to the LPA classification, 22 of participants belonged to NS (59.5%), 5 to mPTSD (13.5%), 3 to sPTSD (8.1%), and 7 to DS-PTSD (18.9%). Also in this case, we were limited by the number of participants available for between-group analyses and restrained from them.

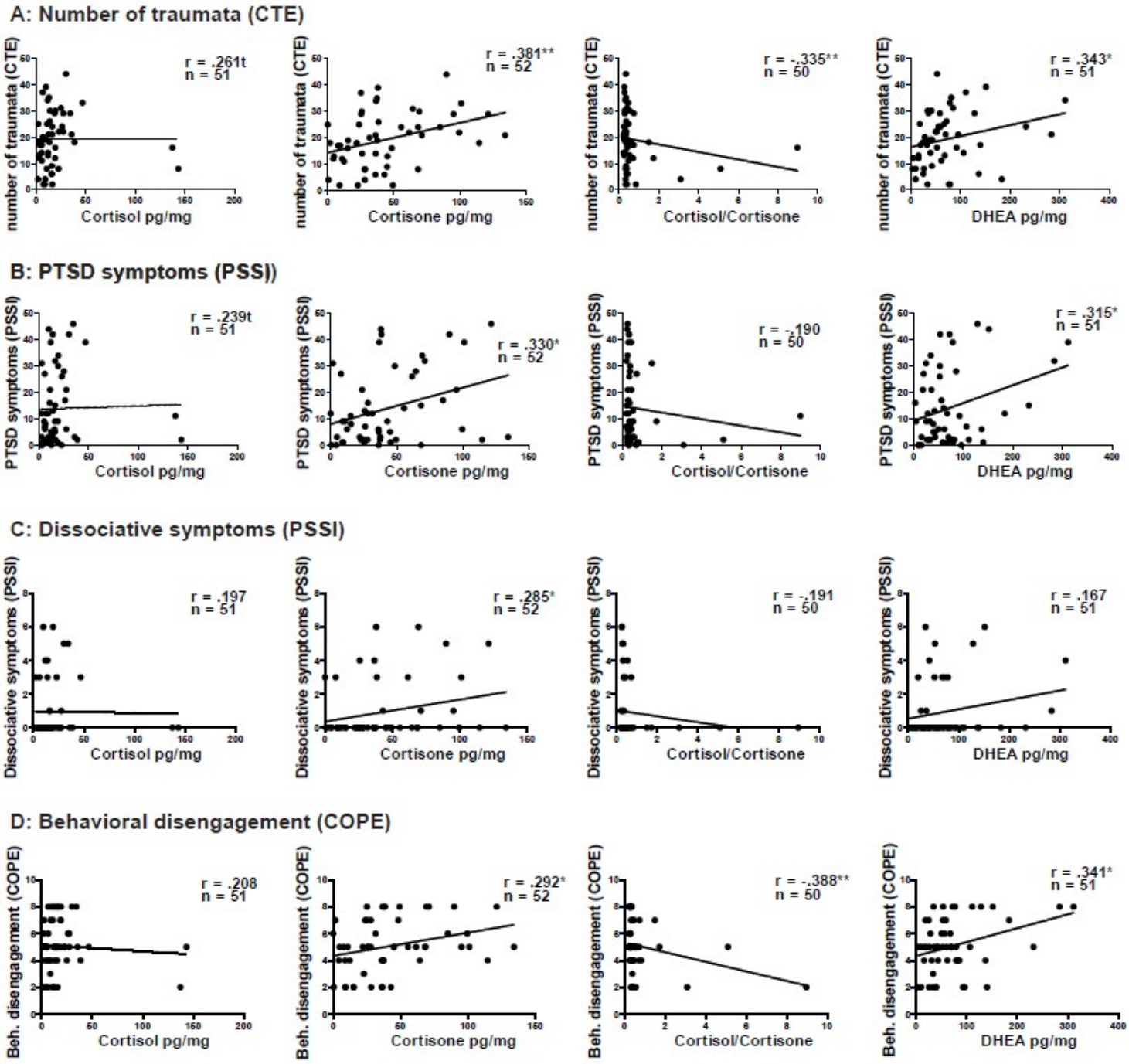

Figure 4.3. *Visualization of correlational analyses between hair stress hormone levels (hCORT, cortisone, hCORT/cortisone, and DHEA) with variables of interest: (A) number of traumata, (B) PTSD symptoms, (C) dissociative symptoms, (D) behavioral disengagement as a coping strategy*

Note. Correlational analyses were performed with Pearson coefficient, in case of not normal distribution, Spearman coefficients were calculated. Abbreviations: r, correlational coefficient; CTE, Checklist for Traumatic Experiences; PTSD, Posttraumatic stress disorder; PSSI, PTSD Symptom Scale; COPE, Brief Stress Coping Questionnaire; DHEA, dehydroepiandrosteron. Symbols: t, p ≤ .1; *, p ≤ .05; **, p ≤ .01.

Table 4.2. *Correlational matrix between saliva CORT as well as percentage CORT response and hair CORT, cortisone and DHEA levels (n = 37)*

Hair **Saliva**	Cortisol	Cortisone	Cortisol/ Cortisone	DHEA
CORT1	***-.344****	-.159	*-.200*	.161
CORT2	*-.264*	-.220	*-.171*	-.136
CORT3	*-.240*	-.138	*-.255*	-.147
CORT response (%) CORT1/CORT2	*-.029*	-.074	*.182*	-.249
CORT response (%) CORT1/CORT3	*-.010*	-.092	*.180*	-.273

Note. Correlational analyses were performed with Pearson coefficient, in case of not normal distribution or categorical data, Spearman coefficients were calculated (marked in *italics*). Abbreviations and symbols: CORT1, cortisol levels at the beginning of the assessment procedures; CORT2, cortisol levels after the assessment of trauma exposure, PTSD and dissociative symptoms; CORT3, cortisol levels at the end of the interview; CORT response CORT1/CORT2, change in cortisol levels between the first and second AT; CORT response CORT1/CORT3, change in cortisol levels between the beginning and the end of the interview; DHEA, dehydroepiandrosteron; *, p ≤ .05. Significant results are marked in bold. Following outliers were identified: saliva CORT3, one; CORT response, one; hair cortisol, one; hair cortisol/cortisone, one; hair DHEA, one.

4.5 DISCUSSION

In this study, semi-standardized assessments of TE and associated psychopathology, such as PTSD, depressive and dissociative symptoms, in individuals highly exposed to trauma, contrary to our hypothesis, did not evoke a systematical biological stress response in terms of significant sCORT increase. These results are in line with the study of Kolassa et al. (2007) also showing a lack of sCORT response to diagnostic interviews in male individuals suffering from severe PTSD. This suggests that standardized diagnostic procedures conducted in a social context, which was safe and controllable did not systematically induce HPA-axis activation. However, this may not be true for all trauma exposed individuals. Our results show that CORT responders (29% of the whole sample) exhibit higher levels of PTSD, especially re-experiencing, and depressive symptomatology as well as lower levels of acceptance, emotional and instrumental support as coping strategies as compared to CORT non-responders. Interestingly, PTSD or depressive symptom severity did not correlate with CORT levels, as this was true for emotional support as a coping strategy (exemplary item: “I’ve been getting emotional support from others”).

Similarly, two other studies, which applied identical methodology, found significant sCORT response to a diagnostic interview only in a subset of individuals. In the first study, in a mixed-sex population, Gola et al. (2012) found upregulation of sCORT in rape survivors, whereas PTSD sufferers without experience of rape showed lack of sCORT response. In the second study, female individuals with a history of childhood sexual abuse exhibited significantly lower sCORT levels following TE assessments as compared to participants without childhood abuse in the past (Schalinski et al., 2015). Interestingly, the latter study demonstrated a paradoxical relationship between tonic and phasic CORT levels related to sexual trauma: low sCORT was associated with higher hCORT levels. In our sample, a corresponding pattern of results was found: sCORT related negatively whereas hCORT positively to sexual trauma.

These findings suggest that sexual trauma may contribute to the frequently observed HPA-axis dysregulations to a stronger degree than other kinds of traumatic experiences. On the one hand maximal body contact with a perpetrator may evoke shut-down self-protective reactions being accompanied by parasympathetic dominance (e.g., Schauer & Elbert, 2010) and possibly reflected in HPA-axis dysregulations too. On the other hand, the emotional extreme stress response with shame and dissociative states that is characteristic for sexual trauma may go along with strong HPA-axis imbalance (e.g., Dickerson & Kemeny, 2004; Gruenewald, Kemeny, Aziz, & Fahey, 2004; Simeon et al., 2008).

Interestingly, in our study, third-party observed dissociative symptoms were negatively correlated with sCORT collected immediately following assessments of TE, PTSD, and dissociative states. This result is intriguing since it proposes phasic reactive low sCORT as a candidate biomarker of acute dissociative states that is not based on self-report data. This kind of a biomarker would have high clinical applicability since it may be easily embedded in diagnostic procedures. However, given the fact that, contrary to our hypothesis, sCORT response did not differ between dissociative and non-dissociative PTSD, its clinical relevance should be proven. Especially, future research needs to clarify how dissociative response to a diagnostic interview corresponds with the occurrence of the dissociative subtype of PTSD (e.g., Dorahy & van der Hart, 2015; Dutra & Wolf, 2017; Lanius et al., 2012). Interestingly, in **Paper 1**, we showed that trauma-related dissociative reactions predict blunted HPA-axis response to a standardized psychosocial stressor. In the study at hand, we validated this result in an independent sample, whereby we demonstrated dissociation-related stress coping (i.e., denial and behavioral disengagement) to be predictive for sCORT levels as measured following assessment of TE, PTSD, and dissociative symptomatology. Moreover, downregulation of the HPA-axis associated with dissociative states as well as upregulation of sCORT related to re-experiencing symptoms would provide further support for the emotion modulation model in PTSD (Lanius et al., 2018, 2010). According to this model, dissociation results from overmodulation of affect being accompanied by prefrontal inhibition of limbic regions. Future research needs to clarify if and how these neural circuits may be related to flattened HPA-axis response being associated with dissociative states.

Furthermore, the striking pattern of negative relationships between phasic and tonic CORT levels needs more explanation. Possibly, a delayed response to stress may occur in individuals showing low phasic and high tonic CORT levels. Koopman et al. (2003) supported this hypothesis by showing a delayed (+24 hours) sCORT response to exposure to trauma reminders in female PTSD sufferers. Interestingly, the +24h sCORT levels were positively associated with acute dissociation assessed as a response to the experimental condition. A negative relationship between sCORT collected following TE, PTSD, and dissociation assessment and hCORT levels, found in this study, may provide further support for the delay hypothesis. However, the lack of relationship between sCORT response and hCORT does not suggest a linear relationship between sCORT decrease corresponding directly with hCORT. This finding is in line with Schalinski et al. (2015) but contradicts results of Steudte-Schmiedgen (2015b). Moreover, we found DHEA hair levels to be positively associated with TE and PTSD,

which is conform with recent meta-analytical findings (van Zuiden et al., 2017). Future research on measures of the HPA-axis activity gathered in multi-method designed studies is urgently needed (see also: Steudte-Schmiedgen et al., 2016).

Furthermore, as discussed in **Paper 1**, distinct factors may contribute to baseline CORT levels as compared to reactive CORT response. Our results suggest that TE itself, especially sexual trauma in our population, may be reflected in general lower sCORT output and higher tonic hCORT. Also other researchers found support for TE but not necessarily PTSD symptom severity being crucial for baseline CORT levels (Dajani, Hadfield, Uum, Greff, & Panter-Brick, 2018; Steudte et al., 2013, 2011). The coping strategies behavioral disengagement, denial and emotional support were negatively associated with the sCORT response. In detail, individuals, who reported getting little emotional comfort from others showed elevated CORT response, whereas those coping with stress through denying what has happened as well as giving up the attempt to cope, exhibited blunted CORT response. Since none of the studies applying a similar methodology, provided additional assessment of coping strategies (Gola et al., 2012; Kolassa et al., 2007; Schalinski et al., 2015), we set out to discuss these findings in light of studies measuring both diurnal CORT output or reactive CORT levels in relationship with coping strategies.

Following, our results are not in line with O'Donnell et al. (2008) as well as Sladek et al. (2017), who showed active engagement in problem solving and seeking for social support to be associated with lower diurnal CORT levels, in older adults and in adolescents girls, respectively. Similarly, they contradict findings of Höhne et al. (2014) demonstrating higher CORT levels as a response to a psychosocial stress challenge (TSST, Kirschbaum et al., 1993) being associated with the employment of negative, maladaptive coping strategies in remitted depression. Moreover, a recent study showed denial state coping to be associated with high peak of CORT in the TSST (Janson & Rohleder, 2017), which also contradicts our results since denial was negatively associated with both sCORT levels following the assessments of TE, PTSD, and dissociative symptoms and the percentage CORT increase. Possible explanations of the contradicted results are differences in applied methodologies and studied samples. Although hypothesized as a potential stressful event, our study procedures did not generally evoke psychobiological stress response, which was the case in Höhne et al. (2014) and in Janson & Rohleder (2017). Following, O'Donnell et al. (2008) and Sladek et al. (2017) focused on diurnal CORT output and not on reactive CORT levels. Moreover, none of the mentioned studies was conducted in refugees, these participants may be unique since they have undergone high

exposure to trauma and by living in a refugee settlement are still situated in a non-safe environment.

Our results need to be discussed in light of several methodological limitations. First, field work did not make it possible to create perfectly controllable conditions for saliva sample collection. The difficulties we met are reflected in the reduced number of saliva samples available for the analyses (74.63% of all studied individuals). Moreover, since both female and male study participants tend to have short haircuts, it made us impossible to collect enough hair material for subsequent analyses. As a result, the analyses were possible in 25.37% of all studied individuals. The same applied for joint analysis of hair and saliva samples, doable in 18.05% of the participants from the whole sample. Due to the fact that a restricted number of samples were available, we were not able to conduct between-group comparisons and needed to limit our analyses to correlational calculations. Second, the observed sCORT decrease throughout the protocol, although conform with other reports (e.g., Kolassa et al. 2007), may be grounded in the study design itself. Measurements of sCORT may be influenced by various factors and in general sCORT shows high instability (e.g., Hellhammer, Wüst, & Kudielka, 2009). For this reason, it is possible that we did not capture the stress-induced CORT increase because we did not assess the CORT levels directly after TE assessments, i.e. following activation of trauma reminders, but after the assessment of PTSD and dissociative symptoms. It remains unclear if the missing CORT increase is because the interview procedures generally do not evoke a psychobiological stress response or because our assessments were not able to capture it. Future studies should apply more frequent saliva assessments throughout study procedures and consider employment of more reliable methods of stress induction, such as the TSST. However, the TSST has been mostly applied in Western populations and its results have been shown to be affected by culture values (Miller & Kirschbaum, 2018). Validation studies in non-Western populations are still needed (see also: Allen et al., 2014). Third, the correlations found in this study were generally weak and did not survive the rather conservative Bonferroni correction for multiple testing (Curtin & Schulz, 1998). These findings question the clinical relevance of the relationship between psychopathological conditions and the HPA-axis measures. Fourth, although conducted by trained mental health experts provided with an interview manual, the interviews were not clinician-based. Fifth, interviewers were assisted by local interpreters and we cannot rule out translation biases completely.

4.6 SUPPLEMENT PAPER 3

Supplement Table 4.1. *Demographic and clinical characteristics of studied subsamples*

	Saliva samples (n = 153) M ± SD	**Hair samples** (n = 52) M ± SD	**Saliva + hair samples** (n = 37) M ± SD	**Statistical test detail**
Age (years)	31.68 ± 10.50	32.83 ± 12.39	34.73 ± 13.20	$\chi^2(2, n = 241) = 1.01, p = .605$
Sex (male/female)	82/71	0/52	0/37	**$\chi^2(2, n = 242) = 72.15, p < .001$**
Country of origin (DRC/Burundi/Rwanda)	114/27/12	44/5/3	30/4/3	$\chi^2(4, n = 242) = 2.99, p = .559$
Regular smoking (yes/no)	1/152	0/52	0/37	$\chi^2(2, n = 242) = .584, p = .747$
Years of education	7.88 ± 4.94	6.29 ± 4.87	5.73 ± 5.00	**$\chi^2(2, n = 242) = 8.27, p = .016$**
Years of stay in the refugee camp	4.98 ± 4.63	5.56 ± 5.41	4.67 ± 4.86	$\chi^2(2, n = 237) = .682, p = .711$
Traumatic events (CTE):				
Number of traumata	22.00 ± 10.43	19.19 ± 10.26	19.84 ± 10.13	$\chi^2(2, n = 242) = 3.41, p = .181$
General traumata	2.78 ± 1.54	2.56 ± 1.65	2.32 ± 1.53	$\chi^2(2, n = 242) = 2.66, p = .265$
War traumata	12.52 ± 6.59	10.92 ± 6.20	11.41 ± 5.90	$\chi^2(2, n = 242) = 3.28, p = .194$
Family and community traumata	6.32 ± 4.37	5.27 ± 4.75	5.65 ± 4.93	$\chi^2(2, n = 242) = 3.99, p = .136$
Sexual traumata	.46 ± .80	.42 ± .50	.41 ± .50	$\chi^2(2, n = 241) = 2.71, p = .258$
Childhood traumata	6.34 ± 7.55	5.00 ± 6.17	4.25 ± 5.29	$\chi^2(2, n = 232) = 2.52, p = .324$
Adult traumata	14.40 ± 10.67	15.24 ± 11.09	16.18 ± 10.79	$\chi^2(2, n = 236) = .699, p = .705$
PTSD symptoms (PSSI):				
PTSD general score	15.79 ± 12.64	13.88 ± 13.99	14.97 ± 14.87	$F(2, 241) = .409, p = .665$
Re-experience	5.08 ± 4.41	4.12 ± 4.33	4.54 ± 4.64	$\chi^2(2, n = 242) = 2.19, p = .334$
Avoidance	6.29 ± 5.12	5.65 ± 5.64	6.03 ± 5.84	$\chi^2(2, n = 242) = 1.86, p = .395$
Hyperarousal	4.42 ± 4.23	4.12 ± 4.72	4.41 ± 5.00	$\chi^2(2, n = 242) = .811, p = .667$
Dissociation	.80 ± 1.56	.92 ± 1.76	1.05 ± 1.93	$\chi^2(2, n = 242) = .221, p = .895$
Dissociative symptoms (DSP-I):				
DSPI-I general score	1.38 ± 3.28	1.54 ± 4.20	2.14 ± 4.85	$\chi^2(2, n = 181) = 1.08, p = .581$

Supplement Table 4.1. *(continued)*

	Saliva samples (n = 153) M ± SD	**Hair samples** (n = 52) M ± SD	**Saliva + hair samples** (n = 37) M ± SD	**Statistical test detail**
Depersonalization	.61 ± 1.65	.62 ± 1.93	.86 ± 2.24	$\chi^2(2, n = 181) = .362$, p = .834
Derealization	.76 ± 1.93	.92 ± 2.52	1.62 ± 3.37	$\chi^2(2, n = 182) = .921$, p = .631
Clinician observed dissociation (CADSS)	1.44 ± 2.46	1.29 ± 2.33	1.62 ± 2.84	$\chi^2(2, n = 239) = .161$, p = .923
Stress coping (COPE) :				
Self-distraction	5.43 ± 1.72	5.40 ± 1.90	5.38 ± 1.96	$\chi^2(2, n = 242) = .099$, p = .952
Active coping	5.48 ± 1.82	5.31 ± 2.17	5.19 ± 2.15	$\chi^2(2, n = 242) = .471$, p = .790
Denial	4.68 ± 1.91	4.92 ± 1.99	4.78 ± 1.92	$\chi^2(2, n = 242) = .695$, p = .707
Substance use	2.34 ± 1.02	2.31 ± .97	2.17 ± .51	$\chi^2(2, n = 239) = .174$, p = .917
Emotional support	5.30 ± 1.94	5.21 ± 2.03	5.38 ± 1.98	$\chi^2(2, n = 242) = .153$, p = .927
Instrumental support	5.41 ± 1.96	4.96 ± 2.14	5.05 ± 2.11	$\chi^2(2, n = 242) = 2.15$, p = .341
Behavioral disengagement	4.33 ± 1.87	5.08 ± 1.97	5.11 ± 2.07	**$\chi^2(2, n = 242) = 8.43$, p = .015**
Venting	4.59 ± 1.86	4.67 ± 2.15	4.62 ± 2.19	$\chi^2(2, n = 242) = .060$, p = .970
Positive reframing	4.71 ± 2.00	4.77 ± 2.15	4.57 ± 1.95	$\chi^2(2, n = 242) = .194$, p = .908
Planning	6.26 ± 1.70	5.75 ± 2.05	5.65 ± 2.14	$\chi^2(2, n = 242) = 3.46$, p = .178
Humor	3.11 ± 1.70	2.90 ± 1.64	2.69 ± 1.37	$\chi^2(2, n = 241) = 2.99$, p = .225
Acceptance	5.72 ± 1.69	5.44 ± 1.99	5.27 ± 1.91	$\chi^2(2, n = 242) = 2.00$, p = .367
Religion	6.73 ± 1.69	7.25 ± 1.25	7.06 ± 1.39	$\chi^2(2, n = 240) = 3.73$, p = .155
Self-blame	4.59 ± 2.02	4.96 ± 2.29	4.76 ± 2.30	$\chi^2(2, n = 242) = .988$, p = .610
Depressive symptoms (PHQ-9)	6.34 ± 6.89	6.08 ± 8.56	6.57 ± 9.37	$\chi^2(2, n = 241) = 3.24$, p = .198
Functionality (WSAS)	3.50 ± 5.48	3.94 ± 6.23	4.65 ± 6.82	$\chi^2(2, n = 240) = .275$, p = .872
Suicidality (M.I.N.I.)	.88 ± 2.76	1.16 ± 3.87	.86 ± 3.34	$\chi^2(2, n = 239) = .181$, p = .913

Note. Subsamples stemmed from a bigger study cohort as described in **Paper 2**. Groups were identified according to available body material collected (≥ 50µl for amount of saliva samples, ≥ 3cm for hair length). Group differences were calculated with: one-way ANOVA, Chi-squared test two-tailed, or Kruskal-Wallis test. Appropriate to test requirements, shown are: Fisher test (F) or results of Chi-squared test (χ^2), respectively. Significant results are shown in bold. Abbreviations

and symbols: SD, standard deviation; DRC, Democratic Republic of Congo; CTE, Checklist for Traumatic Experiences; PSSI, PTSD Symptom Scale; PTSD, posttraumatic stress disorder; CADSS, Clinician-Administrated Dissociative States Scale; COPE, Brief Stress Coping Questionnaire; PHQ-9, Patient Health Questionnaire; WSAS, Work and Social Adjustment Scale; M.I.N.I., Mini International Neuropsychiatric Interview. Excluded outliers: CTE, three (saliva, saliva+hair), DSP-I, three (saliva, hair, saliva+hair); CADSS, one (saliva, hair); COPE, six (saliva, hair, saliva+hair); M.I.N.I., three (saliva, hair, saliva+hair).

Supplement Table 4.2. *Demographic and clinical characteristics of Cortisol Responders (n = 45) and Non-Responders (n = 108)*

	Cortisol responders (n = 45) M ± SD	**Cortisol non-responders** (n = 108) M ± SD	**Statistical test detail**
Age (years)	30.87 ± 9.68	32.02 ± 10.86	F(1, 151) = .379, p = .539
Sex (male/female)	26/19	56/52	$\chi^2(1, n = 153) = .449$, p = .503
Country of origin (DRC/Burundi/Rwanda)	36/2/7	78/10/20	$\chi^2(2, n = 153) = 1.36$, p = .508
Regular smoking (yes/no)	1/152	0/52	$\chi^2(2, n = 242) = .584$, p = .747
Years of education	7.58 ± 5.06	8.01 ± 4.90	U = 2332.000, p = .693
Years of stay in the refugee camp	5.27 ± 5.06	4.85 ± 4.46	U = 2226.000, p = .794
Traumatic events (CTE):			
Number of traumata	23.22 ± 10.58	21.49 ± 10.38	U = 2195.000, p = .346
General traumata	2.89 ± 1.60	2.73 ± 1.52	U = 2297.500, p = .589
War traumata	12.84 ± 6.93	12.39 ± 6.47	U = 2279.500, p = .546
Family and community traumata	7.22 ± 4.26	5.94 ± 4.38	**U = 1957.000, p = .057**
Sexual traumata	.49 ± .73	.44 ± .84	U = 2239.500, p = .402
Childhood traumata	5.98 ± 8.32	6.75 ± 7.70	U = 2278.000, p = .538
Adult traumata	16.11 ± 12.00	13.69 ± 10.03	U = 2145.000, p = .253
PTSD symptoms (PSSI):			
PTSD general score	18.69 ± 12.38	14.58 ± 12.60	**U = 1940.000, p = .050**
Re-experience	6.24 ± 4.32	4.60 ± 4.38	**U = 1861.500, p = .022**
Avoidance	7.18 ± 5.00	5.92 ± 5.14	U = 2021.500, p = .101
Hyperarousal	5.27 ± 4.12	4.06 ± 4.24	**U = 1978.500, p = .067**
Dissociation	.80 ± 1.42	.75 ± 1.54	U = 2295.500, p = .675
Dissociative symptoms (DSP-I):			
DSPI-I general score	.73 ± 1.60	1.53 ± 3.64	U = 1235.000, p = .929
Depersonalization	.27 ± .83	.70 ± 1.83	U = 1185.500, p = .544
Derealization	.37 ± .93	.83 ± 2.07	U = 1181.500, p = .550
Clinician observed dissociation (CADSS)	1.30 ± 2.34	1.40 ± 2.32	U = 2312.500, p = .927
Stress coping (COPE) :			
Self-distraction	5.38 ± 1.66	5.45 ± 1.76	U = 2304.500, p = .609
Active coping	5.36 ± 1.85	5.53 ± 1.82	F(1, 152) = .282, p = .596
Denial	4.53 ± 1.95	4.74 ± 1.91	U = 2256.500, p = .482
Substance use	2.30 ± .93	2.30 ± .91	U = 2337.000, p = .901
Emotional support	4.31 ± 1.64	5.71 ± 1.92	**U = 1413.500, p < .001**
Instrumental support	4.91 ± 1.79	5.61 ± 2.00	**U = 1882.500, p = .026**
Behavioral disengagement	4.07 ± 1.85	4.44 ± 1.88	F(1, 152) = 1.23, p = .269
Venting	4.38 ± 1.80	4.69 ± 1.89	U = 2236.000, p = .430
Positive reframing	4.87 ± 1.90	4.65 ± 2.05	F(1, 152) = .377, p = .540

Supplement Table 4.2. *(continued)*

	Cortisol responders (n = 45) M ± SD	**Cortisol non-responders** (n = 108) M ± SD	**Statistical test detail**
Planning	6.09 ± 1.58	6.33 ± 1.75	U = 2154.500, p = .257
Humor	3.02 ± 1.53	3.15 ± 1.78	U = 2369.000, p = .782
Acceptance	5.24 ± 1.76	5.92 ± 1.63	**U = 1874.000, p = .024**
Religion	6.53 ± 1.80	6.81 ± 1.64	U = 2192.500, p = .298
Self-blame	4.80 ± 1.89	4.51 ± 2.08	U = 2211.500, p = .376
Depressive symptoms (PHQ-9)	6.34 ± 6.89	6.08 ± 8.56	**U = 1692.500, p = .004**
Functionality (WSAS)	3.50 ± 5.48	3.94 ± 6.23	U = 1988.500, p = .158
Suicidality (M.I.N.I.)	.88 ± 2.76	1.16 ± 3.87	U = 2337.500, p = .932

Note. Significant Cortisol response to diagnostic procedures was defined as a 15.5% increase of Cortisol between the first and the second assessment time (Miller et al., 2013; Zaba et al., 2015). Group differences were calculated with: one-way ANOVA; Mann-Whitney-U-test, or Chi-squared test two-tailed, appropriate to test requirements, shown are: Fisher test (F), U value (U), or results of Chi-squared test (χ^2), respectively. For details see Method section. Significant or trendwise significant results are marked in bold. Abbreviations: SD, standard deviation; DRC, Democratic Republic of Congo; CTE, Checklist for Traumatic Experiences; PSSI, PTSD Symptom Scale; PTSD, posttraumatic stress disorder; CADSS, Clinician-Administrated Dissociative States Scale; COPE, Brief Stress Coping Questionnaire; PHQ-9, Patient Health Questionnaire; WSAS, Work and Social Adjustment Scale; M.I.N.I., Mini International Neuropsychiatric Interview. Excluded outliers: CTE, one responder (resp.), one non-responder (non-resp.); PSSI, one resp.; DSP-I, two resp., one non-resp.; CADSS, one resp., one non-resp.; COPE, one resp., one non-resp.; WSAS, one resp., one non-resp., M.I.N.I., one resp., one non-resp.

Supplement Table 4.3. *Correlational matrix between CORT levels throughout the protocol as well as percentage CORT response and clinical characteristics in the whole sample (n = 153)*

	CORT1	CORT2	CORT3	CORT response (%) CORT1/ CORT2	CORT response (%) CORT1/ CORT3
Traumatic events (CTE):					
Number of traumata	*-.094*	*-.011*	*.023*	*.022*	*.088*
General traumata	***-.165****	*-.063*	*.046*	*.080*	***.158**^{t}*
War traumata	*-.091*	*.009*	*.038*	*.012*	*.090*
Family and community traumata	*-.065*	*-.010*	*.005*	*.060*	*.070*
Sexual traumata	***-.246*** **	***-.188****	***-.142**^{t}*	*-.031*	*.068*
PTSD symptoms (PSSI):					
PTSD general score	-.073	*-.020*	.004	*.051*	*.087*
Re-experience	*-.028*	*.036*	*.080*	*.106*	*.119*
Avoidance	*-.080*	*-.098*	*-.046*	*.018*	*.065*
Hyperarousal	*-.016*	*.036*	*.025*	*.044*	*.048*
Dissociation	*-.018*	*.008*	*-.037*	*-.030*	*-.025*
Dissociative symptoms (DSP-I):					
DSPI-I general score	*.036*	*-.073*	*-.067*	*-.107*	*-.055*
Depersonalization	*.084*	*-.056*	*-.045*	*-.149*	*-.107*
Derealization	*.051*	*-.107*	*-.058*	***-.161**^{t}*	*-.058*
Clinician observed dissociation (CADSS)	-.118	***-.197****	-.046	*-.058*	*.063*
Stress coping (COPE):					
Self-distraction	*-.024*	*-.090*	*-.131*	*-.066*	*-.099*
Active coping	*-.091*	*-.112*	*-.106*	*-.048*	*-.068*
Denial	*-.127*	***-.285*****	***-.237****	***-.169****	*-.123*
Substance use	*.116*	***.159**^{t}*	***.183****	*.030*	*.044*
Emotional support	*.084*	*-.064*	*-.019*	***-.227****	***-.160****
Instrumental support	*-.038*	*-.072*	*-.085*	*-.094*	*-.070*
Behavioral disengagement	*.008*	***-.165****	***-.201****	***-.184****	***-.205****
Venting	*.037*	*.010*	*-.080*	*-.018*	*-.094*
Positive reframing	***-.153**^{t}*	*-.081*	***-.153**^{t}*	*.021*	*-.032*
Planning	*-.049*	*-.129*	*-.074*	*-.080*	*-.062*
Humor	*.090*	*.004*	*-.003*	*-.072*	*-.067*
Acceptance	*-.026*	*-.126*	***-.152**^{t}*	*-.130*	*-.113*
Religion	*-.016*	*-.039*	*-.058*	*-.082*	*-.067*
Self-blame	*-.118*	*-.060*	*-.055*	*.019*	*.013*
Depressive symptoms (PHQ-9)	*-.107*	*-.019*	*-.016*	***.146**^{t}*	***.137**^{t}*
Functionality (WSAS)	*-.145*	*-.127*	*-.051*	*.016*	*.072*
Suicidality (M.I.N.I.)	*-.003*	*-.032*	*-.017*	*-.072*	*-.035*

Note. Correlational analyses were performed with Pearson coefficient, in case of not normal distribution or categorical data, Spearman coefficients were calculated (marked in *italics*). Abbreviations and symbols: CORT1, cortisol levels at the beginning of the assessment procedures; CORT2, cortisol levels after the assessment of trauma exposure, PTSD and

dissociative symptoms; CORT3, cortisol levels at the end of the interview; CORT response CORT1/CORT2, response in cortisol levels between the first and second AT; CORT response CORT1/CORT3, response in cortisol levels between the beginning and the end of the interview; CTE, Checklist for Traumatic Experiences; COPE, Brief Stress Coping Questionnaire; PSSI, PTSD Symptom Scale; PTSD, posttraumatic stress disorder; DSP-I, Dissociative Subtype of PTSD Interview; CADSS, Clinician-Administrated Dissociative States Scale; PHQ-9, Patient Health Questionnaire; WSAS, Work and Social Adjustment Scale; M.I.N.I., Mini International Neuropsychiatric Interview; t, $p \leq .1$; *, $p \leq .05$; **, $p \leq .01$; ***, $p \leq .001$. Significant results are marked in bold. Following outliers were identified: CTE, one; DSP-I, one; CADSS, one; COPE, one; M.I.N.I., one; CORT 2, one; CORT 3, one; CORT response, one.

Supplement Table 4.4. *Correlational matrix between hCORT, cortisone, hCORT/cortisone, DHEA levels and clinical characteristics (n = 52)*

	Cortisol	Cortisone	Cortisol/ Cortisone	DHEA
Traumatic events (CTE):				
Number of traumata	***.261^{t}***	***.381****	***-.335****	***.343****
General traumata	*.098*	*.058*	*.038*	*.183*
War traumata	***.244^{t}***	***.390****	***-.390****	***.336****
Family and community traumata	***.257^{t}***	***.282****	*-.141*	***.263^{t}***
Sexual traumata	*.218*	***.275****	*-.234*	***.265^{t}***
PTSD symptoms (PSSI):				
PTSD general score	***.239^{t}***	**.330***	*-.190*	**.315***
Re-experience	*.214*	***.309****	*-.177*	*.086*
Avoidance	***.255^{t}***	***.309****	*-.134*	*.178*
Hyperarousal	***.233^{t}***	***.291****	*-.175*	***.282****
Dissociation	*.197*	***.285****	*-.191*	*.167*
Dissociative symptoms (DSP-I):				
DSPI-I general score	***.273^{t}***	***.361****	*-.187*	*.247*
Depersonalization	***.273^{t}***	***.362****	*-.191*	*.248*
Derealization	***.290^{t}***	***.372****	*-.180*	*.236*
Clinician observed dissociation (CADSS)	***.253^{t}***	*.226*	*-.072*	*.091*
Stress coping (COPE):				
Self-distraction	*.008*	.012	*.054*	**.246^{t}**
Active coping	*-.117*	-.200	*.130*	.043
Denial	*.047*	.004	*-.008*	**.263^{t}**
Substance use	***.311****	***.341****	***-.262^{t}***	*.211*
Emotional support	***.250^{t}***	.154	*.139*	.084
Instrumental support	*.139*	.057	*.141*	-.127
Behavioral disengagement	*.208*	**.292***	***-.388****	**.341***
Venting	*.113*	.154	*.034*	.059
Positive reframing	*.001*	**-.242^{t}**	*.170*	-.022
Planning	*-.128*	*-.080*	*-.015*	***.259^{t}***
Humor	*.007*	*.028*	*-.016*	*.001*
Acceptance	*-.173*	-.050	*.129*	.198
Religion	*.023*	*-.128*	*.165*	*.160*
Self-blame	*.008*	.112	*.058*	**.268^{t}**
Depressive symptoms (PHQ-9)	*.186*	*.228*	*-.145*	*.139*
Functionality (WSAS)	***.287****	***.329****	*-.147*	*.116*
Suicidality (M.I.N.I.)	*.110*	*.175*	*-.087*	*.178*

Note. Correlational analyses were performed with Pearson coefficient, in case of not normal distribution or categorical data, Spearman coefficients were calculated (marked in *italics*). Abbreviations and symbols: DHEA, dehydroepiandrosteron; CTE, Checklist for Traumatic Experiences; COPE, Brief Stress Coping Questionnaire; PSSI, PTSD Symptom Scale; PTSD, posttraumatic stress disorder; DSP-I, Dissociative Subtype of PTSD Interview; CADSS, Clinician-Administrated Dissociative States Scale; PHQ-9, Patient Health Questionnaire; WSAS, Work and Social Adjustment Scale; M.I.N.I., Mini International Neuropsychiatric Interview; t, p

≤ .1; *, p ≤ .05; **, p ≤ .01. Significant results are marked in bold. Following outliers were identified: Cortisol, one; Cortisol/Cortisone, one; DHEA, one; DSP-I, one; CADSS, one; COPE, two; M.I.N.I., one.

Supplement Table 4.5. *Linear regression analyses for hCORT, cortisone, hCORT/cortisone, DHEA levels and variables of interest (n = 52)*

	Model characteristics			Variables in the equation		
	R	F	p	ß	T	p
Cortisol	.105	.128	.972			
Number of traumata (CTE)				.014	.071	.943
PTSD symptoms (PSSI)				.123	.503	.617
Dissociative symptoms (PSSI)				-.055	-.236	.814
Behavioral disengagement (COPE)				-.115	-.631	.531
Cortisone	.409	2.362	.067			
Number of traumata (CTE)				.268	1.546	.129
PTSD symptoms (PSSI)				.237	1.029	.309
Dissociative symptoms (PSSI)				-.108	-.510	.612
Behavioral disengagement (COPE)				.110	.666	.509
Cortisol/Cortisone	.280	.961	.438			
Number of traumata (CTE)				-.130	-.700	.488
PTSD symptoms (PSSI)				.126	.514	.610
Dissociative symptoms (PSSI)				-.045	-.193	.848
Behavioral disengagement (COPE)				-.245	-1.376	.176
DHEA	.386	2.011	.109			
Number of traumata (CTE)				.102	.575	.568
PTSD symptoms (PSSI)				.228	1.005	.320
Dissociative symptoms (PSSI)				-.139	-.644	.523
Behavioral disengagement (COPE)				.231	1.362	.180

Note. Linear regression analyses were run applying following variables as a predicted criterion: Cortisol, Cortisone, Cortisol/Cortisone, and DHEA. Abbreviations: CTE, Checklist for Traumatic Experiences; PTSD, Posttraumatic stress disorder; PSSI, PTSD Symptom Scale; COPE, Brief Stress Coping Questionnaire; DHEA, dehydroepiandrosterone.

5. GENERAL DISCUSSION

5.1 Summary of results

The aim of this dissertation was to contribute to the explanation of conflicting results on HPA-axis dysregulations associated with TE and PTSD (e.g., Klaassens et al., 2012; Meewisse et al., 2007; Miller et al., 2007) by focusing on the analysis of the variance in emotional stress response, in particular with regard to dissociation and stress coping strategies. Two studies on HPA-axis reactivity and its psychological correlates were conducted: the first in a German sample of female PTSD patients, female traumatized and non-traumatized HC as presented in **Paper 1**, the second in a mixed-sex sample of highly traumatized East African refugees settled in Uganda as presented in **Paper 2** and **Paper 3**. In the first study, the HPA-axis response was induced via a standardized laboratory psychosocial stressor, the TSST (Kirschbaum et al., 1993). In the second study, the HPA-axis reactivity was analyzed as a response to an interview assessing TE, PTSD, and dissociative symptomatology.

Paper 1 repeated the findings of Zaba et al. (2015) demonstrating the HPA-axis reactivity to be lower in PTSD patients as compared to the studied HC groups. However, this effect was driven by the presence of a non-responder subgroup constituting around half of the total PTSD sample. The other half of the studied PTSD patients exhibited a CORT response that did not differ from that of ntHC. Basal CORT levels and psychological stress reactivity did not vary between PTSD-R and PTSD-NR. However, PTSD-NR had experienced a higher trauma dose (ELT+AT), showed higher levels of dissociative symptoms and a higher prevalence of psychiatric comorbidity than PTSD-R. Moreover, **Paper 1** extended the results of Zaba et al. (2015) by validating the finding of dissociation and dissociation-related phenomena (trauma-related avoidant coping, sleeping difficulties, and fear of death and dying) being more pronounced in PTSD-NR than in PTSD-R. Whereby dissociation was measured with both self-report questionnaires (RIQ and DES) and with an expert interview (SCID-D). Additionally, in PTSD, dissociative symptom levels but not TE, PTSD symptom severity, or the intensity of psychiatric comorbidity predicted the HPA-axis blunting.

Paper 2 provided evidence for the cultural sensitivity of the Dissociative Subtype of PTSD (DS-PTSD, American Psychiatric Association, 2013) in a non-Western population. Similarly to hitherto conducted studies, the DS-PTSD was characterized by high trauma load, especially

family and sexual trauma, high psychopathology in terms of high depressive symptoms and suicidality as well as low functionality. Moreover, a newly developed expert-based interview, the DSP-I (Eidhof et al., *accepted*), assessing the DS-PTSD, was employed. Through its excellent psychometric properties found in the Ugandan sample, this tool was shown to capture dissociative symptoms in a cultural sensitive way.

In **Paper 3**, semi-standardized assessments of TE, PTSD, and dissociative symptoms did not evoke a significant salivary CORT response, at least not at the tested assessment time. However, significant biological stress response was found in a subset of individuals (29% of the total sample) who were high on PTSD, especially re-experiencing, and depressive symptomatology as well as exhibited low acceptance, low emotional and instrumental support as coping strategies. Elevated CORT response was best predicted by low emotional support, whereas low sCORT levels by sexual trauma and dissociation-related stress coping (i.e., high levels of behavioral disengagement and denial). Interestingly, higher expert-observed dissociation symptoms were correlated with lower sCORT levels collected immediately following assessments of TE, PTSD, and dissociation. Furthermore, salivary and hair stress hormone levels correlated inversely with each other.

5.2 Theoretical implications

Both studies showed that low reactive CORT levels are associated with trauma-related dissociation and dissociation-related stress coping strategies such as denial and behavioral disengagement. These findings are compelling in the context of the emotion modulation model in PTSD (Lanius et al., 2018, 2010) stating that dissociative symptoms might be linked to a prefrontal inhibition of limbic regions resulting in emotion overmodulation. Several fMRI studies, although conducted in small study samples, supported this model (e.g., Lanius et al., 2002; Nicholson et al., 2015, 2017). Interestingly, the hypothesized hypoactivation of limbic regions under threat was found exclusively upon its conscious processing (Felmingham et al., 2008). This suggests an involvement of strong cognitive control as a dissociative response to highly arousing stimuli (see also: Krause-Utz, Frost, Winter, & Elzinga, 2017). In our studies, dissociative tendencies were related to reaction control (**Paper 1**) or denial and behavioral disengagement (**Paper 3**), i.e., stress coping strategies possibly involved in emotion overmodulation processes. Furthermore, they were found to be reflected in HPA-axis downregulation. Future research should clarify if the HPA-axis non-response may be related to

neural circuits proposed to underlie dissociative symptomatology in PTSD (see also: Lanius et al., 2018).

Moreover, the link between low CORT levels, dissociation and high trauma load, as found in **Paper 1** and **Paper 3**, is worth discussing in the context of the cascade model of dissociative response following traumatic stress (Schauer & Elbert, 2010). According to this model, the individuals who had dissociated during the trauma, would subsequently dissociate during exposure to trauma reminders. Physiologically, under threat, they went down the whole defense cascade ("freeze-flight-fight-fright-flag-faint") and their stress response was characterized by parasympathetic dominance. Indeed, several reports provided empirical support for the link between dissociative trauma response and suppression of autonomic physiological processes (Bichescu-Burian, Steyer, Steinert, Grieb, & Tschöke, 2017; Griffin, Resick, & Mechanic, 1997; Lanius et al., 2010). Additionally, a correspondence between blunting of both the HPA-axis and physiological measures in relation to dissociation has been found (Ehring, Ehlers, Cleare, & Glucksman, 2008; Simeon et al., 2008). The fact that, in our study (**Paper 3**), dissociative symptoms were related to coping strategies denial and behavioral disengagement and to low sCORT and high hCORT levels, would propose further behavioral and endocrine components of the defense cascade model. Empirical evidence for this reasoning is definitely needed.

Furthermore, since PTSD-NR was found to be characterized by features typical for the DS-PTSD (**Paper 1**), such as high psychiatric comorbidity, high trauma load and high prevalence of combined ELT+AT (Armour et al., 2014; Hansen et al., 2017; McKinnon et al., 2016), future studies should answer the question whether the HPA-axis blunting may be seen as a marker for the DS-PTSD. This question was not possible to address in **Paper 1**, since no further stratification of dissociative and non-dissociative PTSD was performed as well as no instrument allowing to assess the DS-PTSD was employed. **Paper 2** and **Paper 3** provided only partial support for this hypothesis. CORT response to standardized assessments of TE, PTSD, and dissociative symptoms did not differ between DS- and non-DS-PTSD. However, in all studied individuals, lower CORT levels were related to expert-assessed dissociation as well as to dissociation-related stress coping strategies (i.e., high behavioral disengagement and denial). Similarly, negative linear relationship between reactive CORT levels and dissociation were found in Wichmann et al. (2017).

Moreover, as described in **Paper 2**, although the prevalence of dissociation-related stress coping (i.e., behavioral disengagement) was the highest in the identified DS-PTSD group, it did

not significantly differ between DS-PTSD and sPTSD. This suggests that dissociation-related stress coping strategies accompanied by low reactive CORT levels may be characteristic for high-end PTSD severity and not necessarily for the DS-PTSD construct. These results are in line with recent research demonstrating avoidant coping not to be typical for the DS-PTSD (Haagen et al., 2018) as well as add to the hypothesis that PTSD itself might be best characterized as a dissociative disorder (e.g., Dorahy & van der Hart, 2015). Thus, generally, PTSD may go along with the employment of (dysfunctional) dissociation-related coping strategies with stress and trauma (Ehlers & Clark, 2000). Such reasoning questions the relevance of the DS-PTSD diagnosis itself and suggests that phenomenology of dissociative symptoms in PTSD may be better explained as a continuum (Dalenberg & Carlson, 2012).

However, several reports, including **Paper 2** of this dissertation, on the DS-PTSD identification and characterization provided evidence that dissociative symptoms of clinical relevance are best conceptualized as a subtype being present in a proportion of PTSD patients changing the clinical manifestation of the disease. Based on the results from **Paper 1** and **Paper 3**, it can be concluded that employment of dissociation-related stress and trauma coping strategies may be not characteristic for the DS-PTSD. Possibly, PTSD patients exhibit dissociative phenomena in a response to stress but the DS-PTSD may tend to show additional, more persistent forms of dissociation. Hitherto, severe traumatization, especially ELT and sexual trauma, has been found as a most reliable correlate of the DS-PTSD (Hansen et al., 2017, **Paper 2**). For this reason, in order to explore psychobiological processes specific for the DS-PTSD, their manifestations during traumatization as well as their actualization under confrontation with trauma reminders should be studied (see also: Lanius et al., 2018; Schauer & Elbert, 2010).

Besides that, in the TSST study, in comparison to PTSD and ntHC, tHC exhibited the highest CORT blood levels and also showed absorption levels, a non-pathological form of dissociation, to not differ from that of PTSD patients and be lower than that of ntHC. This finding supports the recent integrative model linking TE and PTSD development with CORT secretion (Steudte-Schmiedgen et al., 2016) and suggests an incremental value of parallel assessment of dissociative symptom trajectory. Both high dissociation (Gandubert et al., 2016; Orr et al., 2012) and low CORT levels following TE (Mouthaan et al., 2014) were found independently to be significant predictors for PTSD. For this reason, accounting for dissociative symptom development may depict one of the missing pieces of the puzzle of the complex link between TE, PTSD and CORT secretion. It can be suggested that following TE, raise of CORT levels may be

paralleled by high levels of non-pathological dissociation. Each additional trauma may lead to CORT blunting in the long-term (for a meta-analysis see: Miller et al., 2007) possibly being associated with the development of pathological forms of dissociation. Longitudinal research is needed to address this hypothesis.

Finally, the findings are interesting beyond TE and PTSD research. Dissociative symptoms as well as high comorbidity have been found to be transdiagnostically associated with greater illness burden and worse treatment outcomes (Bae et al., 2016; Lyssenko et al., 2018; McKinnon et al., 2016). For these reasons, it is worth conducting further research on the question whether the HPA-axis blunting may be considered a hallmark of chronic stress due to TE early in life (for a meta-analysis see: Fogelman & Canli, 2018) and/or long persistent psychopathology (e.g., Petrowski et al., 2010, 2013) or if it may result from a genetic risk factor (e.g., Wolf et al., 2014).

5.3 Clinical implications

There are possible clinical implications of the results. In both samples, salivary/plasma reactive CORT levels were stronger associated with maladaptive coping and psychopathology (**Paper 1** & **Paper 3**), whereas salivary/plasma baseline levels with TE (**Paper 1** & **Paper 3**). This may explain why, under treatment with glucocorticoids (GC), raise of basal, “resting” levels of CORT were not found to have a therapeutical effect in full-blown PTSD (Graebener et al., 2017; Ludäscher et al., 2015). On the contrary, it was successful when applied within a critical period of time following TE ("window of opportunity", Carmi et al., 2016), or under activation of trauma reminders (de Kleine, Rothbaum, & van Minnen, 2013). For a similar approach, when administrating oxytocin, see the work of Sack and colleagues (2017). Moreover, high tonic levels of hCORT as shown in **Paper 3**, were associated with TE, maladaptive coping and psychopathology as well as negative relationships between hair/tonic and salivary/phasic CORT levels were found. Future studies need to clarify how GC treatment affects phasic versus tonic CORT measurements and relate them to changes in therapeutical outcomes.

Furthermore, the strong link between dissociation-related stress coping strategies and low reactive CORT levels found in both studies need to be discussed considering implications for psychotherapeutical treatment. Newest research suggests the DS-PTSD to profit from exposure-based cognitive behavioral therapy (CBT) to the same extent as non DS-PTSD

(Burton, Feeny, Connell, & Zoellner, 2018; Haagen et al., 2018; Wolf et al., 2016; Zoet, Wagenmans, van Minnen, & de Jongh, 2018). However, these studies were conducted mostly in veteran samples with a relatively short follow-up of six months not allowing for reliable judgments about the long-term treatment outcome. Moreover, the fact that in Wolf et al. (2016) post-treatment dissociative symptoms were shown to still be on high levels, despite the reduction of total PTSD symptoms, left the room for speculations on a high chance of relapse in the DS-PTSD group. The question needs to be answered, in terms of relapse-prevention, whether more therapeutical efforts such as stress management targeting dissociation-related stress coping strategies in the DS-PTSD are needed (for a similar approach see STAIR: Cloitre, Petkova, Wang, & Lu Lassell, 2012). Since active, emotion involving stress coping was found to be associated with higher diurnal CORT output (O'Donnell et al., 2008) and distraction but not avoidance or denial with higher CORT stress reactivity in HC (Janson & Rohleder, 2017), future research needs to clarify if therapeutical strategies targeting coping strategies may modulate the HPA-axis activity and contribute to the dampening of dissociative tendencies.

Moreover, the paradox relationship between phasic versus tonic CORT levels (**Paper 3**) suggest that according to the delay hypothesis (Koopman et al., 2003), PTSD patients with dissociative tendencies may exhibit strong delayed, between-session emotional and endocrine stress responses to diagnostic or therapeutical (e.g., trauma exposure) in-session procedures. This shows the importance of arrangements between client and therapist considering safety skills that can be used between-sessions as well as contact possibilities that should be discussed beforehand (see also: Ehlers, 1999; Fiedler, 2013).

Paper 2 provided data on applicability of the DS-PTSD construct in a non-Western population. These findings suggest that both researchers and clinicians may expect a clinical picture as well as correlates/risk factors of the DS-PTSD to be comparable across cultures. Research is needed on therapeutical outcomes in non-Western populations as well. Moreover, the newly developed instrument, the DSP-I (Eidhof et al., *accepted*), was shown to be a cross-culturally sensitive instrument capturing the symptoms of depersonalization and derealization while showing excellent psychometric qualities. It is recommended to integrate this 10-minute tool as an add-on assessment into standardized PTSD diagnostic and treatment planning procedures.

5.4 Limitations and strengths

Finally, the results need to be discussed in light of their main limitations and strengths. With respect to limitations: First, in both studies relatively small samples were analyzed. Second, in the TSST study only female individuals were included. Third, both studies were based on cross-over designs and do not allow causal conclusions to be made. Fourth, although focusing on dissociative reactions, both studies employed protocols (TSST and interview procedures) that were not specifically conceptualized to evoke dissociative states. A follow-up study concentrating on direct provocation of dissociative symptoms, for example using mirror-gazing (Brewin & Mersaditabari, 2013; Schäflein et al., 2018), rubber hand illusion (Rabellino et al., 2018, 2016), or trauma script exposure (Lanius et al., 2010; Sack et al., 2017), and parallel assessment of the HPA-axis function is urgently needed. Moreover, to understand the role of HPA-axis for TE, PTSD, and dissociation different stress protocols (e.g., psychological, pharmacological, and physical challenge tests) should be applied and compared in the same individuals. Fifth, how PTSD-NR as identified and characterized in **Paper 1** as well as the DS-PTSD as described in **Paper 2**, relate to the construct of the complex PTSD according to the planned 11th Revision of the International Classification of Diseases (ICD-11) (e.g., Cloitre, Garvert, Brewin, Bryant, & Maercker, 2013; Karatzias et al., 2017), needs to be elaborated as well.

The strengths of the conducted studies are as follows: in the TSST study: First, methodological strengths of controlled experimental procedures combining data collection on psychological and biological stress response. Second, replication and validation of the previous findings of Zaba et al. (2015). Third, inclusion of three samples: PTSD, traumatized and non-traumatized HC gave a possibility to disentangle the relationship between TE, PTSD, and dissociative symptomatology. In the Ugandan study: First, expert-based interviews combining self-report and third-party data were conducted. Second, as in the TSST study, psychological and biological parameters were collected enabling for elucidating psychobiological stress mechanisms. Third, mixed-sex sample ruled out a possible gender bias.

6. RECORD OF ACHIEVEMENT

Paper 1:

Dissociative symptoms but not trauma exposure or PTSD symptoms are decisive for HPA-axis blunting in female PTSD patients

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Author contributions: MS designed the study, performed the diagnostic procedures and the TSST experiments, analyzed the data, conceptualized and wrote the manuscript; BN performed the TSST experiments and the laboratory analyses; TK and BW collected the blood samples and critically revised the study design; XF performed the TSST experiments; US designed and supervised the study, performed the diagnostic procedures and collected the blood samples, conceptualized and critically revised the paper.

Paper 2:

Cross-cultural validity of the dissociative subtype of PTSD: evidence from refugees settled in Uganda

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Author contributions: MS designed the study, performed the interviews, analyzed the data, conceptualized and wrote the manuscript; SS critically revised the study design and performed the interviews; HA and TH critically revised the study design; GZR critically revised the study design and supervised the study; US designed and supervised the study, critically revised the paper.

Paper 3:

Sexual trauma and dissociation-related stress coping predict blunted cortisol levels as a response to a diagnostic interview in East African refugees

Monika Schreckenbach, Bozidar Novak, Thomas Elbert, Ulrike Schmidt

Author contributions: MS designed the study, performed the interviews and collected the body samples, analyzed the data, conceptualized and wrote the manuscript; BN critically revised the study design and performed the laboratory analyses; TE supervised the study, critically revised the study design and the paper; US designed and supervised the study, critically revised the paper.

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