From psychopathology to pathophysiology: a multi-level approach towards understanding trauma

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Abbreviations

PTSD	Posttraumatic stress disorder
ADHD	Attention deficit hyperactivity disorder
ACE	Adverse childhood experiences
HPA	Hypothalamic-Pituitary-Adrenal
EEG	Electroencephalography
MEG	Magnetoencephalography
fMRI	Functional magnetic resonance imaging
PET	Positron emission tomography
ERP	Event-related potentials
EPN	Early posterior negativity
RSVP	Rapid serial visual presentation
FKBP5	FK506 binding protein 5
CpG	Cytosine-phosphate-Guanine dinucleotide
GR	Glucocorticoid receptor
DNA	Deoxyribonucleic acid
RDoC	Research Domain Criteria
DSM	Diagnostic and Statistical Manual of Mental Disorders
ICD	International Statistical Classification of Diseases and Related Health Problems

Summary

Traumatic experiences are known to affect the body and mind by impacting both psychological and physiological health. Particularly, patients' risks of developing stress-related disorders, most prominently PTSD, increase with cumulative exposure to traumatic events (Kolassa & Elbert, 2007). Traumatic events also heighten the likelihood of the onset of a broad range of physical diseases, ranging from cardiovascular and metabolic diseases to premature ageing and death (Agorastos, Pervanidou, Chrousos, & Baker, 2019; Gassen, Chrousos, Binder, & Zannas, 2017; Lohr et al., 2015). Research on biological mechanisms involved in trauma- and stress related disorders appear to be crucial to gain more knowledge about the implementation of preventative measures.

The aim of the present thesis is to investigate both psychopathological aspects following trauma exposure and the underlying neurobiological mechanisms of trauma-related psychopathology. The three studies comprising this thesis present investigations on correlates of traumatic exposure on the behavioral, neural and molecular level.

First, the link between traumatic experiences, especially childhood adversities and psychopathology is examined. The study examines the relationship between different types of childhood adversities on symptoms of both posttraumatic stress disorder (PTSD) and attention deficit hyperactivity disorder (ADHD) using path analysis. While both traumatic events and childhood neglect predict PTSD symptom severity, for ADHD only childhood neglect is found to impact symptom severity. Results confirm a positive association of adverse childhood adversities to psychopathology, thereby replicating the findings of other studies which highlight the detrimental impact of early life stress on mental health problems. Further, the results of this study reveal that the impact of childhood neglect on ADHD was mediated in part by PTSD severity. The potentially mediating role of PTSD has not received

much attention. Results of this thesis encourage the consideration of childhood neglect and PTSD in treatment of ADHD. Moreover, preventive measures aimed at reducing childhood maltreatment and traumatic stress seem essential to minimize both ADHD and PTSD.

The second study demonstrates an effect to transdiagnostic psychopathology following trauma on neural activity. We use an event-related potential, the Early Posterior Negativity as a marker of attention allocation toward emotional material. Transdiagnostic stress-related symptoms, particularly problems concentrating, sleeping difficulties, and mistrust are found to be linked with an reduced affective distinction between high-arousing and low-arousing pictures represented by the Early Posterior Negativity (EPN). Sex predicts the magnitude of the EPN and males display a stronger EPN suppression than females, suggesting that emotional processing of positive arousing stimuli is modulated by sex.
In essence, we conclude that stress symptoms might induce the functional reorganization of the emotional processing streams and may be reflected in dampened cortical affective differentiability to emotional stimuli.

The brain reacts to stressors in various dynamic ways. After examining trauma-related psychopathology on the neural level, the third study shifts the focus to molecular modifications. Epigenetic mechanisms are involved in the regulation of all biological processes, and furthermore are sensitive to environmental influences such as traumatic stressors. Thus, the study examined associations between epigenetic aging and the number of lifetime traumatic events experienced, and PTSD symptom severity. The results indicated that neither time-limited stressors like adverse childhood experiences nor lifetime trauma exposure per se, but rather PTSD symptom severity, may accelerate epigenetic aging, a molecular marker that is associated with a number of premature aging-related disease

phenotypes. It can be assumed, that individuals that suffer from PTBS and show accelerated epigenetic aging, might also be more likely to develop premature age-related diseases.

The present thesis has contributed further knowledge on correlates of trauma exposure. Its results encourage multidisciplinary research beyond behavioral symptoms in order to yield new insights into the neural and physiological basis of normal and abnormal behavior. Further this knowledge is pivotal to expand current etiological models for psychiatric disorders.

Research on both psychopathology and pathophysiology increases the knowledge of various aspects of dysfunction, thereby fostering the understanding of trauma.

Zusammenfassung

Traumatische Erfahrungen können sich auf die psychische wie auch die physische Gesundheit, und somit auf den Körper und Geist auswirken. Das Risiko einer stressbedingten Erkrankung, insbesondere der Posttraumatischen Belastungsstörung, steigt mit der Anzahl an traumatischen Erfahrungen an (Kolassa & Elbert, 2007). Zudem erhöhen traumatische Erfahrungen auch die Auftretenswahrscheinlichkeit einer Reihe von körperlichen Erkrankungen, die von kardiovaskulären und metabolischen Erkrankungen bis hin zu frühzeitigem Altern und Tod reichen können (Agorastos, Pervanidou, Chrousos, & Baker, 2019; Gassen, Chrousos, Binder, & Zannas, 2017; Lohr et al., 2015). Eine wichtige Voraussetzung um effektive Präventionsmaßnahmen entwickeln zu können, ist auch die an den Erkrankungen beteiligten biologischen Mechanismen zu erforschen. Die vorliegende Dissertation befasst sich sowohl mit psychopathologischen Aspekten infolge traumatischer Erfahrungen als auch mit möglichen zugrundeliegenden neurobiologischen Mechanismen von Traumafolgestörungen. In den drei Studien der Dissertation werden Korrelate traumatischer Erfahrungen auf der Verhaltensebene als auch auf der neuralen und molekularen Ebene untersucht.

In der ersten Studie wird der Zusammenhang zwischen traumatischen Erfahrungen, insbesondere belastenden Kindheitserlebnissen und der auftretenden Psychopathologie auf der Verhaltensebene beleuchtet. Der Effekt von Traumaerlebnissen wurde mittels einer Pfadanalyse auf die Posttraumatische Belastungsstörung (PTBS) und die Aufmerksamkeitsdefizit-Hyperaktivitätsstörung (ADHS) untersucht. Während die Symptomschwere von PTBS sowohl durch die Anzahl traumatischer Lebenserfahrungen als auch durch frühe Vernachlässigungserfahrungen vorhergesagt werden kann, wird für die ADHS Symptomschwere allein ein Zusammenhang mit frühen Vernachlässigungserfahrungen festgestellt. Die bedeutsame Rolle von frühen belastenden

Kindheitserlebnissen auf die Psychopathologie bestärkt Forschungsbefunde, welche vor allem die schädlichen Auswirkungen von frühen Stresserlebnissen auf die psychische Gesundheit betonen. Darüber hinaus zeigt die vorliegende Studie, dass der Effekt von früher Vernachlässigung auf die ADHS-Symptomatik zum Teil durch die PTBS-Symptomschwere vermittelt wird. Dieser Mediatoreffekt von PTBS hat bisher wenig Aufmerksamkeit in der Forschung gefunden und regt dazu an, bei der Behandlung von ADHS auch Vernachlässigungserfahrungen und eine mögliche PTBS diagnostisch zu überprüfen. Somit kommen auch den Präventionsmaßnahmen zur Verhinderung traumatischer Ereignisse und belastender Kindheitserfahrungen eine wesentliche Bedeutung zu, um das Erkrankungsrisiko für ADHS und PTBS zu reduzieren.

Die zweite Studie konzentrierte sich auf die Untersuchung von Psychopathologie und neuronaler Aktivität. Hierfür wurde ein ereigniskorreliertes Potenzial im Elektroenzephalogramm, die Early Posterior Negativity (EPN), ein Marker für Aufmerksamkeit auf emotionale Reize, untersucht. Es stellte sich in einer transdiagnostischen Symptomanalyse heraus, dass Konzentrationsstörungen, Schlafstörungen und Misstrauen im Zusammenhang mit einer reduzierten affektiven Unterscheidung zwischen hocherregenden und weniger erregenden Bildern stehen, welche durch die EPN repräsentiert wird. Zudem zeigt sich, dass das männliche Geschlecht der Untersuchungsteilnehmer sowohl auf die Stärke als auch auf die Unterdrückung der EPN einen Einfluss hat. Somit scheint die emotionale Verarbeitung von positiven erregenden Bildreizen geschlechtsspezifisch zu sein. Wir folgern daraus, dass die genannten stressassoziierten Symptome möglicherweise eine funktionelle Reorganisation der emotionsverarbeitenden Bahnen induzieren können, welche sich in der reduzierten Diskriminierung affektiver Stimuli wiederspiegelt.

Das Gehirn reagiert auf Stressoren in verschiedenartig dynamischer Weise. Nachdem die traumaassoziierte Psychopathologie auf neuraler Ebene untersucht wurde, liegt der Fokus der dritten Studie auf der molekularen Ebene. Epigenetische Mechanismen sind an der Regulation aller biologischer Prozesse beteiligt und werden zudem auch durch Umwelteinflüsse wie traumatischen Stress beeinflusst. Somit untersucht die dritte Studie den Zusammenhang zwischen der Anzahl traumatischer Erlebnisse und PTSB-Symptomschwere und dem epigenetischen Alter. Die Ergebnisse weisen darauf hin, dass es nicht zeitbegrenzt auftretende Stressoren wie belastende Kindheitserlebnisse oder die Anzahl der insgesamt widerfahrenden traumatischen Erlebnisse sind, die das epigenetische Altern beschleunigen, sondern die PTBS-Symptomschwere. Die Beschleunigung des epigenetischen Alters ist ein molekularer Marker, der auch mit einer Reihe von vorzeitig eintretenden altersbedingten Erkrankungen assoziiert wird. Somit könnte es sein, dass PTBS Patienten, die ein erhöhtes epigenetisches Alter vorweisen, zudem eine erhöhte Wahrscheinlichkeit haben, eine altersassoziierte Erkrankung zu entwickeln.

Mit der vorliegenden Dissertation konnten Kenntnisse über Korrelate von Traumata gewonnen werden. Es wurde deutlich, dass interdisziplinäre Forschungsansätze, die über die beobachtbaren Verhaltens- und Erlebenssauffälligkeiten hinaus gehen von Relevanz sind, um vertiefte Erkenntnisse zu neuralen und physiologischen Grundlagen von normalem und abweichendem Verhalten zu erlangen und in die Modelle zur Ätiologie psychischer Störungen zu integrieren. Daher bedarf es sowohl Forschung zur Psychopathologie als auch zur Pathophysiologie, um Traumata ganzheitlicher zu verstehen.

1. General introduction

The majority of the general population throughout the world is affected by traumatic experiences. In a study by the World Health organization analysing over two dozen countries, over 70% of the participants reported having experienced one or more traumatic episodes over the course of their lifetimes, ranging from disasters, accidents, war related trauma, to physical or sexual violence (Kessler et al., 2017). While trauma exposure is very common, a significant minority of the affected individuals develop long-term mental health impairments (Atwoli, Stein, Koenen, & McLaughlin, 2015; Bonanno, Westphal, & Mancini, 2011). Moreover, with an increase of cumulative trauma exposure, resilience towards the development of chronic posttraumatic stress symptoms diminishes (Neuner et al., 2004; Wilker et al., 2015). Traumatic experiences, especially when experienced early in life, enhance a patient's likelihood of being diagnosed with psychiatric disorders, most prominently Posttraumatic Stress Disorder (PTSD; Stevens, van Rooij, & Jovanovic, 2018). A World Mental Health survey reported a lifetime prevalence of PTSD ranging from 3.0 – 4.4% worldwide (Stein et al., 2014). In refugee populations greater prevalence was reported with estimates around 30% or even higher (Fazel, Wheeler, & Danesh, 2005; Morina, Akhtar, Barth, & Schnyder, 2018).

Apart from PTSD, disorders for which the onset and course is impacted by trauma range for example from depression, anxiety, substance abuse (Teicher & Samson, 2013), to psychosis (for review, see Varese et al., 2012) or attention deficit hyperactivity disorder (ADHD; Rucklidge, Brown, Crawford, & Kaplan, 2006). Additionally, trauma is found to be associated with a premature development of age-related physical health problems, ranging from cardiovascular and metabolic diseases to premature death (Gassen, Chrousos, Binder, &

Zannas, 2017; Lohr et al., 2015). Overall, there is mounting evidence for long-lasting detrimental effects of trauma exposure manifested in a broad range of psychiatric and pathological presentations. Research on contributing factors as well as biological mechanisms involved in trauma- and stress related disorders appear to be crucial to gain more knowledge about the implementation of preventative measures because trauma-related disorders can constitute incapacitating conditions and are generally accompanied by substantial annual medical and societal costs.

The present thesis seeks to elucidate psychopathological aspects of the lasting imprints following trauma exposure. It further aims to explain common underlying mechanisms of trauma-related psychopathology. There are several factors that must be considered in contemplating the interplay between traumatic experiences, stress responses, and pathology. Trauma is not only associated with lasting traces on a behavioral level but also with modifications of the brain on a neuronal and molecular level. Potential mechanisms for physiological alterations following traumatic stress that also affect the clinical phenotype include epigenetic modifications as well as neuroplastic adaptions (Elbert & Schauer, 2014b). The following chapters outline how traumatic experiences shape the body and mind on the behavioral, neural and epigenetic level. Subsequently, empirical studies and their results are described and discussed. An overall discussion, implications and a final conclusion follow.

1.1. Traumatic stress and the clinical phenotype

Traumatic experiences involve actual or threatened death, serious injury, or threat to physical integrity. Reactions to the shocking and emotionally overwhelming situations vary considerably

from mild to severe. Following traumatic experiences, the majority of individuals show short term normative symptoms but are able to cope with the traumatic experience and do not develop ongoing PTSD (Stein et al., 2014). However, a small but significant minority of approximately one third of the individuals exposed to severe traumatic experiences fail to recover, showing abnormal behavioral and physiological responses to the traumatic experiences manifested in posttraumatic stress disorder (PTSD; Davidson, 2004). Due to this inherent variability in the psychological responses of individuals to traumatic experiences, individual PTSD risk factors require focused investigation. In a review Tortella-Feliu et al., (2019) confirmed female gender, a history of physical disease and family history of psychiatric disorder and cumulative exposure to potentially traumatic experiences and trauma severity to be robust risk factors for developing PTSD. Moreover, early life stress and adverse childhood experiences are one of the strongest risk factors for a number of psychiatric disorders including PTSD (Lupien, McEwen, Gunnar, & Heim, 2009; Provencal & Binder, 2015). The cumulative exposure to traumatic experiences amplifying PTSD onset and severity in a dose dependent manner has been described as *building block effect* (Kolassa & Elbert, 2007; Neuner et al., 2004; Schauer et al., 2003). At extreme levels of trauma exposure, there is no ultimate resilience towards the development of chronic post-traumatic stress (Kolassa et al., 2010). PTSD is a condition characterized by persistent re-experiencing of the traumatic event, avoidance of traumatic triggers, negative alterations in cognition and mood, and increased arousal and reactivity (American Psychiatric Association, 2013). The majority of individuals with PTSD have at least one and up to 3 comorbid psychiatric conditions such as major depression, generalized anxiety disorder, substance use disorders, impulsive or dangerous behavior, or self-harm. The high comorbidity rates might be either due to a predisposition to experience traumatic events when

having a psychiatric history (Brewin, Andrews, & Valentine, 2000) or to traumatic events or PTSD itself triggering the manifestation of other psychiatric disorders. In general, trauma exposure and PTSD are associated with complex psychiatric presentations manifested in behavior, body, and brain. Traumatic experiences from episodic threats to adverse childhood experiences, are thought to remodel the functioning of the brain by impacting brain circuitry, neurochemistry, cellular, immune, endocrine and metabolic functions (Kolassa, Illek, Wilker, Karabatsiakis, & Elbert, 2015). In short, biological systems adapt in response to traumatic stressors with neural and molecular modifications. Accordingly, PTSD might be regarded as clinical manifestation of stress-induced changes in neurobiological systems. The following chapters will elaborate on the physiological changes on the neural and molecular level following trauma exposure.

1.2. Neural representations of traumatic stress

The brain reacts to stressors in a dynamic and often surprisingly flexible manner. The above-mentioned building block effect is believed to be a result of the development of the neural representation of (accumulated) traumatic cues, that constitute a pathological memory structure. All aspects of traumatic experiences are stored in this fear network (Elbert & Schauer, 2002; Rockstroh & Elbert, 2010), from cognitions and emotions to sensory and physiological responses. It is formed by memory processes such as fear conditioning and principles of synaptic plasticity such as long-term potentiation and consolidation (Wilker & Kolassa, 2013) and offers due to its pathological fragmentation of autobiographic context memory an etiology of PTSD symptoms. Increasingly, psychiatric disorders are understood as disorders of circuits

(Hyman, 2000), disturbing normal functioning within and among brain systems. The development of PTSD involves multiple neural networks, such as those regulating emotion, memory, and learning. More specifically, it is associated with a dysregulation of the human stress reaction systems, including the hypothalamic-pituitary-adrenal axis (HPA axis). With respect to trauma-related neurocircuitry models (Admon, Milad, & Hendler, 2013; Cisler, Privratsky, Smitherman, Herringa, & Kilts, 2018; Pitman et al., 2012), there is evidence from functional neuroimaging studies suggesting a hyperactivity of the amygdala and dorsal anterior cingulate cortex (dAAC) and hypoactivity of the hippocampus and medial prefrontal cortex (mPFC). Abnormalities in either one of these brain regions and altered functional connectivity are associated with a dysregulation of the HPA-axis function and hence maladaptive responses to stress (Heim & Nemeroff, 2009). Additionally, the amygdala constitutes a pivotal structure for both emotion processing and the coordination of the stress response. In contrast to EEG or MEG signals, the low temporal resolution of neuroimaging research often prevents the elucidation of rapid, ongoing neural activity in responses to emotional stimuli. Evaluating these early cortical responses, Burgmer et al., (2013) and Adenauer, Pinosch, et al., (2010) found an enhanced PFC response in trauma exposed individuals representing the ignition of the fear network (Rockstroh & Elbert, 2010), which is then likely to be followed by the hypoactivation of prefrontal regions as mentioned above (Elbert et al., 2011).

There is a wide range of research focusing on the neurobiology underlying trauma-related disorders, and the presented findings reflect only a small part relevant for the present thesis. For a more comprehensive review see Pitman et al., (2012). It should be noted that aside from neural alterations in the traumatized brain, molecular mediators should not be omitted in understanding the impact of trauma.

1.3. Molecular mechanisms in trauma-related disorders

The brain is affected in various ways by traumatic experiences. The neural representations of traumatic stress and the pathogenesis of PTSD are not entirely determined by past experience per se, but also by factors on the molecular level, such as genetic factors and epigenetic modifications. Twin studies reported, that genetic susceptibility factors account for 40–50% of the vulnerability to develop PTSD (Afifi, Asmundson, Taylor, & Jang, 2010). Yet, the remaining vulnerability is thought to develop in interaction with environmental factors, such as the type or/and the number of traumatic events. For instance, gene x environment association studies found strong support for the influence of variants of the FKBP5 gene, which regulates glucocorticoid receptor sensitivity, on PTSD when interacting with trauma exposure (e.g. Hawn et al., 2019). Glucocorticoids promote the endocrine stress response mediated by the hypothalamic – pituitary - adrenal (HPA) axis and play a critical role in terminating the stress response through glucocorticoid receptor activation. The involvement of a dysfunction of the HPA axis, particularly a hypersensitivity of the glucocorticoid receptor (GR) is well documented for PTSD (Daskalakis, Lehrner, & Yehuda, 2013; Yehuda, Golier, Halligan, Meaney, & Bierer, 2004). Alterations in FKBP5 have functional consequences on glucocorticoid response system sensitivity, leading to a slower return to baseline of stress-induced cortisol levels and a prolonged stress response, that in turn enhances the risk for stress-related psychiatric disorders and PTSD (Binder, 2009; Yehuda, 2009). Thus, gene × environment interactions can influence clinical phenotypes, and these interactions can be further mediated by inherited or environmentally-induced epigenetic modifications (Skinner, Manikkam, & Guerrero-Bosagna, 2010). Increasing evidence suggests that epigenetic mechanisms play an crucial role in the pathophysiology of PTSD and other trauma and stress-

related disorders by linking environmental exposure to trauma to biological systems (for reviews see Blacker, Frye, Morava, Kozicz, & Veldic, 2019; Morrison, Miller, Logue, Assef, & Wolf, 2019). The major epigenetic mechanisms include DNA methylation and histone modification, which influence the gene expression, respectively the transcriptional accessibility of DNA without changing its structure. For PTSD, there is much empirical support for an altered gene expression via epigenetic mechanisms in genes involved in HPA-axis regulation, immune function, and transcription of neural and endocrine proteins (Sheerin, Lind, Bountress, Nugent, & Amstadter, 2017). The relationship between DNA methylation of genes involved in the HPA axis and immune system and PTSD has been found in both candidate-gene as well as epigenome-wide studies (Morrison et al., 2019). Using epigenome-wide studies, a related phenomenon following traumatic experiences can be studied. Several studies have shown associations of posttraumatic stress with somatic illnesses commonly seen with advanced age (Gassen et al., 2017; Glaesmer, Brähler, Gündel, & Riedel-Heller, 2011) and early mortality (Lohr et al., 2015), raising the possibility of accelerated biological aging. The epigenetic age, an indicator of biological aging, can be derived from epigenome wide DNA methylation patterns. Epigenetic aging is likely to be a key mechanism linking chronic stress with accelerated aging and heightened disease risk for stress-related disorders. Although the exact molecular mechanisms underlying this elevated risk warrant further research, studies have shown that accelerated epigenetic aging, the difference between the DNA methylation-predicted age and the chronological age, is associated with a variety of ageing-related and chronic diseases (Fransquet, Wrigglesworth, Woods, Ernst, & Ryan, 2019; Horvath & Ritz, 2015; Levine, Lu, Bennett, & Horvath, 2015; Pagiatakis, Musolino, Gornati, Bernardini, & Papait, 2019).

To conclude, genetic, epigenetic, and environmental factors such as early life stress and trauma exposure act together to determine both an individual's susceptibility to PTSD and its clinical phenotype. Epigenetic mechanisms such as DNA methylation are suggested to influence neurobiological processes on a molecular and cellular level by modulating stress-related gene expression. Overall the etiology of stress-related disorders is complex and multifactorial. In order to limit the impact of traumatic stress on both an individual and societal level, it is crucial to gain more knowledge of the underlying biological mechanisms.

1.4. Rationale for the thesis

Parallel to advances in (epi)genetic, neurobiological, and behavioral research unravelling the role of circuits and (epi)genetics in psychopathology, the value of traditional characterizations of psychopathology via observation-based categorical diagnoses has been questioned. In order to understand mental illness in all its complexity, an integrative understanding of psychopathology is required. Psychiatric disorders are increasingly regarded as disruptions of basic brain mechanisms, including dysregulations of neural circuits and epigenetic modifications, that result in maladaptive behaviors. The National Institute of Mental Health's Research Domain Criteria (RDoC) initiative proposed a new research framework for interdisciplinary psychopathological research incorporating a dimensional approach to psychopathology with less emphasis on traditional diagnoses and an integration of behavioral and related neurobiological systems (Cuthbert & Insel, 2013). The RDoC approach supports the development of hypotheses about how alterations in the neurobiological systems produce maladaptive behavior and thereby also intends to provide avenues for future therapeutic

discovery. With regards to sequelae of trauma, various clinical conditions are commonly observed. Trauma-related disorders are heterogeneous in terms of both their incidence following a trauma and with respect to the attendant symptoms. The diversity of responses to trauma emphasizes the need for both a better understanding of physiological commonalities and a more fine-grained approach. This highlights the value of the RDoC framework considering broader transdiagnostic dysfunctions manifested in the brain, body and behavior following traumatic exposure.

In the following sections of the thesis, research is presented inspired by Research Domain Criteria (RDoC) initiative studying traumatic stress across multiple units of analysis. Epigenetic, neural and behavioral correlates of trauma exposure are presented.

The first study focuses on the relationship between traumatic experience, especially childhood adversities and psychopathology on the behavioral level. In response to adverse childhood experiences cognitive and emotional disruptions such as hyperarousal, restlessness, disorganization and difficulties concentrating often occur and manifest symptoms of PTSD and/or ADHD according to the nosology of the DSM. Stress-related disorders might be a result of an disruption of the development and function of limbic structures following childhood trauma (Nemeroff, 2016). In a sample of adolescents, the study examined the relationship between different types of childhood trauma on both, symptoms of PTSD and ADHD using path analysis. Also the link between PTSD and ADHD symptoms was determined.

In order to identify correlates of trauma exposure on the neural level, the second study of the thesis focused on cortical brain activity using Electroencephalography (EEG). Both cortical correlates of affective picture processing assessed via event-related potentials (ERPs) during emotional scene viewing and an exploratory transdiagnostic analysis are presented. The study

aimed to investigate cortical correlates of emotion processing in a transdiagnostic sample of 90 adolescents with varying degrees of trauma exposure.

Lastly, for a better understanding of factors potentially mediating the effects of traumatic experiences on stress-related pathology, epigenetic alterations were explored. Lifetime trauma exposure, adverse childhood experiences and PTSD symptom severity were assessed in 104 females. The study addresses the relationship between traumatic stress as well as its associated psychopathology and accelerations in biological aging processes via epigenetic modifications.

The three introduced studies are presented separately in the style of self-contained manuscripts with the common repeating structure (introduction, methods, results and discussion) in the following chapters.

2. ADHD and PTSD following adverse childhood experiences. A study with adolescents.

2.1. Abstract

Objective: Adverse childhood experiences (ACE) have been linked to a spectrum of mental health impairments. Common symptoms include those of PTSD and ADHD with frequent co morbidity. In adolescents, we investigated these disorders and their interrelatedness in relation to a history of ACE.

Method: Standardized semi-structured interviews were conducted with 74 adolescents with diverse ethnic backgrounds. A path analysis was used to uncover links between different types of ACE and clinical symptoms of PTSD and ADHD.

Results: Both, non-domestic traumatic stressors and childhood neglect predicted PTSD symptom severity. For ADHD, a direct path from childhood neglect but not for other types of traumatic stress was demonstrated. Moreover, ADHD symptoms were predicted by the severity of PTSD symptoms. The link between childhood neglect and ADHD symptoms was partially mediated by PTSD severity.

Conclusions: The results indicate the significant role of ACE for the severity of PTSD, ADHD and their combined presentation. The greater the cumulative exposure to stressors, the more likely the development of PTSD . Childhood neglect not only promotes PTSD but is also linked to symptoms of ADHD. The observation that the impact of childhood neglect on ADHD is mediated in part by PTSD is a novel finding, that needs to be confirmed in other samples that have been exposed to a varying degree to ACE and traumatic stressors.

2.2. Introduction

Adverse childhood experiences (ACE) shape the vulnerability for mental health problems across different diagnostic categories including depression, aggressive behavior, internalizing and externalizing behavior or posttraumatic stress disorder (PTSD; Connor, Steingard, Cunningham, Anderson, & Melloni, 2004; Felitti, 1998; Gershoff & Grogan-Kaylor, 2016; Christine Heim, Plotsky, & Nemeroff, 2004; Hodgdon et al., 2018; Kilpatrick et al., 2003). The greater the co-occurrence of different forms of early maltreatment, the higher the likelihood of subsequent psychopathologies (Hodgdon et al., 2018; Teicher, Samson, Polcari, & McGreenery, 2006). Teicher & Samson (2013) showed, that individuals with a history of childhood adversities and a psychiatric disorder can be characterized by an earlier age at onset, greater symptom severity, a greater risk for suicide and an increased comorbidity than non-maltreated individuals with the same diagnoses. Childhood adversities are a strong push factor for PTSD (Breslau et al., 2014; McLaughlin et al., 2017; Scott, Smith, & Ellis, 2010). A clear cumulative effect of exposure to multiple types of traumatic experiences and PTSD symptom severity has been reported (Kolassa & Elbert, 2007; Maggie Schauer et al., 2003; Wilker et al., 2015). Moreover, it has been shown that adverse childhood experiences strongly relate to attention deficit/hyperactivity disorder (ADHD) symptoms (Brown et al., 2017; Glod & Teicher, 1996; Kulacaoglu, Solmaz, Ardic, Akin, & Kose, 2017; Semiz, Öner, Cengiz, & Bilici, 2017; Weder, 2015) and can be considered as a risk factor for developing ADHD and the consequential psychosocial impairments (Biederman et al., 1995; Fuller-Thomson & Lewis, 2015). Moreover, high comorbidity between ADHD and PTSD has commonly been reported (Adams, Adams, Stauffacher, Mandel, & Wang, 2015; Antshel et al., 2013; Famularo, Fenton, Kinscherff, & Augustyn, 1996; Kessler, Adler, Barkley, & Biederman, 2006; Weinstein,

Staffelbach, & Biaggio, 2000). Given that ADHD is associated with risk-taking behavior, impulsivity and an earlier onset than that of PTSD, it has been discussed as a potential antecedent risk factor for PTSD. However, a meta-analysis (Spencer et al., 2016) reported a robust bidirectional association between attention-deficit/hyperactivity disorder (ADHD) and posttraumatic stress disorder. One suggestion is that ADHD may constitute a vulnerability factor for developing PTSD. However, exposure to traumatic stress and other childhood adversities may not only increase the likelihood for PTSD, but also for ADHD symptoms when occurring early in live. Supplementing the latter point, Glod & Teicher (1996) found higher levels of activity up to hyperactivity in maltreated children than in non-maltreated children whereby the higher activity level was primarily accounted for by the co-occuring PTSD symptoms. For children without PTSD, the activity level was not influenced by the history of maltreatment. One possible explanation might be the overlapping symptoms of the disorders and thus ADHD symptoms masking PTSD symptoms in maltreated individuals. Furthermore, PTSD symptoms were only found to be associated with inattention problems via dissociation (Kaplow, Hall, Koenen, Dodge, & Amaya-Jackson, 2008). A better understanding of the relationship between ADHD and PTSD has important clinical and scientific implications. It could impact diagnostics and treatment by alerting clinicians to screen for the triad of ADHD, trauma exposure and trauma symptoms. From a scientific perspective, further knowledge could advance research efforts to gain insight into the pathophysiology of disorders following adverse childhood experiences.

The current study investigates a sample with varying degrees of exposure to ACE and to non-domestic violence. The associations between the exposure to stressors and psychopathology was uncovered using a path analysis. Thereby multivariate relations between effects were

simultaneously incorporated in one model. Childhood adversities were clustered into abuse and neglect. We assumed that (1) experienced childhood adversities within the family as well as non-domestic traumatic events would impact on both, ADHD and PTSD symptoms. Furthermore, it was predicted (2) that PTSD symptoms following traumatic stress are positively associated with ADHD symptoms.

2.3. Methods

2.3.1. Procedure

Data collection took place as part of larger study investigating the influence of genetic and environmental factors on response to stressful life events between January 2015 and September 2016 at the Centre of Excellence for Psychotraumatology, University of Konstanz.

Individuals who had been exposed to a varying degree of traumatic stressors and other forms of threats were addressed. Individuals were referred to the center by social workers, human rights organizations, medical doctors or lawyers for diagnostic clarification. Further recruitment strategies included announcements in accommodation centers for asylum seekers, counseling centers, intercultural meeting places and newspaper advertisement. Informed consent was provided from caregivers and also from children. Standardized clinical interviews were conducted with participants who met inclusion criteria (age over 12, absence of any history of a neurological or psychotic disorders, no current or past psychoactive medication) by experienced psychologists and if needed with trained translators. If necessary, participants received a psychodiagnostic report and arrangement of treatment (this service is offered to all individuals referred investigated at the center, irrespectively of study participation) and were

reimbursed for travel expenses. The Ethical Committee of the University of Konstanz (Germany) approved the study.

2.3.2. Participants

The present assessment set was completed for 74 adolescents/young adults (N_{female} = 45, N_{male} = 29) aged between 12 and 21 years (M = 15.3, SD = 2.43). The most frequent regions of origin were Europe (n = 44), followed by the Middle East (n=19) and the Balkans (n = 11). On average, participants had completed over 8 years of education (SD = 2.36, range 1-13).

2.3.3. Psychometric measures

All measures were applied as semi-structured interviews. In addition to socio-demographic data, the following measures were assessed. Psychopathology was defined by symptom criteria (and not by a categorial diagnosis).

2.3.3.1. Adverse childhood experiences

Childhood maltreatment, experienced under age 18, was assessed with the German version (KERF; Isele et al., 2014a) of the Maltreatment and Abuse Chronology of Exposure (MACE; Teicher & Parigger, 2011). The KERF consists of 20 questions covering physical and emotional abuse by parents and siblings, sexual abuse, physical neglect, emotional neglect, witnessed violence towards parents and siblings, and peer violence. Items are coded dichotomously (yes/no) and subscales range from 0 to 10. An overall score (0 – 100) can be calculated by summing up the interpolated scales. Cronbach's alpha was .78 for the overall score of the

present study. The subscale neglect comprised physical neglect and emotional neglect and subscale abuse the remaining constructs.

2.3.3.2. Traumatic events and severity of post-traumatic stress disorder

Lifetime traumatic load, self-experiences or witnessed, was examined by the Event List of the Posttraumatic Diagnostic Scale (Foa, Cashman, Jaycox, & Perry, 1997). Event types were assessed by a dichotomously coded event list with 12 items (yes/no) (Ehlers, Steil, Winter, & Foa, 1996). The sum score of the events list served as an indicator of the experienced event types, ranging between 0 and 10. Two event types relating to violence within the family were excluded in order to obtain a measure for traumatic events not perpetrated by family members. The German translation of the PTSD Symptom Scale Interview Version (PSS-I; Ehlers et al., 1996; Foa, Riggs, Dancu, & Rothbaum, 1993) was used for the assessment of PTSD symptom severity according to DSM-IV criteria (American Psychiatric Association, 2000). Utilizing a four-point Likert scale, the scale consists of 17 items (Foa et al., 1993). Possible sum scores range between 0-51. The PSS-I has proven to be a valid and reliable instrument (Foa & Tolin, 2000). Internal consistency for the current study was high (Cronbach α= .92).

2.3.3.3. ADHD Symptoms

ADHD Symptoms were assessed using the ADHD Self Rating Scale (ASRS -v 1.1), developed by the World Health Organization (Kessler et al., 2005). The ASRS includes 18 items about frequency of recent ADHD symptoms based on the DSM-IV criteria. The scale provides information suggesting the need of a more in-depth diagnostic evaluation. On two subscales attention-deficit and hyperactivity/impulsivity symptoms, respectively are assessed. Each item

is rated from 0 (never) to 4 (very often). Also for the German speaking validation study, the ASRS showed good psychometric properties including high levels of internal consistency (Cronbach's α coefficient of the sum score = .88) (Mörstedt, Corbisiero, & Stieglitz, 2016). In the present study Cronbach's α coefficient was .91.

2.3.4. Data analysis

For bivariate associations, Spearman´s Roh was calculated. To test for multivariate patterns, path analyses were performed. Maximum-likelihood parameter estimation with robust standard errors and a Yuan-Bentler test statistic was performed. This approach allows analyzing non-normal data with small sample sizes (Savalei & Bentler, 2005). The first model included paths from experienced traumatic events types and both childhood neglect and abuse to ADHD symptom scores and PTSD severity. To control for a possible impact of having a refugee background, a dummy variable was included in the path analyses, with those having a refugee status coded as "1" (n =31) and those born and raised in Germany as "0" (n = 43). Nonsignificant paths were removed from the model. Moreover a path included a mediation analysis. According to multiple fit indices the final model was chosen. Root-mean-square error of approximation (RMSEA) below .06 and standardized root-mean-square residual (SRMR) below .08 indicate good fit (Hu & Bentler, 1999). Tucker–Lewis index (TLI) and comparative fit index (CFI) close to .90 are acceptable (Hu & Bentler, 1999). Different models were compared by means of small sample-size-corrected Akaike and adjusted Bayesian information criteria (corrAIC, adjBIC, respectively). Larger values imply worse fit. All statistical analyses were performed using IBM SPSS Statistics version 25 for Mac or R for Mac version 3.3.2. Path analysis and mediation analysis was performed using the lavaan

package for R (Rosseel, 2012).

2.4. Results

2.4.1. Psychometric analysis

As expected and illustrated in Table 2.1, trauma-related variables (childhood maltreatment, traumatic event types, PTSD symptom severity) were all correlated. More surprising was that ADHD symptom severity was also significantly associated with all trauma variables, most strongly with childhood neglect and PTSD symptom severity.

Table 2.1. Descriptive Statistics and Correlations for Childhood Maltreatment, PTSD, ADHD and traumatic event types.

Variable		1	2	3	4	*M*	*SD*	Range
1.	Childhood neglect	-				2.88	4.21	0 – 13
2.	Childhood abuse	.35 **	-			6.64	7.18	0 – 30
3.	Traumatic event types	.28 *	.23 *	-		1.32	1.33	0 – 5
4.	PTSD symptoms	.49 ***	.40 ***	.57 ***	-	3.92	6.87	0 – 26
5.	ADHD symptoms	.42 ***	.34 **	.27 *	.43 ***	14.74	11.35	0 – 47

Note. Spearman´s rho coefficient was calculated. PTSD = posttraumatic stress disorder, ADHD = attention-deficit/hyperactivity disorder, *M* = mean, *SD* = standard deviation.

* $p < .05$. ** $p < .01$. *** $p < .001$.

2.4.2. Path analysis

According to the best fitting model (Figure 2.1), both trauma events and childhood neglect predicted PTSD symptom severity in the direction that more events (β=.27, *SE*=.52, $p < .01$) and neglect (β =.43, *SE* =.26, $p <.001$) indicated higher PTSD symptom load. Having a refugee background was also positively related to PTSD severity (β =.23, *SE* =1.45, $p <.05$). The predictors accounted for 50% of the variance in PTSD symptom severity.

Moreover, neglect not only predicted PTSD symptoms but also ADHD symptom severity (β = .20, *SE* =.27, $p <.05$). ADHD symptoms were not only predicted by childhood neglect but also by PTSD symptom severity (β =.38, *SE* =.15, $p < .001$). Interestingly, childhood abuse was not a significant predictor of PTSD or ADHD symptoms and was excluded in a stepwise manner from the model. Exploratory analyses revealed an indirect mediation path between childhood neglect and ADHD symptoms via PTSD severity. The relationship between neglect and ADHD symptoms was significantly reduced by PTSD severity scores from a standardized beta of .20 to a standardized beta of .16 ($p<.001$). Thus the Sobel test (Preacher & Hayes, 2004) confirmed a partial mediation effect ($z = 2.74$, $p < .01$). The model explained 28% of the variance in ADHD symptoms. Significant associations were found between the exogenous variables refugee background and traumatic event types (r = .41, p < .01), between refugee background and childhood neglect (r = .35, p < .01) as well as between traumatic event types and childhood neglect (r = .28, p < .05). Fit indices of the final model (Figure 1) presented good fit, $\chi 2$(2, *N*=74) = 0.37, $p = 0.83$, RMSEA < .001, 90% confidence interval (CI) [.00, .19], SRMR = .03, both TLI and CFI > .95, corrAIC = 1757.09, adjBIC = 1777.82. The whole model is displayed in Figure 2.1.

Moreover, the reversed direction of path from ADHD symptoms to PTSD symptoms did not fit the data $\chi 2(1, N=74) = 2.13$, $p = 0.14$, RMSEA = .13, 90% CI [.00, .00], SRMR = .04, TLI = .86, CFI = .97, corrAIC = 1887.23, adjBIC = 1876.22.

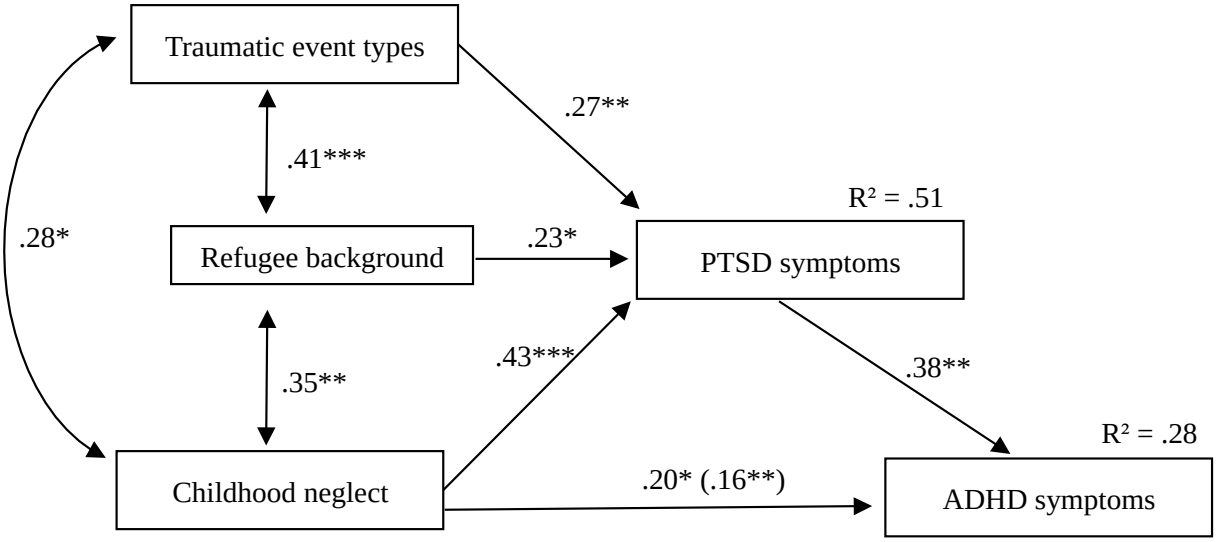

Figure 2.1. Path analysis from experiences of childhood neglect and traumatic event types to PTSD symptoms and ADHD symptoms (N = 74). Paths with one arrowhead indicate direct associations. Double-headed arrows represent co-variances. Standardized path coefficients are shown. * $p < .05$, ** $p < .01$, *** $p < .001$.

2.5. Discussion

The present study assessed adverse childhood experiences in familial context and beyond and aimed to determine its associations with symptoms of psychopathology in a multi-ethnical sample of adolescents. In particular, refugees were included in order to obtain the full variety of stressors children may be exposed to. Cognitive and emotional disruptions such as hyperarousal, restlessness, disorganization and difficulties concentrating often occur in response to adverse childhood experiences, and may reach manifest symptom levels of PTSD and/or ADHD. The results show positive associations between different types of adverse childhood experiences and symptoms of PTSD or ADHD. The greater the exposure to traumatic events, the more intense PTSD symptoms became. This previously well documented the *building block effect* (Catani et al., 2008; Neuner et al., 2004; Maggie Schauer et al., 2003) validates the present data. On the other hand, there was no link between experienced traumatic event types and ADHD symptoms. Some studies reported higher prevalence of traumatic events among children diagnosed with ADHD (Ford et al., 2000; Schilpzand et al., 2018). It is important to note, that the concept of traumatic events used in studies usually incorporates childhood maltreatment by parents. In the present study, traumatic events and childhood maltreatment by parents were treated as distinct variables.

In line with the Adverse Childhood Experiences study (Felitti, 1998) and other research (Finkelhor, Turner, Hamby, & Ormrod, 2011; Norman et al., 2012), our results demonstrate a positive association between maltreatment by parents and mental health outcomes. In particular, the more childhood neglect was reported in our study, the more severe ADHD symptoms were found. One may infer, the development of ADHD symptoms is particularly driven by adversities within families, whereas non-domestic traumatic events have little or no effect. The

results match well previous findings where childhood maltreatment was found to be more common among individuals with ADHD (Brown et al., 2017; Rucklidge et al., 2006; Semiz et al., 2017). In a prospective twin study Stern et al. (2018) showed strong associations between childhood neglect/abuse and ADHD in young adulthood. Some authors argue, that adverse childhood experiences might increase the vulnerability for ADHD (Dinkler et al., 2017) and even constitute an environmental risk factor for ADHD in adulthood (Capusan et al., 2016). A positive association was also found between childhood neglect and PTSD severity. This is in line with previous research on PTSD (Heim & Nemeroff, 2001; Schalinski et al., 2016; Spinazzola et al., 2014; Widom, 1999) and highlights the perniciousness of neglectful caregiver behavior leading to PTSD symptoms. It indicates that traumatic events may aggravate PTSD especially in those who miss parental care.

Contrary to our assumptions one type of maltreatment, childhood abuse, was not associated with the present indicators of mental health. A recent study by Serpeloni et al., (2019) conducted in a high violence community, suggested that when mother are abused both during *and* after pregnancy, violence-related psychiatric problems are less frequent in their children, as a different, potentially protective, pattern of epigenetic changes occurs. The findings indicate that like other animals, humans are primed via epigenetic changes to face the environment their parents have been exposed to. This may hold for abuse, but not for neglect and in fact, the present results clearly corroborate the detrimental impact of neglect. Abuse refers to deliberate aggressive behaviors or attitudes that interfere with a child's mental or physical health as threatening, insulting, ridiculing and confining of the child. Whereas neglect can also be a threat to integrity as it is an act of omission and relates to an absence of parental care and a failure to

meet a child´s basic and essential needs. In contrast to a violent environment, there may be no adaptive behavior that can cope with neglect.

Independently from the confirmation of this suggestion, the present study shows a direct association between childhood neglect and both, PTSD and ADHD symptoms. With respect to experiencing traumatic events including abuse there seems to be a direct association only to PTSD symptoms. Apart from the direct association between childhood neglect and ADHD symptom severity, our results indicate an indirect association between traumatic events and ADHD symptoms via PTSD severity: more traumatic events means more PTSD and more PTSD seems positively associated with ADHD symptoms. Moreover, the association between childhood neglect and ADHD symptoms proved to be mediated in part by PTSD symptoms. This corroborates with (Husain, Allwood, & Bell, 2008) who reported related findings concerning the mediating role of PTSD. The authors found PTSD symptoms to mediate the relationship between trauma exposure and attention problems in children that survived the Bosnian war. However, behavioral similarities between the two disorders should be noted. The overlap of ADHD and PTSD symptoms relate to symptoms of irritability, concentration difficulties, impulsive behavior, and exaggerated startle responses (Daud & Rydelius, 2009).

The methodologies employed in our study present limitations: path analysis cannot prove causality or determine whether a specific model is correct; it can determine whether the data are consistent with the model. Given the correlational nature of this cross-sectional study, the direction of the associations cannot be determined. Another limitation of the study is its reliance on retrospective self-reports and thus is subject to the typical criticism of reliability of retrospective memories and recall-bias. However, a review by Brewin, Andrews, & Gotlib (1993) and Newbury et al. (2018) found limited support for this criticism.

2.5.1. Conclusion

The present study confirmed a positive association of adverse childhood adversities to psychopathology, thereby replicating the findings of other studies which demonstrated the detrimental impact of ACEs on mental health problems. In particular the results emphasize the devastating impact of emotional and physical neglect. Exposure to neglect may increase the vulnerability to developing ADHD and PTSD symptoms. The possible mediating role of PTSD has not received much attention. Our mediation testing demonstrated, that childhood neglect may play a positive and crucial role in ADHD symptoms, directly and through PTSD symptoms. From a clinical perspective, it is important that the possibility of a trauma history, including childhood neglect should be considered in the assessment of both, ADHD and PTSD referrals. Our findings suggest that prevention aimed at reducing ACE and traumatic stress is essential to minimize both ADHD and PTSD symptoms in adolescents. Finally, we suggest that for the treatment of ADHD, childhood trauma should be considered and if present, also be treated with child-friendly trauma-focused therapies such as NET (Schauer, Neuner, Elbert, 2011).

2.6. Acknowledgements

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3. Rapid brain responses to affective pictures indicate dimensions of trauma-related psychopathology in adolescents

3.1. Abstract

A variety of mental disorders are related to deviant brain activity. But these neural alterations do not validate psychiatric diagnostic categories. High symptom overlap and variable symptom patterns encourage a dimensional approach. Following the logic of the Research Domain Criteria (RdoC), we investigated trauma survivors for symptom clusters that might be associated with characteristics of event-related brain potentials, in particular with the early posterior negativity (EPN) elicited during affective picture processing. In rapid serial visual presentation, 90 adolescents (40male/50 female, age M = 15.0 ± 2.5 years) who had been exposed to varying amounts of traumatic stress passively viewed a stream of highly arousing positive and low arousing neutral pictures taken from the International Affective Picture System. Using standardized interviews, symptoms of trauma-related mental disorders were assessed (including those for PTSD, depression, borderline personality disorder and behavioral problems). A principal component analysis was performed to derive potential dimensions of psychopathology. Multiple regression analysis confirmed a factor comprising *problems concentrating*, *sleeping difficulties* and *mistrust* as a predictor of a larger EPN difference between high arousing positive and low arousing neutral IAPS pictures (β = .19, p < .05). Sex predicted the magnitude of the EPN (β = .45, p < .001). Males displayed a stronger EPN suppression than females. The result suggests that *problems concentrating*, *sleeping difficulties* and *mistrust* seem to be transdiagnostic elements related to diminished early emotional

discrimination represented by the EPN. Furthermore, our findings indicate that the EPN in response to emotional processing is modulated by sex.

3.2. Introduction

Attention is primarily regulated by motivation, which is often activated by distinct unconditioned emotional stimuli. This *natural selective attention* (Bradley, 2009) reflects an evolutionary inheritance. According to the *motivational model of emotion* (Bradley, 2009; Lang & Bradley, 2010; Lang, Bradley, & Cuthbert, 1997), stimuli with an inherent biological meaning that are significant for survival or reproduction capture attention due to their motivational relevance. Affects are organized around two distinct motivational subsystems: the appetitive and the defensive system. The appetitive system is active in contexts that promote physical survival, such as ingestion, copulation and nurturing progeny, and evoke pleasant affects. The defense system is involved in contexts that threaten survival and are associated with unpleasant affects. Both systems can vary in intensity of activation, reflecting the arousal level (Lang et al., 1997).

Using event-related brain potentials (ERP), the time course of emotional picture processing has been investigated with millisecond resolution (Hajcak, Macnamara, & Olvet, 2010; Junghöfer, Bradley, Elbert, & Lang, 2001; A. Keil et al., 2002; Olofsson, Nordin, Sequeira, & Polich, 2008). A relatively early processing stage reflecting the differential processing of emotional compared to neutral stimuli is the Early Posterior Negativity (EPN). This neural activity typically observed over posterior scalp regions develops as early as 150 ms after the onset of arousing pleasant and unpleasant pictures relative to non-arousing neutral pictures and is maximally enhanced around 250-300 ms (Elbert et al., 2011). The EPN can be considered as a marker of attention allocation toward emotional material (Schettino, Keil,

Porcu, & Müller, 2016) and is reliably evoked in normal individuals. It is also found in paradigms using a serial flood of discrete visual events, such as Rapid Serial Visual Presentation (RSVP; Junghöfer et al., 2001). The EPN is reported to be suppressed in individuals with various psychiatric diagnoses, including affective disorders, schizophrenia and borderline personality disorder. It is also altered in individuals with a history of severe childhood adversities (Matz, Elbert, Weber, Wienbruch, & Rockstroh, 2010; Weber et al., 2009). In MDD, a reduced arousal modulation of the right-temporo-parietal activation evoked by visual stimuli was found (Moratti, Rubio, Campo, Keil, & Ortiz, 2008). Modulated early visual processing of emotional stimuli was also recorded in individuals suffering from PTSD, depression symptoms and dissociation (Adenauer, Pinosch, et al., 2010; Burgmer et al., 2013; Elbert et al., 2011; Keil, Adenauer, Catani, & Neuner, 2009; Schalinski, Moran, Schauer, & Elbert, 2014). Such deviations in neural activity are assumed to be characteristic for this psychopathology. However, the conceptualization of diagnoses in the American Psychiatric Association's Diagnostic and Statistical Manual (APA, DSM) and the International Classification of Diseases (ICD) have largely been based on subjective reports. High comorbidity among categories and an overlap of symptoms for different disorders are common. Disorders are not distinct, and the construct validity of the diagnostic concepts is disputable (Kendell & Jablensky, 2003). Hence, the National Institute of Mental Health's Research Domain Criteria (RdoC) have proposed a dimensional approach, putting forward a new research framework for interdisciplinary psychopathological research with less emphasis on traditional diagnoses and the integration of psychological and related neurobiological systems. In the present study, an exploratory transdiagnostic analysis is presented based on the heuristic outlined by the RdoC. Dimensions of psychopathology were investigated in adolescents who have been exposed to a varying

degree of traumatic stressors such as war, violence or childhood maltreatment.

The sample included German adolescents from both immigrant and non-immigrant families as well as refugee youth, as these groups have been frequently exposed to severe threats and present with trauma-related symptoms (Maggie Schauer, 2016). Adolescents were chosen as they can be selected to have no history of diagnosis and treatment including psychoactive medication or drug abuse. Clinical measures included symptoms of PTSD, depression, borderline personality disorder and behavior problems. The analysis of potential underlying dimensions was related to the response to affective picture processing in the parietal cortex. The affective RSVP design is known to produce variations with affective arousal (Junghöfer et al., 2001, 2006; Peyk, Schupp, Elbert, & Junghöfer, 2008) and was used to study participants with electroencephalography-based assessment of regional brain activity. The cortical reaction to high arousing pleasant pictures in comparison with low arousing neutral pictures in an event-related potential study was assessed. For ethical concerns related to the age range (including adolescents at age 12 years) and the trauma history of the sample, negative valence pictures were not included. The decision was based on earlier findings (Elbert et al., 2011) that most individuals with PTSD were reminded of their traumatic experiences, even though negative valence pictures were identical for each subject and no personalized cues were presented. Thus, the negative valence stimuli turned out to be strong reminders of their traumatic experiences with the potential to induce flashbacks and should only be applied when clinically indicated. In the present study we evaluated the association of differential cortical affective processing with potential dimensions of psychopathology. Some authors reported sex differences in affective processing including the early processing of arousing stimuli (Junghöfer, 2010; Sabatinelli, Flaisch, Bradley, Fitzsimmons, & Lang, 2004;

Stevens & Hamann, 2012). Hence, the potential influence of sex was also analyzed. In particular, a reduced modulation of cortical activity to pleasant arousing pictures in the EPN window was expected to be correlated with a greater presentation of symptoms.

3.3. Methods

3.3.1. Participants

This study was part of a larger research project on the transgenerational effects of stressful life events. Adolescents together with their mothers were recruited through newspaper advertisements, accommodation centers for asylum seekers and intercultural meeting places. Moreover, individuals who referred to the Centre of Excellence for Psychotraumatology, University of Konstanz by human rights organizations, social workers, medical doctors or lawyers for diagnostic clarification were offered participation in this study in order to obtain a sample that has been exposed to traumatic stressors to a varying degree. Data were collected between January 2015 and September 2016. Exclusion criteria were neurological or psychotic disorders and current or past psychoactive medication. After the introductory phase, three subjects were not included because they felt anxious or stressed when thinking about participation, and six could not be included in the analysis due to technical failure. Included in the final data analysis were 90 adolescents (N_{female} = 50 , N_{male} = 40) aged between 12 and 21 years (*M*=15.0, *SD*= 2.5, Median = 15.0). The most frequent regions of origin were Central Europe (*n* = 46), followed by the Middle East (*n*=25) and the Balkans (*n* = 11). *N*= 7 participants originated from Asia, n=1 from Eastern Europe. Participants had completed 8.0 years of education (*SD* = 2.64, *range* = 0-13).

3.3.2. Materials and procedure

After having obtained written informed consent from children and their mothers, the participants underwent an extensive standardized clinical interview administered by experienced psychologists and, if needed, with the help of trained translators. The clinical interviews were carried out prior to EEG measurement. Adolescents and their mothers were introduced to the laboratory equipment, and the task (passive viewing) was explained to them. EEG recording of all participants began with a 5- to 10-minute resting period (eyes closed and eyes opened measurements) followed by rapid serial visual presentation (RSVP) including 800 stimuli with 333-ms (3-Hz) presentation time per picture. The pictures were presented in 4 blocks of 200 pictures each. Within each block, 100 low-arousing and 100 high-arousing stimuli were presented in alternating order, whereas the type of picture varied randomly within each block and category (high- and low-arousal). The pictures were chosen based on normative arousal and pleasure ratings. The two categories differed significantly from each other in IAPS normative arousal ratings (low arousing: $M_{arousal}$ = 2.86, SD = 0.37; highly arousing $M_{arousal}$ = 5.67, SD = 0.65). Mean valence level for the high arousing category ($M_{valence}$ = 6.94, SD = 0.62) was significantly higher than for the low arousing pictures ($M_{valence}$ = 5.30, SD = 0.68). Physical picture parameters such as brightness, contrast, color spectra and physical complexity (JPEGfile size at 90% quality) did not differ across picture categories. In each block, pictures were shown in a pseudorandom order to keep the alternation sequence constant. Participants were advised to passively view the pictures, with their eyes focused on a small fixation cross shown at the center of the screen. Participants sat 1 m in front of the screen, which was connected to a video projection system. After recording, participants rated the affective pictures for emotional valence and arousal without time limits in a randomized picture order, using a computerized version of the Self-Assessment Manikin (SAM) self-report scale (Lang, Bradley, & Cuthbert,

2008). The affective dimensions of arousal and valence were evaluated on a 9-point scale, with higher numbers indicating an evaluation as more pleasant or arousing. All participants (mothers and adolescents) received reimbursement of their travel expenses, and, if necessary, a psychodiagnostic report and arrangement of treatment (this service is offered to all individuals referred investigated at the center, irrespective of study participation). Participants were compensated 60 euros for participation in addition to their travel expenses. All experimental procedures were in accordance with the Declaration of Helsinki and were approved by the Ethics Committee of the University of Konstanz (Germany).

3.3.3. Data acquisition

3.3.3.1. Stimulation equipment and EEG data recording

Visual stimulation was carried out with the software Presentation (Neurobehavioral Systems, Inc.). Stimuli were presented using a PC Dell precision 390 with Intel ® Core TM 2CPU 2.13 Hz processor with 2 RAM. A 27.5-inch LCD visual display was used (Hanns.G HG281DJ). Electrical brain activity was monitored by a high-density, 256-channel EGI EEG system with a HydroCel Geodesic Sensor Net (Electrical Geodesics, Inc., Eugene, OR) using NetStation 4.3 on a Mac OSX with 1.25 GHz PowerPC G4 processor and 1 GB DDR SD RQM. The EEG was recorded continuously with a sampling rate of 1000 Hz with 0.1 Hz high-pass and 400 Hz low-pass hardware filters and the vertex (Cz) electrode as reference. Electrode impedances were kept below 30 kohm (kΩ).

3.3.3.2. Psychopathological symptoms

Depression symptoms were assessed using the Patient Health Questionnaire (Kroenke, Spitzer, & Williams, 2001). The PHQ-9 rates each of the nine DSM-IV criteria on a four-point Likert

scale from 0 *("not at all"*) to 3 *("almost every day").* Scores were summed, with a possible maximum of 27 (*M* =4.33, range = 0-21, SD = 5.46). With its very good psychometric properties, the PHQ-9 can establish the diagnosis of major depressive disorder according to DSM-IV(Gilbody, Richards, Brealey, & Hewitt, 2007). Cronbach's alpha was .91 for the current study. The number of types of traumatic experiences was examined by the Event List of the Posttraumatic Diagnostic Scale (Foa, Cashman, Jaycox, & Perry, 1997). Items were coded dichotomously (yes, no) and summed up to produce a score between 0 and 12 (M = 2.14, range = 0-10, SD = 2.15). The German translation of the PTSD Symptom Scale Interview Version (PSS-I) (Ehlers, Steil, Winter, & Foa, 1996; Foa, Riggs, Dancu, & Rothbaum, 1993) was administered in order to assess PTSD symptom severity according to DSM-IV criteria (American Psychiatric Association, 2000). The scale consists of 17 items on a four-point Likert scale (Foa et al., 1993). Each item refers to one symptom of PTSD grouped into the three symptom clusters (intrusion, avoidance, hyperarousal). Items were summed up to produce a score between 0 and 51 (*M* = 5.18, *range* = 0-38, *SD* = 8.06). The PSS-I has proven to be a valid and reliable instrument (Foa & Tolin, 2000). For the present study, Cronbach's α was .93. Borderline symptoms were assessed using the German version of the Borderline Symptom List-23 (Bohus et al., 2009). Its 23 items are scored on a five-point Likert scale ranging from 0 to 4 (0 = *not at all,* 4 = *very strongly*) depending on their applicability for the last week. Excellent psychometric properties have been published (Bohus et al., 2009). A severity sum score ranging from 0 to 92 can be calculated (*M* = 9.36, *range* = 0-43, *SD* = 12.17), with scores $\geq$ 64 (76th percentile) indicating clinically relevant symptom levels (Bohus et al., 2009). Cronbach's α coefficient for this sample was .92. Behavioral problems over the six months preceding the interview were screened using the German, self-reported version of the Strengths and

Difficulties Questionnaire (SDQ) (Goodman, Meltzer, & Bailey, 1998; Klasen et al., 2000). On a three-stage scoring (0 = *not true*, 1 = *somewhat true*, 2 = *certainly true*), 20 items were summed up to gain a total difficulties score indicating the severity and the content of the psychosocial problems, with a maximum possible score of 40. The reliability and validity of the total difficulties score is reported to be satisfactory (Lohbeck, Schultheiß, Petermann, & Petermann, 2015). In our sample, the Cronbach's α for the total difficulties score was .79. The average total difficulties score was 11.65 (*range* = 2-30, *SD* = 6.63). Based on the heuristic outlined by the Research Domain Criteria (RDoC), an exploratory transdiagnostic analysis was performed using the intercorrelated sum scores of the instruments, which are described above. Principal components analysis was used due to the primary purpose of identifying factors underlying these instruments.

3.3.4. Data analysis

3.3.4.1.SAM Ratings

SAM Arousal and Valence ratings were analyzed using IBM SPSS Statistics Version 24 for Mac in separate repeated ANOVAs, with sex as the between-subject factor and stimulus category (low arousing, high arousing) as the within-subject factor.

3.3.5. EEG data analysis

3.3.5.1. Event-related potentials analysis

Epochs of 500 ms pre- to 500 ms post-stimulus onset were extracted from the continuous data using the MATLAB-based toolbox FieldTrip(Oostenveld et al., 2011). All trials per condition were retained in subsequent analyses. Data were band-pass filtered using a sine windowed finite

impulse response filter .5 - 40Hz (Widmann, Schröger, & Maess, 2015). Subsequently, the data were re-segmented into epochs of 0 to 300 ms after the stimulus onset. This ensured that potential filtering artifacts remained outside of the analysis time window of interest. No baseline correction was applied. Average event-related potentials for the low arousing and high arousing picture category were calculated for each electrode. Analysis focused on the interval from 0 to 300 ms after stimulus onset, including the window of the early posterior negativity (EPN) reported in Junghöfer et al. (2001), Peyk et al. (2008) and Schupp et al. (2006).

3.3.5.2. Source analysis

Source estimates were computed by applying a time-domain adaptive spatial filtering algorithm (linearly constrained minimum variance, LCMV; Van Veen, van Drongelen, Yuchtman, & Suzuki, 1997). This algorithm uses the covariance matrix from the EEG data and the lead field derived from the forward model to construct a spatial filter for a specific location (voxel). These spatial filters were estimated on the basis of all trials (pooling high and low arousing conditions). A single standard anatomical MRI and standard digitized electrode positions were co-registered to a common coordinate system (Montreal Neurological Institute, MNI) by applying an initial coarse registration between the fiducial locations (nasion and left and right pre-auricular points) and subsequently refined matching between the scalp surface extracted from the standard MRI and the standard digitized electrode positions. A three-compartment (skin, skull, brain) pseudo-realistic boundary-element forward solution was constructed on the basis of a standard MRI (MNI152 linear template) and applied to all participants.

3.3.5.3. Statistical analysis

Quantification of time domain condition differences was carried out using a cluster-based approach based on randomizations (Maris & Oostenveld, 2007). This approach identifies clusters of activity (in time and space, i.e., electrodes or voxels) on the basis of which the null hypothesis that the data in the high and in the low arousing conditions is exchangeable can be rejected, while addressing the multiple-comparison problem (Maris & Oostenveld, 2007). Clusters of electrodes were identified as differentially active when the difference between stimulus categories exceeded a threshold of significance at the 5% level. Via 1000 random permutations of the data, the cluster level statistic was defined as the sum of *t*-values within each cluster containing at least 5 adjacent electrodes. The null-hypothesis probability (no difference between stimulus categories) of observing a maximum (minimum) cluster-level statistic larger (smaller) than the observed cluster-level statistic is indexed by the obtained p-values. This procedure was applied to both sensor and source level evaluation. Mean EPN values were extracted per condition per subject from posterior electrode clusters judged representative after cluster-based evaluation. The relative difference potential (high arousing amplitude minus low arousing amplitude) was calculated as a measure of EPN for further analyses.

3.3.6. Principal component analysis (PCA)

A principal component analysis (PCA) with orthogonal rotation (varimax) was conducted on the 55 items of the questionnaires (BSL-23, SDQ and PHQ-9) and the 17 items of the interview (PSS-I). Initially, the factorability of the items was examined. Several well-recognized criteria for the factorability of a correlation were used. Variables with diagonal anti-image correlations of less than .6 were excluded from the analysis. Values less than .6 indicate that the sampling

is not adequate (Cerny & Kaiser, Henry, 1977; Dziuban & Shirkey, 1974). It was observed that all remaining items correlated at least .3 with at least one other item, suggesting reasonable factorability. The *Kaiser-Meyer-Olkin* measure (KMO) of sampling adequacy was .84 ("superb" according to Field, 2009) and all KMO values for individual items; the diagonals of the anti-image correlation matrix were also all over .6. *Bartlett's test of sphericity* was significant ($\chi 2$ (630) = 2412.95, $p < .001$) indicating that correlations between items were sufficiently large for PCA. Finally, the *communalities* were all above .4, further confirming that each item shared some common variance with other items. Given these overall indicators, factor analysis was deemed to be suitable, with 36 items.

3.3.6.1. Association between EPN and behavioral data

To test the relationship between the factors of the PCA and the EPN, a multiple sequential regression analysis was conducted. Sex was included as a possible confounding variable, as substantial gender differences were found in emotional processing (Stevens & Hamann, 2012). After controlling for the influences of sex and age, the PCA factors and the number of traumatic events experienced were added to the model. The regression model fulfilled all necessary quality criteria for linear regression analyses. The residuals of the regression analysis were normally distributed and independent, assumptions of homoscedasticity and linearity were met. Multicollinearity was of no concern. All analyses were two-tailed and based on $\alpha = .05$ level of significance. Our metric for a small effect size was $f^2 \geq .02$, for a medium effect, $f^2 \geq .15$; and for a large effect, $f^2 \geq .35$. Data were analyzed using IBM SPSS Statistics Version 24 for Mac.

3.4. Results

3.4.1. Behavioral data

Sample characteristics are shown in Table 3.1. Participants were exposed to a broad range of 0 to 10 different traumatic event types (M = 2.14, SD = 2.15). Sex differences were found for PHQ-9 and BSL-23 scores only. Females reported higher depression symptoms (M = 5.4, SD = 5.95) than males (M = 2.7, SD = 4.02; $t(88) = -2.42$, $p < .05$) and also higher borderline symptoms (M = 12.97, SD =13.58) than males (M = 4.84, SD = 1.33); $t(88) = -3.31$, $p < .01$). 18% (n=16) of adolescents fulfilled a PTSD diagnosis according to DSM-IV. With respect to borderline symptoms (BSL-23), none of the participants reached a diagnostically relevant symptom score. A total of 28 % (n=25) showed elevated behavioral difficulties according to SDQ.

Table 3.1. *Subjectively reported symptoms of the study group (N=90).*

Measure	M	SD	Mdn	Range
Depression (PHQ-9)	4.33	5.46	2.00	0 - 21
PTSD symptoms (PSS-I)	5.18	8.06	0.00	0 – 38
Traumatic event types (PSS-I)	2.14	2.15	1.00	0 - 10
Borderline symptoms (BSL-23)	9.36	12.17	4.00	0 - 43
Behavioral difficulties (SDQ)	11.65	6.63	10.83	2 – 30

Note. M = mean, SD = standard deviation, Mdn = median.

3.4.2. Validation of paradigm

3.4.2.1. Affective ratings

Figure 3.1 presents the boxplot of the arousal and valence ratings separately for male and female participants.

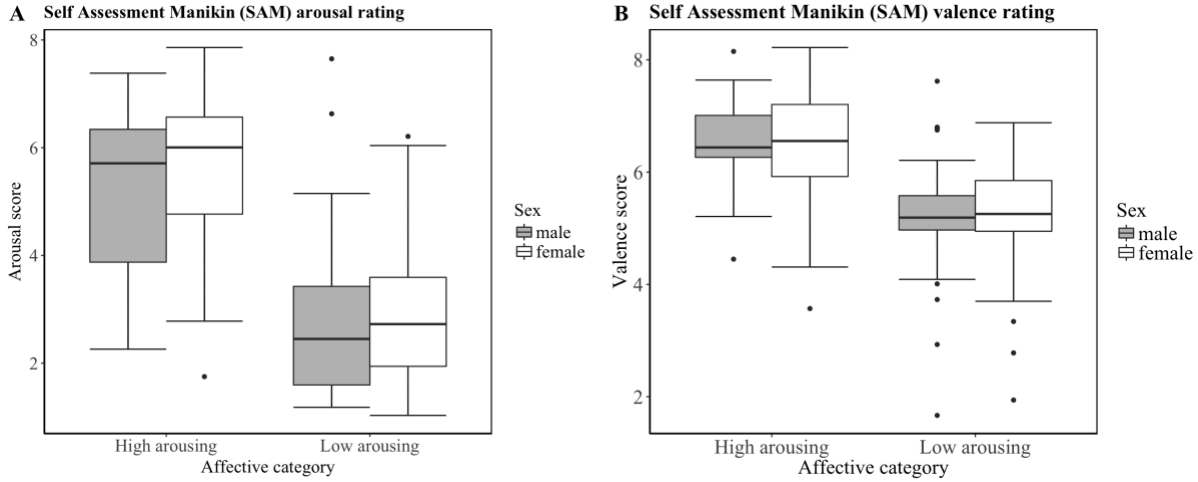

Figure 3.1. This figure presents the Self Assessment Manikin arousal (Figure 1 A) and valence ratings (Figure 1 B) of males and females as a function of picture categories (low arousing, high arousing pictures; possible values range from 1 to 9 for arousal and for valence). The box frames the lower and upper quartile. The line inside the box indicates the median. The upper and lower whiskers indicate variability outside the lower and upper quartiles. Circles illustrate outliers.

There was no main effect of and/or interaction with sex, indicating similar evaluations of valence and arousal scores of the pictures in female and male participants. As expected, the arousal ratings differed as a function of affective category ($F(1,88) = 181.53$, $p < .001$, partial $\eta^2 = .71$), with high arousing pictures rated as more arousing than low arousing pictures. Valence ratings for all participants also varied across picture categories ($F(1, 88) = 85.66$, $p <$

.001, partial $\eta^2 = .53$), with high arousing pictures rated as more pleasant than low arousing pictures. Examining correlations and scatterplots, we found that SAM ratings were not related to age. These results indicate that arousal ratings of males and females varied, as reported in Lang, Bradley & Cuthbert (2008), depending on the affective category of the stimuli.

3.4.2.2. Early posterior negativity

The early selective processing of high arousing pleasant stimuli was associated with stronger negativity (i.e. less positivity, Figure 3.2.A) over bilateral parieto-occipital electrodes than low arousing stimuli (Figure 3.2.B). A pronounced ERP difference for the processing of low arousing and high arousing pleasant pictures developed around 150 ms, which was maximally pronounced around 200-300 ms (Figure 3.2. A and B, $p < 0.001$, non-parametric cluster permutation test). Source analysis revealed cortical generators in the right parieto-occipital cortex (Figure 3.2. C).

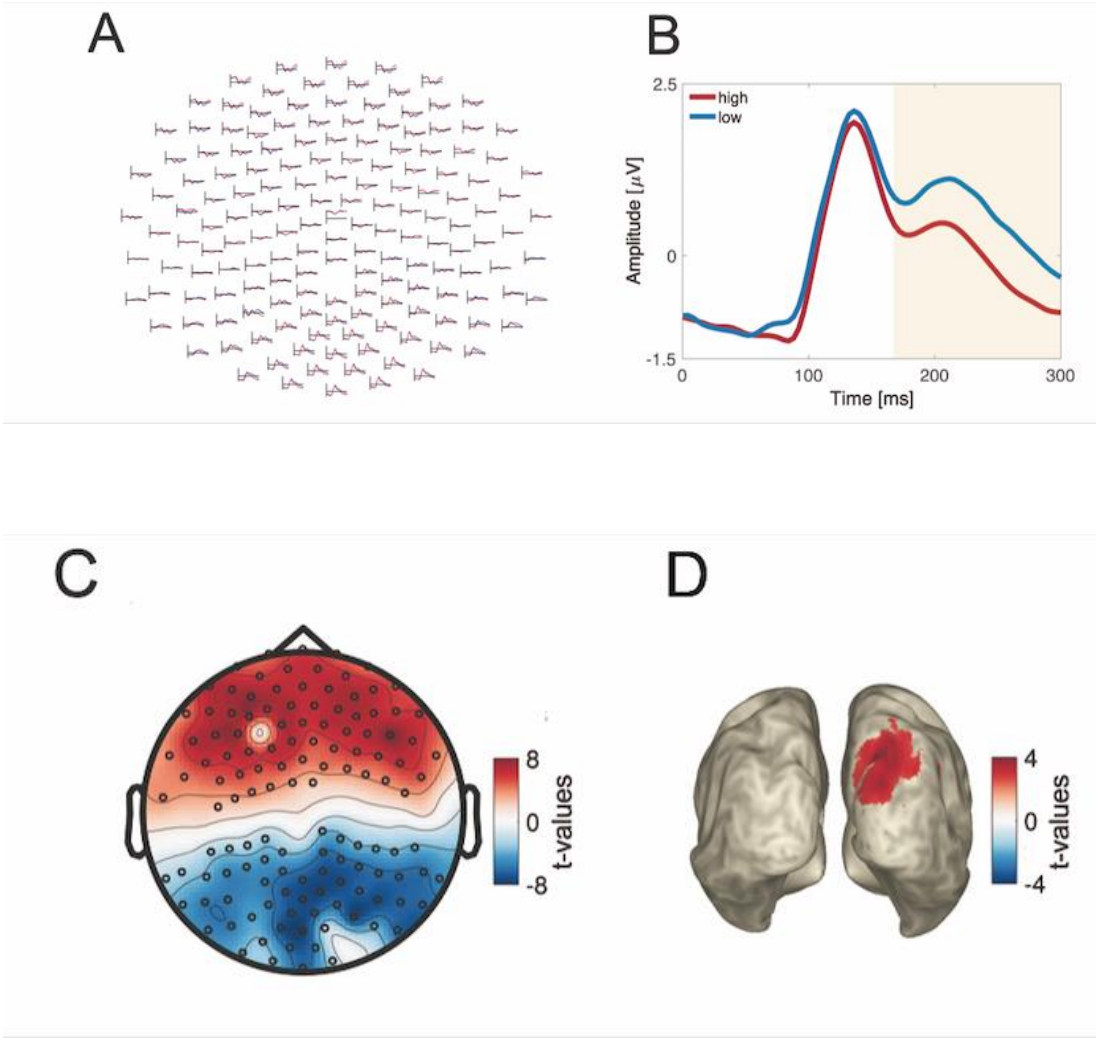

Figure 3.2. A. Multi channel representation of the event-related potential split by condition: high arousing (red) and low arousing (blue). **B.** Event-related potentials illustrating brain responses during high (red) and low (blue) arousing conditions averaged over posterior cluster of electrodes depicted in C. Shading background highlights the EPN. **C.** Topography of the high minus low contrast expressed in units of t-values. Circles highlight electrodes belonging to clusters confirming significant condition differences ($p < .001$). **D.** Source-level high minus low contrast corresponding to the topography in C. The inflated brain surface is shown from the back of the head, highlighting the areas of occipital and parietal cortex. Note that C and D present statistical maps for the difference and not one of the electric potential or its differences.

3.4.3. Dimensions of psychopathology

The PCA produced eight factors with eigenvalues greater than 1. The inflexion point of the scree plot (Cattell, 1966) occurred at the fifth eigenvalue. The five-factor solution, which explained 61% of the variance, was preferred because of the "leveling off" of eigenvalues on the scree plot after five factors as well as the insufficient number of primary loadings and difficulty of interpreting the subsequent factors. Factors I, II, III, IV and V accounted for 14%, 14%, 13%, 7% and 6% of the variance in the behavioral data, respectively. The last dimension of psychopathology, Factor V implies motoric disquiet. Table 3.2 lists factor loadings after rotation. Internal consistency for each of the factors was examined using Cronbach's alpha. Representing dimensions of psychopathology, the five factors proved to be legitimate clinical variables for further analyses.

Table 3.2. *Summary of items and factor loadings for varimax orthogonal five-factor solution*

Questionnaire	Item	Factor loading
	Factor I (α = .89)	
PSS-I	Unwanted distressing memories about the trauma	.83
PSS-I	Being emotionally upset when reminded of the trauma	.77
PSS-I	Having physical reactions when reminded of the trauma	.74
PSS-I	Efforts to avoid thoughts or feelings related to the trauma	.66
PSS-I	Efforts to avoid activities, situations, or places that remind you of the trauma	.64
	Factor II (α = .84)	
BSL	Feeling lonely	.73
PHQ	Feeling bad about yourself or that you are a failure or have let yourself or your family down	.68
PHQ	Feeling tired or having little energy	.61
PHQ	Trouble falling or staying asleep, or sleeping too much	.61

	Factor III (α = .88)	
BSL	Not trusting other people	.81
PHQ	Trouble concentrating on things, such as reading the newspaper or watching television	.76
PSS-I	Difficulties falling or staying asleep	.66
BSL	Hard concentrating	.63
PSS-I	Having difficulties concentrating	.61
	Factor IV (α = .76)	
SDQ	Being often accused of lying or cheating	.81
PSS-I	Acting more irritable or aggressive	.66
PSS-I	Feeling as if your future plans or hopes will not come true (for example, you will not have a career, marriage, children, or a long life)	.61
	Factor V (α = .82)	
SDQ	Constantly fidgeting or squirming	.81
SDQ	Being restless, unable to stay still for long	.79

Note. N=90; items are grouped by proposed factor assignment and listed by factor loading size in descending order.

3.4.4. Dimensions of psychopathology and EPN

As displayed in Table 3.2, factor II yielded modest, and factor III moderate correlations with EPN suppression. In addition, the number of experienced traumatic events was found to be negatively associated with the early posterior negativity in the visual cortex.

Table 3.3. *Correlations between variables*

	Measure	1	2	3	4
1.	ΔEPN	- -			
2.	age	**.22** *	- -		
3.	sex	**.49** **	.24 *	- -	
4.	No. traumatic events	**.25** *	.13	-.02	- -
5.	Factor I	.19	.07	.12	**.33** **
6.	Factor II	**.22** *	.09	.09	**.24** **
7.	Factor III	**.30** **	.11	.12	**.27** **
8.	Factor IV	-.03	-.04	-.16	**.42** **
9.	Factor V	.01	-.25 *	-.21	.08

Note. Pearson correlations were calculated. ΔEPN = relative difference potential (high arousing amplitude minus low arousing amplitude). Significant correlations are printed in bold.
Asterisks indicate level of significance: * $p < .05$, ** $p < .01$.

The first regression model with sex and age as predictors explained 24% of the variability of the EPN (R_{adj2} =.24, $F(2,87) = 14.67$, $p < .001$, $f_2 = .32$). The inclusion of factors II and III along with the *experienced events* as additional predictors improved the model significantly ($F(3,84) = 4.87$, $p < .01$, $f_2 = .47$). This updated model explained 33% of the variance. Because of the inherent associations between experiencing traumatic stress and psychopathology, the number of experienced traumatic events as a potential modulator of affective processing was included in the analysis. Results are presented in in Table 3.4. Factor III was associated with EPN suppression, whereas the number of experienced traumatic events was not a significant predictor. The total regression model explained 32% of the variability of the EPN. Adding interaction terms or controlling for ethnicity did not improve the model in terms of higher

variance explained, and significance was not reached. Thus, *problems concentrating, sleeping difficulties and mistrust* (factor III) showed to be related to EPN suppression. Figure 3 shows the relation between factor III and EPN suppression for males and females.

Table 3.4. *Results of regression analysis predicting EPN*

	Early Posterior Negativity				
Predictor Variables	*B*	*SE of B*	β	*T*	
Step 1					
Sex	7.18	1.47	.46	4.87	***
Age	0.37	0.30	.11	1.23	
Step 2					
Sex	6.93	1.41	.45	4.93	***
Age	0.21	0.29	.07	0.74	
Factor II	0.95	0.71	.12	1.34	
Factor III	1.50	0.71	.19	2.11	*
No. of traumatic events	0.63	0.34	.17	1.82	

Note. adjR2 = .32, f_2 = .47, n = 90, *B*: unstandardized regression weight, *SE*: standard error, β = standardized regression weight, *T*: t-test statistics. The constant is not shown for a better readability. *p ≤ .05, **p ≤ .01, ***p≤ .001.

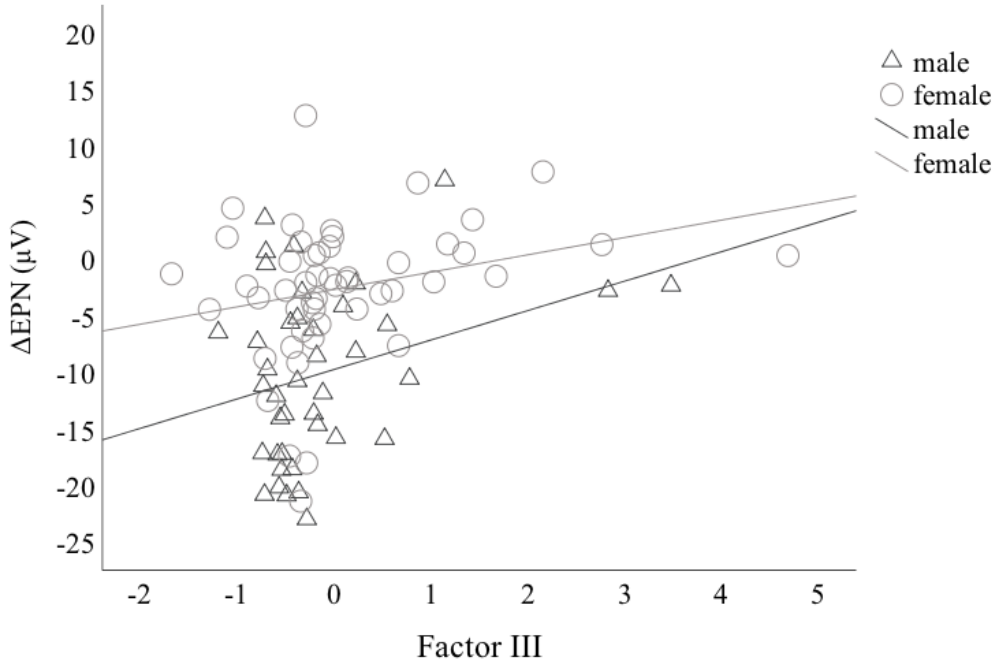

Figure 3.3. Scatter plot of factor III and ΔEPN with separate fitted linear regression lines for males and females.

3.5. Discussion

The currently used classification systems (DSM and ICD) have largely been based on subjective reports, and the diagnostic categories (but not necessarily the symptoms) lack validation from translational research of mental disorders, the research domain criteria (RDoC) project was launched, incorporating psychological and related neurobiological systems (Cuthbert & Insel, 2013). Therefore, the aim of this study was to apply a transdiagnostic approach following the logic of RDoC and examine the association between dimensions of psychopathology and affective picture processing as measured by the ERP method. As expected, our findings confirm an arousal-driven modulation of affective picture processing in adolescents during the EPN interval, as discovered by Junghöfer et al. (2001) for adults and Wessing, Fürniss, Zwitserlood, Dobel, & Junghöfer, (2011) for 8- to 10-year-old children. Arousing pleasant stimuli evoked a

more negative amplitude deflection over posterior brain regions 150 to 300 ms after stimulus onset than did low arousing stimuli even using RSVP, meaning that the EPN can be recorded for briefly presented stimuli that are shown at a rapid rate. Our results support the notion of EPN being a well-founded neural correlate of affective stimulus discrimination (Junghöfer et al., 2006, 2001; Olofsson et al., 2008; Peyk et al., 2008; Schupp et al., 2004). Likewise, these findings are in line with the concept of natural selective attention (Bradley, 2009), as the perceptual processing of emotional stimuli seems facilitated. However, prior work has shown that ERPs during affective processing can be deviant in individuals with psychiatric disorders (Adenauer, Pinosch, et al., 2010; Burgmer et al., 2013; Elbert et al., 2011; Felmingham, Bryant, & Gordon, 2003; Holmes, Nielsen, & Green, 2008; Kemp et al., 2009; Matz et al., 2010; Rockstroh, Junghöfer, Elbert, Buodo, & Miller, 2006; Weber et al., 2009). In the current study, psychopathological symptom clusters were identified using principal component analysis. Interestingly, the factor comprising of *problems concentrating, sleeping difficulties and mistrust* was associated with a reduced affective distinction between high arousing and low arousing pictures. Within a similar time interval, further studies have also found reduced posterior discrimination in response to affective faces (Chu, Bryant, & Gatt, 2016; Felmingham et al., 2003), affective pictures (Matz et al., 2010; Weber et al., 2009) or words (Kounios et al., 1997) in trauma-related psychopathology. Much clinical research has focused on emotional processing of aversive material. Our result provides additional support for EPN suppression also using pleasant emotional material. This matches well with Adenauer et al. (2010) and Burgmer et al. (2013), confirming a reduced differential responding not only to unpleasant, but also to pleasant visual stimuli in PTSD.

Sex was found to modulate emotional processing, as male participants displayed a stronger affective differentiability in our study. A meta analysis of neuroimaging studies (Stevens & Hamann, 2012) confirmed sex as a potential factor modulating emotional processing. In accordance with our study, Stevens & Hartman (2012) found males to be more responsive to pleasant emotional material than females. In particular, stress symptoms such as problems concentrating, sleeping difficulties and mistrust (factor III) might influence affective processing modes, as stress has been found to influence stress-sensitive systems such as the hypothalamus-pituitary-adrenal (HPA) axis (Champagne et al., 2008; Lo Iacono & Carola, 2018; Lupien et al., 2009; McEwen, 2004; S. M. Smith & Vale, 2006; Ulrich-Lai & Herman, 2009). Hence, emotion-modulated psychophysiological responses (Adenauer, Catani, Keil, Aichinger, & Neuner, 2010; Niermann et al., 2017) and affective processing seem to be altered. Reduced brain response indicated by EPN suppression might also reflect neuronal plasticity, an adaption of the neuronal system to stress-induced conditions (Berlucchi & Buchtel, 2009; Duman, 2004; Power & Schlaggar, 2017). Correspondingly, research demonstrated grey matter abnormalities in primary and secondary visual cortices (Tomoda, Navalta, Polcari, Sadato, & Teicher, 2009) as well as in regions involved in affect control (Lim, Radua, & Rubia, 2014) in individuals with a history of early life stress. Mueller-Pfeiffer et al. (2013) also reported a diminished neural activity in the visual system in PTSD patients. Likewise, studies have reported white matter abnormalities, suggesting alterations in neural pathways (Akiki, Averill, & Abdallah, 2017; O'Doherty et al., 2018). An alternative explanation for the EPN inhibition might be an adaptive adjustment of emotion processing to arousing material after experiencing traumatic stress with a subsequent heightened arousal state. Our findings indicate that the ability to modulate arousal-

related cortical structures to emotionally visual content seems impaired when problems concentrating, sleeping difficulties and mistrust are present.

Some limitations of the current study need to be considered: For ethical concerns, no negative valence pictures were presented to adolescents in our lab. The present EPN effect might have been driven by overlapping valence and arousal characteristics. Furthermore, data are cross-sectional and hence correlational in nature, precluding determination of causality. The sample comprised adolescents from diverse ethnic backgrounds and represented a broad age range. This may have increased the variability, and thus effects may have gone undetected. However, the observed effects seem to hold across this broad range. The ethnic background varied greatly so that it cannot have systematically confounded the outcome. However, it may well be possible that this increased "noise" in the dependent variables. Moreover, symptom levels of the majority of participants were low, which may have contributed to low correlations. In our data, at least the first two factors of the PCA seem to reflect the instruments used. It is not possible to assess the full spectrum of potential psychopathology in such a study. Regarding the RDoC framework, one might argue that a discrete domain was not assessed. However, RDoC suggests expanding analysis beyond categorical diagnoses by classifying dimensions of behavior and including other units of analyses such as circuits or physiology. Using PCA to ground self-reported symptoms in biological phenomena can be seen as exploratory transdiagnostic analysis based on the RDoC heuristic.

In sum, we suggest that *problems concentrating, sleeping difficulties and mistrust* seem to be common transdiagnostic elements related to a reduced early affective discrimination represented by the EPN. These findings furthermore extend those of prior research on emotional processing in trauma survivors (Adenauer, Pinosch, et al., 2010; Burgmer et al., 2013; Elbert et

al., 2011; Felmingham et al., 2003), confirming that EPN suppression can also be found in adolescents. We conclude that stress symptoms might induce the functional reorganization of the emotional processing streams and may be reflected in dampened cortical affective differentiability to emotional stimuli.

3.6. Acknowledgements

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4. Post-traumatic stress accelerates epigenetic aging

4.1. Abstract

Chronic psychological stress may accelerate cellular aging and lead to a variety of age-related disorder. Traumatic stressors increase the likelihood to develop PTSD. The present study examined associations between the number of lifetime traumatic events experienced, intensity of PTSD symptoms and accelerated aging. Based on the DNA methylation status of several gene loci the epigenetic age can be estimated using an algorithm developed by Horvath (2013). The deviations between the determined epigenetic age and the chronological age reflect aspects of accelerated aging. The impact of traumatic stress on epigenetic aging was investigated in 104 females from diverse ethical backgrounds with varying numbers of traumatic experiences. As expected, the epigenetic age predicted chronological age ($r = .88$, $p < .001$). Strong associations between trauma exposure, adverse childhood experiences and PTSD symptom severity were also found. Multiple regression analysis identified PTSD symptom intensity as a significant predictor for accelerated epigenetic aging, the epigenetic age estimates by Horvath residualized for chronological age ($\beta = .24$, $t\ (97) = 2.24$, $p < .01$). The results suggest that PTSD severity is linked to accelerate aging and might constitute a risk factor for an earlier onset of age-related disorders.

4.2. Introduction

Aging processes can notably be accelerated by chronic psychological stress which constitutes an essential determinant for the development and the progression of both, stress- and age-related disorders such as cardiovascular diseases and cancer. The most intense form of psychological stress derives from the experience of threats to life and biological fitness, i.e. traumatic events, since they activate biological programs that require substantial resources that when chronic, inevitably lead to strain and injury including neuro-hormonal modifications. The latter are assumed to play a crucial role in cellular aging and in the development of age-related diseases. With an increasing number of traumatic experiences the stressors become perceived as a permanent threat, and the arising mental health problems have been summarised as post-traumatic stress disorder (Elbert & Schauer, 2002, 2014a). PTSD was found to be associated with more rapid cellular aging (Moreno-Villanueva et al., 2013) and an elevated risk for a variety of age-related diseases (e.g. Burri, Maercker, Krammer, & Simmen-Janevska, 2013; Edmondson & von Känel, 2017; Rosenbaum et al., 2015; Ryder, Azcarate, & Cohen, 2018). In order to understand the factors influencing aging processes, their shared underlying molecular mechanisms are of interest. Epigenetic research has emerged as a promising link for the understanding of pathophysiological pathways underlying physical and mental health and disease, particularly in age- and stress-related conditions (Murphy & Mill, 2014). Since epigenetic modifications are associated with both, aging (Benayoun, Pollina, & Brunet, 2015) and morbidities (Argentieri, Nagarajan, Seddighzadeh, Baccarelli, & Shields, 2017), they have the ability to function as a reliable biomarker for both chronological and biological age. Powerful algorithms emerged for the prediction of biological age based on epigenetic modifications, allowing the investigation of deviations between biological, epigenetic and

chronological age. The “epigenetic clock”, a robust epigenetic age calculation algorithm based on DNA methylation status (DNAm Age) of 353 cytosine-phosphate-guanosine sites (CpGs) across the genome has been developed by Horvath (2013). This tool provides a highly accurate prediction of epigenetic age. The positive deviations between chronological and epigenetic age (DNAm Age), indexed as age acceleration has been found to be reliable for the prediction of one’s state of health (Chen et al., 2016). Studies addressing both chronic stress and epigenetic aging revealed that traumatic stress has substantial, accelerating influence on epigenetic age, indexed by DNAm Age metrics. This supports the assumption, that stress may impact cellular aging via methylation pathways (Gassen et al., 2017; Wolf et al., 2018) and promote an early onset of age-related disease.

The present study aimed to provide insight into the impact of traumatic stress on the state of health at a molecular genetic level by measuring whether traumatic stress and its associated psychopathologies are linked with accelerations in biological aging via epigenetic modifications. The majority of studies published at present evaluated blood samples for the extraction of DNAm Age. However, studies using saliva samples for DNA methylation analysis of psychiatric traits also need to be considered since saliva specimen are known to show a greater relatedness to brain tissues (Smith et al., 2015). Using saliva, stress-related alterations in relevant brain structures were found to be linked with accelerated DNAm Age (Davis et al., 2017). In line with these findings, Jovanovic et al. (2017) extracted DNA from saliva and showed that the experience of traumatic events during childhood were associated with accelerated aging in children, reinforcing the relevance of childhood adversities in the context of trauma and stress.

In the current study we examined epigenetic age acceleration using saliva samples collected from adult women from diverse ethnic backgrounds who had experienced traumata to varying degrees of frequency and severity. Focussing on traumatic stress experienced during childhood and lifetime psychopathologies, we expected that (1) the cumulative exposure to traumatic stressors and Adverse Childhood Experiences (ACEs) in particular are associated with an accelerated epigenetic aging, and (2) a more severe PTSD symptomatology is associated with accelerated epigenetic aging.

4.3. Methods

4.3.1. Participants and Procedure

The sample consisted of 104 women with varying degrees of traumatic stress and threat exposure. Seven participants were excluded from the analysis due to missing data (n = 4 did not complete the questionnaires, n = 2 did not provide saliva samples and for n = 1 the epigenetic analyses did not pass quality control). The sample comprised females from diverse ethnic backgrounds and represented a broad age range M = 44 years (SD = 7.3; range 27 - 61). This selection allowed to include survivors of considerable traumatic stress and due to the varying living conditions made a systematic bias of factors like nutrition or life-style less likely. The most frequent regions of origin were Central Europe (n = 42), including Germany and Poland, followed by the Middle East (n = 30) including Iran, Iraq and Syria. N = 14 originated from Balkan countries (Albania, Bosnia, Czech Republic and Kosovo). From Asia, Afghanistan, Brazil, Russia and India originated n = 1 participants and one was from Brazil. Participants had completed M = 8.0 years of education (SD = 2.6, *range* = 0-13).The assessment took place at the "Kompetenzzentrum für Psychotraumatologie" (KZP) of the University of Konstanz.

Participants provided written informed consent. The study was approved by the ethical committee of the University of Konstanz.

4.3.2. Psychometric Assessment

Experienced members of the university's centre for psychotraumatology carried out the diagnostic interviews in order to assess the number of lifetime traumata and the extent of psychological impairment. If needed, translators in diagnostic procedures were provided in the participants' mother-tongue. After having obtained written informed consent from children and their mothers, the participants underwent an extensive standardized clinical interview. PTSD-Symptoms were assessed using the *Posttraumatic Stress Diagnostic Scale* (PDS, Foa, 1995). The PDS is a self-report screening instrument assessing a diagnosis and the severity of PTSD based on DSM-IV Criteria. The PDS was found to be a valid and reliable instrument (Foa & Tolin, 2000) and can be adapted to DSM-V diagnostic Criteria for PTSD (Blevins, Weathers, Davis, Witte, & Domino, 2015). The first section of the PDS consists of a trauma checklist for a systematic assessment of number and form of traumatic events experienced or witnessed during lifetime. Twelve "Yes"/"No" items list types of events, including natural disasters, major accidents, experiences of interpersonal, familiar or sexual violence, war trauma, torture and life-threatening illnesses. The trauma checklist does not provide the total number of traumatic events experienced, but reflects how many different types of events a person has been exposed to. The trauma checklist is followed by a symptom assessment surveying distress, intrusions, post-traumatic avoidance and hyperarousal. For reliability analysis, Cronbach's alpha was calculated to assess the internal consistency, which was excellent ($\alpha = .94$).

In addition to lifetime traumata, we also assessed Adverse Childhood Experiences (ACE) using the German version of the *Maltreatment and Abuse Chronology of Exposure Scale* (Isele et al., 2014; Teicher & Parigger, 2011). The German translation consists of 20 items organized in ten subscales capturing different types of interpersonal maltreatment during childhood on a dichotomous scale ("Yes"/"No"): Physical abuse by caregivers/parents, physical abuse by siblings, emotional abuse by caregivers/parents, emotional abuse by siblings, sexual abuse by caregivers/parents or strangers, physical neglect, emotional neglect, witnessed violence towards caregivers/parents, witnessed violence towards siblings, and lately physical and emotional peer violence. The MACE was found to have high internal consistency and validity (Isele et al., 2014). Cronbach's alpha calculated for this sample was $\alpha = .86$.

4.3.3.DNA Methylation Measurement

Saliva samples were collected using the Oragene-Discover (OGR- 600) Collection Kit (DNA Genotek, Ontario, Canada) and DNA was extracted according to the manufacturer´s standard protocol. DNA quality and concentration were assessed using spectrophotometry (Nanodrop 2000; ThermoScientific, USA) and fluorometry (Qubit dsDNA BR Assay Kit, Invitrogen). DNA was then bisulfide-converted using EZ DNA Methylation-Gold ™ kit (Zymo Research Europe GmbH, Germany) following standard protocols. Methylation analysis was carried out using the HumanMethylation EPIC BeadChip Infinium 850k microarray (Illumina, Inc., San Diego, CA, USA), at Genome Scan (Leiden, NL). This microarray method measures the proportion of methylated Cytosine-Guanine Dinucleotides (CpGs) at over 850´000 sites across the epigenome. It provides accurate and valid results (Moran, Arribas, & Esteller, 2016). The $N = 98$ specimen were processed as a single batch, with a randomized plate assignment.

BeadChips were scanned for quality assessment, using GenomeStudio v1.8 (Illumina Inc, San Diego). The pre-processing and postprocessing pipelines were performed as described previously (Vukojevic et al., 2014). The 353 CpG-Sites necessary for estimating the epigenetic age were exported from the data matrix containing beta values indicating the proportion of cytosines methylated at a given CpG (0 = non methylated) to (1 = all methylated). The epigenomic data analyses were performed at the Transfaculty Research Platform Molecular and Cognitive Neurosciences (*MCN*) (http://mcn.unibas.ch/) and at the Scientific Computing Core Facility of the University of Basel.

4.3.4. Epigenetic Age Evaluation

Epigenetic age was calculated using an epigenetic age algorithm developed by Horvath (2013). This method is applicable across several cell types, tissues and organs including whole blood, brain, breast, kidney, liver, lung and saliva. Although saliva specimen consist of heterogeneous cell types, DNAm Age estimation has been shown to be robust in this tissue source (Davis et al., 2017). The DNAm Age has been found to estimate chronological age most accurately with r = .96 in subjects aged between 0 to 100 (Gibbs, 2014). Further, it can be utilized to predict mortality, independent of health, life-style or genetic factors (Lowe, Horvath, & Raj, 2016; Marioni et al., 2015).

Metrics of the Epigenetic Clock algorithm provide (1) the predicted age, referred to as DNAm Age or epigenetic age, (2) the difference between epigenetic age and chronological age (ΔDNAm Age) and (3) the Age Acceleration Residuals (AAR), the studentized residuals calculated by regressing chronological on DNAm Age, with positive residual value indicating faster aging and negative value suggesting slower aging. Due to its independence of

chronological age, it is recommended to use the AAR variable as a biomarker of ageing (Horvath, 2013; Horvath, Pirazzini, et al., 2015). The age acceleration variable served as the dependent variable for further statistical analyses.

4.3.5.Data analysis

Statistical analyses were carried out using IBM SPSS Statistics Version 25. Number of trauma exposure was defined as the sum-score of the PDS trauma event checklist, including all traumatic event types reported, self-experienced or witnessed. PTSD symptom severity was assessed as the sum-score of all PTSD symptoms reported at the PDS. The number of ACEs was calculated by summing up the checked items of the ten subscales of the MACE.

4.3.5.1.Preliminary Analyses

Correlational analyses were conducted to assess the simple associations between, PTSD symptom severity, trauma exposure during lifetime and ACE. To test the accuracy of Horvath's epigenetic age estimation, the correlation coefficient between chronological age and DNAm Age was calculated. Correlational analyses were carried out between AAR and self-reported country of origin. A correlation matrix with Pearson´s Correlation Coefficients (*r*) and a scatter plot were generated in order to illustrate the relationships assessed as displayed in results section.

4.3.5.2.Inferential statistics

The hypotheses were tested using a multiple regression model. This model was applied to examine the influence of traumatic stress and psychopathology on epigenetic aging effects. The

following variables served as predictors: (1) number of ACEs, (2) number of trauma exposure, (3) PTSD symptom severity. The level of significance was set at $\alpha < .05$. Confidence intervals were calculated for each predictor-criterion association.

The regression model fulfilled all necessary quality criteria for linear regression analyses. The residuals did not significantly deviate from normality (Shapiro-Wilk-Test, $p > .05$), linearity, or homoscedasticity. Multicollinearity was of no concern (Variance Inflation Factor = 1.00 to 1.34). All analyses were two-tailed and based on an $\alpha = .05$ level of significance.

4.4. Results

4.4.1. Traumatic stress variables

The evaluation of the instrument KERF revealed $M = 13.2$ ($SD = 12.2$) of reported ACEs. Participants reported to have been exposed to $M = 3.6$ ($SD = 2.2$) different traumatic stressors and the PDS evaluation revealed a PTSD symptom severity of $M = 6.0$ ($SD = 8.8$).

Correlational analyses within the traumatic stress variables confirmed internal consistency of the psychometric data. The PTSD symptom severity correlated with trauma exposure, $r = .35$ ($p < .001$) and Adverse Childhood Experiences, $r = .29$ ($p < .01$).

4.4.2 Epigenetic Age analyses

The distribution of DNAm Age studentized residuals, AAR, was $M = .001$ ($SD = 1$, *Range:* -1.9 – 2.5). As reported in Horvath (2013), we found a highly significant correlation between DNAm Age and chronological age ($r = .88$, $p < .001$), displayed in Figure 4.1 . In contrast, AAR, were not associated with chronological age ($r = .001$, $p > .96$) and ranged from 1.9 to 2.5 years. A one-way between groups analysis of variance (ANOVA) has been carried out with

geographical origin as categorical variable and AAR as independent variable in order to check for possible confounding effects. T-tests for independent samples between the variables binary coded medication intake, alcohol consumption and smoking. The ANOVA revealed no statistically significant effect between the geographical origins of the participants and AAR. T-Tests between substance use and AAR showed that neither medication intake had a significant impact on epigenetic aging, $t(94) = 1.49$, $p = .14$, nor did smoking, $t(94) = .62$, $p = .53$ or alcohol consumption, $t(94) = 1.09$, $p = .28$. Based on these results the variables have not been included in further inferential statistical analyses.

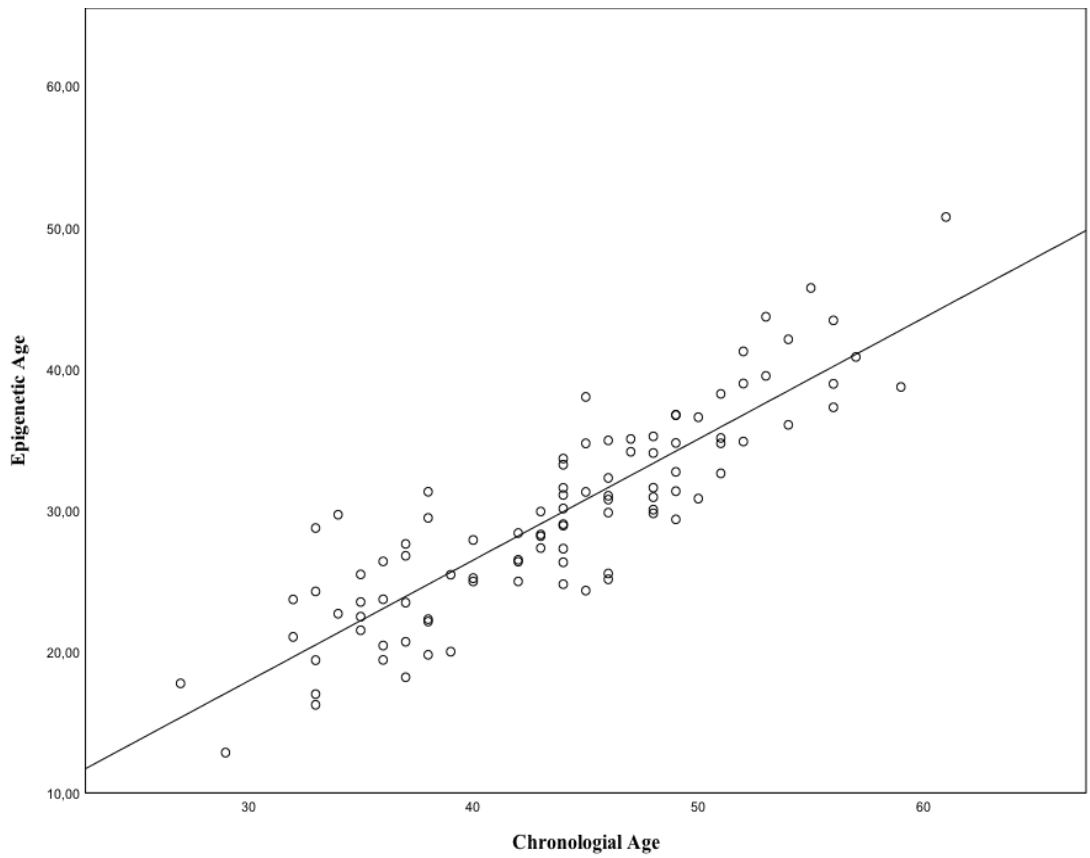

Figure 4.1. Prediction accuracy of epigenetic age calculation displayed as relationship between Chronological Age in years and Epigenetic Age, $r = .88$

4.4.3. Age Acceleration and Traumatic Stress

In a multiple linear regression analysis, Age Acceleration Residuals (AAR) were regressed on ACE, trauma exposure during lifetime and PTSD Symptom Severity. The results of the model indicated that the model was a significant predictor of AAR, $F(3, 92) = 2.66$, $p = .048$.

The regression model explained 8% of the variability of AAR. Coefficients of the model are presented in in Table 4.1.

Table 4.1 *Results of regression analysis predicting AAR*

Variable	*B*	*SE*	β	*T*
ACE	-.01	.01	-.14	-1.4
Trauma Exposure	.05	.05	.10	.91
PTSD Symptoms	.02	.01	.21	**2.0***

Note. Total regression model explained 8% of the variability of AAR: $R^2_{adj} = .08$, n = 96; *B*: unstandardized regression weight, *SE*: standard error, β = standardized regression weight, *T*: t-test statistics. The constant is not shown for a better readability. Asterisks indicate level of significance *$p \leq .05$. Significant results are printed in bold.

4.5. Discussion

The present study investigated the relationship between traumatic stress as well as its associated psychopathology and accelerations in biological aging processes via epigenetic modifications. Associations between trauma exposure, ACE and PTSD symptom severity indicated internal consistency and are in line with the repeatedly demonstrated building block effect, a dose-dependent relationship between experiencing traumatic events and PTSD

Severity (Schauer et al., 2003; Wilker et al., 2015). As expected, our findings confirm the accuracy of DNAm Age as a reliable biomarker for the estimation of chronological age (Horvath, 2013). Further, this research showed that PTSD symptom severity was associated with accelerated epigenetic aging estimated from saliva using the Horvath method. It complements prior research findings on traumatic stress applying the Hannum method (Hannum et al., 2013) for the determination of age acceleration estimated from blood (Wolf et al., 2016, 2017). It can be concluded from the findings, that not stress exposure itself but stress-associated psychopathology is primarily linked to accelerated DNA methylation age. PTSD symptoms translate to feeling of a deep and subtle anguish, the definite sensation of an impending threat, even when in a peaceful relaxed environment, apparently without tension or affliction, whereby many clues will activate an alarm or a shutdown response (Schauer, Neuner, & Elbert, 2011). Therefore it can be assumed that it is the continuous responding to perceived threats, real or imagined, that alter epigenetic indicators of aging. From biomedical and psychophysiological research it is known that trauma-related symptomatology is associated with profound neurophysiological and -structural alterations (Elbert et al., 2006; Kolassa & Elbert, 2007). These alterations are manifested in modifications of the physiological stress response, glucocorticoid levels, pathways and metabolism (Cohen et al., 2012; Ehlert, Wagner, Heinrichs, & Heim, 1999; Karl et al., 2006) which have been found to be associated with distinct methylation alterations on relevant gene sites (e.g. Vukojevic et al., 2014). The latter in particular is underpinning the relevance of the epigenetic modifications since they are representing the ability of an organism to adapt and evolve in response to environmental stimuli through alterations on a molecular genetic base (Kanherkar, Bhatia-Dey, & Csoka, 2014; Zannas & West, 2014). It is also assumed that these adaptations are largely driven by increased

oxidative stress parameters, cytokines, growth factors, the release of neurotrophic factors and alterations in hormonal levels, even though the exact underlying molecular physical mechanisms remain to be clarified (Cohen et al., 2012; Kanherkar et al., 2014; Kremling, 2012; Miller & Sadeh, 2014; Morath et al., 2014). Concurrently, the factors relevant for epigenetic adaptions themselves have been found to play a key role in many physical impairments (Schubert & Singer, 2015), immune- and inflammatory diseases (Bauer & De la Fuente, 2016), cancer proliferation (Meier & Noll-Hussong, 2014) and most relevant for this study, with parameters of aging (Bersani et al., 2016; Fulop et al., 2014; Gassen et al., 2017). Consequently, it is plausible that the psychopathology of PTSD is associated with epigenetic modifications that determine aging as indicated by this study.

Contrary to the first hypothesis of this study, trauma exposure itself and Adverse Childhood Experiences were not significantly associated with age acceleration. In contrast, previous studies found an association between epigenetic age acceleration and general life stressors, violence, and trauma exposure (Boks et al., 2015; Jovanovic et al., 2017; Zannas et al., 2015). Yet, in these reports the estimated DNAm age on chronological age was not residualized for the prediction of age acceleration and did not include PTSD symptomatology in the analyses. However, the relationship to stress seems a consistent finding, whereby in survivors of traumatic stress it seems the post-traumatic, i.e. actual threat rather than the experiencing of events itself.

4.5.1. Limitations

Data are correlational in nature and thus cannot prove causality. Subjects did not show acute physical health impairments but this does not exclude that previous diseases may have biased

the outcome. Furthermore, since the age spectrum of the women was very broad (27 – 61 years) some might have already been through menopause, from which it is known that it influences the epigenetic age (Levine et al., 2016). This variable was not surveyed in this study. Moreover, epigenetic aging was examined in saliva only. The proportion of epithelial cells and leukocytes in saliva varies between individuals and can be a confounding factor. In general however, DNA methylation in saliva was found to be very similar to methylation patterns from brain regions, providing an easily accessible and relevant tissue for biomarker research.

4.5.2. Conclusion

PTSD symptom severity predicts accelerated epigenetic aging. It is evident from these findings to consider chronic traumatic stress and PTSD symptomatology as risk factors for age-related health deteriorations due to their ability to impact molecular cellular processes causing modifications on the epigenome. Our findings further suggest that DNA methylation-based age prediction using saliva and the Horvath method may be a useful and easy to collect molecular marker to be incorporated in future studies examining the effects of stress and posttraumatic stress.

4.6. Acknowledgements

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5. General discussion

Trauma exposure may well cause permanent disturbances in brain-body signaling that manifest in a variety of psychopathological conditions. The present thesis examined a selection of psychopathological presentations following traumatic events. It further addressed potential mechanisms upon which stress might induce neurobiological alterations that impact the clinical phenotype. These include epigenetic modifications as well as neural adaptations. The three studies that constitute the main part of this thesis presented investigations on correlates of traumatic exposure incorporating the behavioral, neural, and molecular level of psychobiological organization. The findings of the studies will be summarized and discussed in the following. Thereafter, subsequent implications for research and practice are presented.

The first study entitled “ADHD and PTSD following adverse childhood experiences: a study with adolescents” focused on behavioral aspects of pathology. Prior research has shown that in response to adverse childhood experiences, affected individuals develop cognitive and emotional disruptions such as hyperarousal, restlessness, disorganization and difficulties concentrating that often reach manifest symptoms levels of PTSD and ADHD (Brown et al., 2017; McLaughlin et al., 2017). Associations between the disorders have been suggested, but open questions such as the directionality remain unclear. Accordingly, the study examined the effect of traumatic experiences on both PTSD and ADHD symptom severity. Adverse childhood experiences were divided into non-domestic traumatic events and childhood maltreatment including neglect and abuse by parents. Overall and consistent with prior research,

a positive association of adverse childhood adversities and psychopathology was confirmed (for review see Nemeroff, 2016). Using path analysis, associations between traumatic stressors and symptoms of ADHD and PTSD were unraveled. As predicted by the building block effect (Catani et al., 2008; Schauer et al., 2003), the greater the exposure to traumatic events, the more intense PTSD symptoms became. Contrary to our expectations, one type of domestic maltreatment, childhood abuse, did not predict any of the present indicators of mental health. In contrast, our findings highlight the impact of neglect on both, PTSD and ADHD symptom levels. Neglect is often defined as a threat of the child´s safety, health and well-being due to a failure of a parent to provide shelter, food, medical care or supervision and our finding emphasized the potential detrimental effect of this type of missing parental care. In line with our result, previous studies reported a greater prevalence of childhood maltreatment among individuals with both ADHD (Brown et al., 2017; Rucklidge et al., 2006; Semiz et al., 2017) and PTSD (Heim & Nemeroff, 2001; Schalinski et al., 2016; Spinazzola et al., 2014; Widom, 1999). Relative to PTSD, ADHD symptomatology seemed particularly affected by family adversity, whereas non-domestic traumatic events had little or no effect. The results of our study also demonstrated an indirect link between traumatic events and ADHD symptoms via PTSD severity: more traumatic events means more PTSD and more PTSD seems to predict ADHD symptoms. Moreover, the link between childhood neglect and ADHD symptoms proved to be mediated in part by PTSD symptoms. That finding aligns well with another study which reported that PTSD symptoms mediate the relationship between trauma exposure and attention problems (Husain et al., 2008). Yet the potential mediating role of PTSD has not received enough attention; our finding provides further evidence for PTSD's mediatory potential. In conclusion, the potential harm of emotional and physical neglect on mental well-being was

demonstrated. Childhood maltreatment, in particular neglect, is suggested to increase the vulnerability to develop ADHD and PTSD symptoms. Moreover, the findings highlight the importance of supportive intra-familial relationships by illustrating that childhood neglect may play a vital role in ADHD symptoms, directly and mediated by PTSD symptoms. The increased vulnerability to develop psychopathology following early life stress is believed to be linked with stress-induced changes in neurobiological systems. There is considerable evidence for persistent biological alterations in neuronal and endocrine systems following childhood maltreatment and trauma that contribute to a dysregulation of the HPA axis and other stress-sensitive neurobiological systems (Lupien et al., 2009; Nemeroff, 2016). Moreover, there is mounting evidence that epigenetic mechanisms may mediate the long-term effects of trauma in particular neurobiological and behavioral disruptions (for review see Kundakovic & Champagne, 2015). Trauma-related biological alterations and mechanisms will be further illuminated in the following sections.

Psychiatric disorders are increasingly conceptualized as disorders of circuits. This perspective motivated us to delve deeper into the biological factors influencing clinical phenotypes in the second study. For a better understanding of neural correlates associated with stress-related psychopathology, the study entitled “Rapid brain responses to affective pictures indicate dimensions of psychopathology in adolescents” (Sill, Popov, Schauer, & Elbert, 2020) assessed cortical brain activity using Electroencephalography (EEG). The use of EEG technology takes account of different stages of (disturbed) emotion processing and provides insight into the timing and the course of effects in neural representations of psychopathology. Prior research has shown that event-related potentials are altered across a variety of psychiatric

disorders from schizophrenia (Rockstroh et al., 2006) to PTSD (Adenauer, Pinosch, et al., 2010; Burgmer et al., 2013; Elbert et al., 2011; Felmingham, Bryant, & Gordon, 2003) and depression (Holmes et al., 2008; Kemp et al., 2009; Weber et al., 2009). However, construct validity of the traditional diagnostic concepts is disputable (Kendell & Jablensky, 2003) and it remains unclear which aspect of behavioral observed symptoms is associated with reported alterations. In order to tackle this issue and inspired by the RDoC framework we analyzed underlying dimensions of psychopathology in a sample of 90 adolescents with varying trauma exposure. The Early Posterior Negativity (EPN), an event-related potential representing attention allocation toward emotional material, was used to decode the translation of trauma exposure into psychopathological symptoms. Basically, our findings confirmed that adolescents also exhibit the arousal-driven modulation of affective picture processing during the EPN interval that Junghöfer et al. (2001) discovered for adults. Arousing stimuli evoked a more negative amplitude deflection over posterior brain regions 150-300 ms after stimulus onset than low arousing stimuli. Parallel to the aforementioned research, we found the suppression of the Early Posterior Negativity to be associated with psychopathology. Transdiagnostic, dimensional analyses of symptom scores demonstrated that diminished early emotional discrimination, measured by the EPN was particularly associated with impaired concentration, sleep, and trust. Further, sex was found to modulate emotional processing as male participants displayed a stronger affective differentiability in our study. A finding, that aligns well with a meta-analysis of neuroimaging studies (Stevens & Hamann, 2012), which confirmed sex as a potential factor modulating emotional processing to the effect that males were found to be more responsive to pleasant emotional material than females.

The brain is the central organ for stress-induced adaptations. So it seems plausible that dampened cortical activation, including the one demonstrated in our study, reflects stress-related functional brain changes. Aside from methodological limitations of source localizations - along with other limbic structures- an involvement of the amygdala can be speculated due to its widely regarded key function in early emotion processing, selective attention (Pool, Brosch, Delplanque, & Sander, 2015; Pourtois, Schettino, & Vuilleumier, 2013; Sergerie, Chochol, & Armony, 2008) and HPA axis activation (Roozendaal, McEwen, & Chattarji, 2009; Weidenfeld & Ovadia, 2017). Stress exerts an effect on limbic structures involved in the HPA axis (e.g. the prefrontal cortex, hippocampus or the amygdala) and alters glucocorticoid signaling of the HPA axis (Champagne et al., 2008; Lo Iacono & Carola, 2018; Lupien, McEwen, Gunnar, & Heim, 2009; McEwen, 2004; Smith & Vale, 2006; Ulrich-Lai & Herman, 2009). Epigenetic modifications through stress-related gene expression are also thought to interact with these alterations and offer promising means of decoding the psychophysiology of trauma exposure. However, the regulatory network and mechanisms are complicated because multiple functional pathways or circuits are involved in processes relevant to stress, including fear circuits and emotional regulation. With the methods used in the thesis one cannot infer subcortical processes and neuroanatomical pathways related to the decreased affective modulation we have described. Yet, the EPN has not been investigated in a transdiagnostic sample of trauma exposed adolescents and our research has shed new light on the neurobiological alterations associated with stress-related mental health problems.

In essence, our research indicates that the ability to modulate arousal-related cortical structures to emotionally visual content seems reduced when stress-related impairments of concentration, sleep and trust are present. Thus, our findings suggest that traumatic experiences can influence

emotion processing strongly, leading to a manifestation of cognitive and behavioral symptoms. This might represent an adjustment of emotion processing to arousing material after experiencing traumatic stress with a subsequent heightened arousal state. Further it might be understood as a stress-induced protective impairment of attention allocation to prevent body systems from further increase of arousal and allostatic overload, the damaging effects of the biologic stress response.

While the aforementioned studies concentrated on psychological and neural correlates of trauma exposure, the third study transitions to molecular underlying mechanisms. A major role has been assigned to epigenetic modifications. These are molecular mechanisms that regulate gene expression without altering the underlying genetic sequence. Epigenetic modifications are modulated by the environment and thus can be regarded as molecular correlates of trauma exposure. Reflecting the dynamic nature of the epigenome, DNA methylation patterns also reliably change with age across the lifespan. Based on age-associated DNA methylation changes, Horvath (2013) developed an "epigenetic clock", that accurately measures the chronological age, thus offering a valid and reliable biomarker of ageing. The epigenetic clock model also offers an indicator of accelerated aging, meaning that the epigenetic age is older than expected (on the basis of their chronological age).

Several studies suggest, that psychological stress, including lifetime stress exposure (Zannas et al., 2015) and trauma (Boks et al., 2015) effects biological aging and also promotes neurodegeneration and age-related physical health problems (Burri et al., 2013; Cohen, Edmondson, & Kronish, 2015; Danese & McEwen, 2012). In order to extend this line of research, we examined associations between trauma exposure, intensity of PTSD symptoms

and accelerated aging using the Horvath algorithm in 104 females. Our research showed that neither time-limited stressors as adverse childhood experiences nor lifetime trauma exposure per se were associated with accelerated aging whereas PTSD symptom severity was. Unlike other research carried out in this field (e.g. Boks et al., 2015; Jovanovic et al., 2017), we did not find an effect of trauma exposure on accelerated epigenetic aging. However, in these reports the estimated epigenetic age on chronological age was not residualized for the prediction of age acceleration as suggested by Horvath (2013) and did not include PTSD symptomatology in the analyses. However, our results do support previous findings of accelerated aging for individuals suffering from posttraumatic psychopathology (Wolf et al., 2016, 2017). The study also extends previous work that has been limited to the age estimation method developed by Hannum (Hannum et al., 2013) derived from whole blood samples and using fewer DNA methylation markers. In contrast the epigenetic clock created by Horvath (2013) is a multi tissue age predictor, that consists of 353 DNA methylation markers. To our knowledge, the present work is the first study to examine the effects of PTSD on epigenetic age acceleration using salivary DNA and the Horvath algorithm. On the basis of our result that post-traumatic stress is linked with accelerated epigenetic aging, it can be assumed that chronic stress-related conditions, such as a symptomatic phasic activation of fear-related neurocircuitry and elevated autonomic nervous system activity, are potential modulators of biological aging. A proposed mechanism by which chronic stress could impact biological aging involves a dysregulation of the physiological stress response such as the hypothalamic-pituitary-adrenal axis stress hormone system, leading to an aberrant secretion of glucocorticoids (Gassen et al., 2017). Supporting a contribution of glucocorticoid signaling in epigenetic aging, many of the DNA methylation markers included in the epigenetic clock are located within glucocorticoid response elements

(Zannas et al., 2015). Stress and in this case glucocorticoid-induced epigenetic modifications could impact aging-related phenotypes by alterations in the transcriptional regulation of molecular systems that are involved in the aging process. Associations with a great number of age-related conditions and diseases such as cancer, cardiovascular, and all-cause mortality were found in studies evaluating health consequences of epigenetic age acceleration (for review see Horvath & Raj, 2018). Moreover, it is assumed that stress-related neurophysiological adaptations are driven by mechanisms involving increased oxidative stress parameters, cytokines, growth factors, the release of neurotrophic factors and alterations in hormonal levels, even though the exact cascade of events remains to be clarified (Cohen et al., 2012; Girgenti, Hare, Ghosal, & Duman, 2017; Kanherkar, Bhatia-Dey, & Csoka, 2014;Miller & Sadeh, 2014; Morath et al., 2014).

Taken together, an increasing body of evidence including this study have shown that chronic posttraumatic stress may induce changes in epigenetic clock methylation sites, thus accelerating epigenetic aging - a molecular marker that is associated with a number of premature aging-related disease phenotypes.

When working with trauma survivors, impairments of sleep, concentration and trust are commonly reported symptoms. This observation is in line with our transdiagnostic, dimensional analysis of symptom scores following trauma exposure. Further, this symptom cluster of impaired sleep, concentration and trust is often exhibited in both disorders PTSD and ADHD. Thus, one might infer that also in the found associations between ADHD and PTSD, this clinical symptom cluster constitutes a common transdiagnostic feature. The communality of both disorders might be due to a shared underlying pathophysiology, as suggested by our findings of

neural adaptations. The shared pathophysiology also includes the molecular level, in particular epigenetic modifications. It might be assumed, that the reported transdiagnostic symptom cluster representing chronic stress symptoms, is also associated with accelerated epigenetic aging.

However, assumptions should be regarded with caution. Pursuing this line of investigation impairments of sleep, concentration and trust need to be studied according to the domains of the RDoC matrix and across units of analysis. The RDoC functional constructs of *sleep-wakefulness*, *attention* and *affiliation and attachment* may be affected following trauma exposure through multiple units of analysis such as neural circuits and epigenetics. And future studies are needed to further elucidate the neurobiology of trauma and its dimensional manifestation.

5.1. Implications for research and practice

All of the research articles included in this thesis evidence persistent changes in human behavior and physiology following traumatic stress. The thesis demonstrated the pivotal role of adverse childhood experiences for the severity of PTSD, ADHD and their combined presentation according to the nosology of the DSM-IV. It may also be concluded that traumatic events may aggravate PTSD especially in those who lack parental care. The vast majority of cases of child maltreatment go unreported. Preventative measures should foster positive parenting skills and must become priority because there is mounting evidence that childhood maltreatment is associated with more severe psychiatric illness and a poorer treatment outcome (Agnew-Blais & Danese, 2016; Agorastos, Pervanidou, Chrousos, & Baker, 2019; Nanni, Uher, & Danese,

2012; Teicher, 2013). The comorbidity of PTSD and ADHD in clinical populations may be due to shared genetic and environmental causal factors. Also, because of similarities in the clinical presentations of both disorders e.g. inattentiveness, hyperactivity, and impulsivity, PTSD might often be mistaken as ADHD. Either way a careful evaluation of both disorders is suggested. And the treatment of PTSD in people diagnosed with ADHD is a relevant issue that warrants further attention. Clinicians should equally assess ADHD and PTSD symptoms, and if severe symptoms are found then childhood traumas, especially emotional and physical neglect should be evaluated in order to appropriately tailor therapeutic measures. Further, it is advised that for adolescents presenting symptoms of PTSD and ADHD, the prescription of stimulant medication commonly used for treatment of attention deficits in ADHD should be considered thoroughly as these individuals might not benefit equally compared to those with a distinct ADHD diagnosis.

The underlying pathophysiology of both disorders has not been fully understood yet and more work is needed to further examine the dynamic interplay of the found associations. Future investigation should examine domains of impairment that are shared by the disorders as well as disparate areas of dysfunction to develop more accurate models of risk mechanisms. The RDoC framework (Cuthbert & Insel, 2013) promotes a pathophysiologically grounded taxonomy that could help to close the gap between how psychiatric illness are characterized in ICD and DSM and the underlying pathophysiological mechanisms. An improved understanding of common and unique etiological mechanisms underlying the disorders could have a profound impact on the diagnosis and treatment of these disorders. One limitation of our research is that data are cross-sectional as well as correlational in nature, precluding determination of causality. Longitudinal research will be required to determine chronologic sequence of traumatic

experiences in relation to the symptom course of both disorders and to confirm the potential mediating role of PTSD symptoms. Bias due to self-reported measures and associated social desirability cannot be ruled out. While the concurrent use of both self-report and clinician interview data is a strength of the present study, the measures used are not objective in nature. Future studies should also incorporate more objective measures such as biological markers or neuropsychological assessments of e.g. attention or cognitive functions to support any self-report findings. The lack of German language proficiency and the use of interpreters might have led to some loss of nuances or misunderstandings, affecting the data assessment. Also, the measure of trauma exposure did not have details on timing and duration of trauma exposure. These factors complement the cumulative effects of traumatic events with a dose-response relationship. The brain is thought to have sensitive phases during a specific age period, in which they are particularly vulnerable to the effect of traumatic experiences (Teicher & Samson, 2016). It will be important for future research to determine such potential moderating variables. While the limitations may have reduced the significance of findings, it seems less plausible that it can have produced the reported effects.

This thesis also confirmed an arousal-driven modulation of affective picture processing during the EPN interval, as discovered by Junghöfer et al. (2001) for adults and Wessing et al., (2011) for 8- to 10-year-old children. We have shown that also in a sample of adolescents arousing pleasant stimuli evoked an EPN inhibition using RSVP, meaning that the EPN can be recorded for briefly presented stimuli that are shown at a rapid rate. Thus, the affective RSVP design, that is known to produce variations with affective arousal in adults (Junghöfer et al., 2001, 2006; Peyk et al., 2008) seems to be applicable also in adolescents. Further, by conducting a transdiagnostic analysis based on the logic of RDoC, our findings extend those of prior

research on emotional processing in trauma survivors that applied diagnostic DSM/ICD-based categories (Adenauer, Pinosch, et al., 2010; Burgmer et al., 2013; Elbert et al., 2011; Felmingham et al., 2003). Our findings indicate that impairments of concentration, sleep and trust seems to be the common transdiagnostic element related to a reduced early affective discrimination represented by the EPN.

So far, much clinical trauma research has focused on emotional processing of aversive, trauma-related material. Together with the findings of Adenauer, Pinosch et al. (2010) and Burgmer et al. (2013), our results provide support for EPN suppression also occurs when pleasant emotional material is presented. EPN inhibition seems to reflect a general response towards highly arousing pictures instead of a specific response towards trauma-related stimuli. Thus, in case of ethical concerns positive valence stimuli can be used as an alternative to traumatic materials for affective picture processing research in this field as the effect seems mainly arousal-driven (for review see (Olofsson et al., 2008). With that said, ideally studies should be carried out with arousing pleasant and unpleasant stimuli shown to patients affected by traumatic stress. Caution is required regarding the generalizability of our results as the sample is not necessarily representative and limited to adolescents. Additionally, from cross-sectional data nothing can be concluded about the causal status of the reported relationships and the variability in the measures over time. Most of the assessment measures relied on subjective report or recall. Thus, future research should indicate whether the linkage between stress-related symptoms and EPN suppression is also present when combining reported verbal and physiological arousal markers (e.g. cortisol). ERP cannot localize effects, so future neuroimaging research is advised to expand the research on brain circuits using fMRI and PET based research. Additionally, an

important issue to resolve for future studies are epigenetic alterations in stress responsive systems, mediating the effect on cortical activity.

To conclude, for future research it is recommended to pursue an multidisciplinary approach covering several levels of analysis. Large-scale research initiatives have a vast potential for discovering new insights into the pathogenesis of stress-related disorders and treatment targets because it facilitates identifying diagnostic, prognostic, and therapeutic biomarkers. Our findings demonstrate an initial step in examining transdiagnostic emotional dysfunction.

Investigating epigenetic alterations following traumatic stress in study three of the thesis, we propose that chronic posttraumatic stress and PTSD symptomatology accelerates biological aging. The results support the role of epigenetic modifications among mechanisms linking stress and aging. Chronic traumatic stress and PTSD symptomatology can be regarded as risk factors for age-related health deteriorations due to their ability to impact molecular and cellular processes causing modifications on the epigenome. Accordingly, it can be inferred that evidence-based treatments of PTSD may not only reduce symptoms but also the risk of PTSD-related accelerated aging and adverse health effects.

The epigenetic clock provides a promising age-predictive biomarker. It is beneficial as it merely requires blood or saliva samples and a subsequent analysis of DNA methylation. Given the arrival of millions of refugees to Europe, epigenetic age estimators theoretically have the potential to be used for immigration control purposes when the validity of the identification documents is questionable. Existing methods for age determination assess the maturity of bones of individuals and are regarded as imprecise. For that reason it has been suggested to use the epigenetic clock to determine an individual's age and especially to verify the age of minor asylum seekers because this group deserves special care in many countries. However, caution

is required because there is increasing evidence, including our study that confounding factors such as trauma exposure and psychopathology affect epigenetic aging, leading to a biased age estimation.

Our study was conducted in an outpatient clinic addressing mental health impairments due to severe traumatization. In this context it was not feasible to control for potentially confounding variables of physical health such as asthma, diabetes or comparable illnesses. The onset of menopause represents another potential confounding factor, since our sample contained a very broad range of ages (27-61 years). Finally, our sample was limited to females, which limits the generalizability of the results and underscores the need for replication. Additional research is required to address these study limitations. Furthermore, in our study epigenetic age was estimated from saliva samples. Concerns were expressed regarding the correspondence between DNA methylations in peripheral blood and brain tissue (e.g. (Tylee, Kawaguchi, & Glatt, 2013). Horvath (2013) could reduce the concerns by demonstrating that the DNA methylation-based age estimates of the epigenetic clock generalize to brain tissue. Thus epigenetic age estimates from saliva seem to represent a reliable proxy for epigenetic age in the brain.

Future studies should investigate the potential of interventions to reverse stress-related premature aging effects and their underlying biological mechanisms. A recent study reported preliminary findings on a possible reversal effect of the epigenetic clock(Fahy et al., 2019), underpinning the potential effect of interventions. Further, in order to study causal relationships and differentiate between neurobiological correlates of trauma- and stress-related psychopathology from the neurobiological consequences of this symptoms future research should chose a longitudinal study design.

Taken together, DNA methylation-based age prediction using saliva and the Horvath method may be a useful and easy-to-collect molecular marker to be incorporated in future studies examining the effects of stress and posttraumatic stress.

5.2. Conclusion

In a significant fraction of trauma survivors, stress reactions do not simply dissipate. Instead, adverse psychobiological consequences may be observed. In highly traumatized populations, including refugees, PTSD rates are high (for reviews see Fazel et al., 2005; Morina et al., 2018). Moreover, PTSD can be accompanied by a wide range of persistent health impairments, from physical illness to premature age-related disorders and comorbid psychiatric diseases.

The current thesis contributes to research on trauma by employing a multi-level approach to study psychological and psychobiological correlates.

On a clinical level, the thesis shows that both PTSD and ADHD symptoms are associated with adverse childhood experiences. PTSD development following trauma is found to predict ADHD symptoms and might even mediate the effect of adverse childhood experiences on ADHD symptoms. We suggest that the disorders are interrelated and might share transdiagnostic factors closely associated with neurobiological systems.

Elucidating the psychophysiology of trauma exposure, cortical correlates of emotion processing were examined. Transdiagnostic, dimensional analyses of symptom scores demonstrated that impaired concentration, sleep, and trust are associated with impaired early emotional discrimination, represented by the early posterior negativity (EPN) in response to high- versus low-arousing emotional scenes in adolescents with different traumatic experiences. Thus stress

symptoms might induce a functional reorganization of the emotional processing streams in the brain and may affect the processing of external emotional stimuli.

In terms of molecular mechanisms of the traumatized brain, the field of epigenetics has vast potential to discover new insights into biological processes related to health and disease. The findings of this thesis indicate that PTSD may accelerate epigenetic aging. Accelerated epigenetic aging in turn is reported to be linked with premature aging-related impairments (for review see Gassen et al., 2017).

Overall, exposure to traumatic events can have lasting effects on psychopathology and pathophysiology. Extreme or repeated stress exposure might cause lasting neurobiological alterations. The HPA axis is one of the key stress response systems that may transmit the long-term effects (for review see McEwen, 2007) given that a wealth of evidence implicates that stress-related pathologies are associated with a dysregulation of this stress-sensitive system. In addition, epigenetic modifications in the brain have been postulated to underlie alterations in neurobiological systems including the HPA axis. DNA methylation is known to impact the regulation of the HPA axis by affecting the expression of genes involved in HPA axis (for review see Dirven, Homberg, Kozicz, & Henckens, 2017). Moreover, DNA methylation has been suggested as a mediator of neural plasticity, aging, and behavior, including cognition and memory. In conclusion, epigenetic modifications might also constitute the common underlying mechanisms mediating the effect of environmental factors, namely trauma exposure on the psychopathology and pathophysiology presented in this thesis. However, the etiology of trauma-induced illness is complex and multifactorial underscoring the need of multidisciplinary research. Research that goes beyond subjective and observable behavioral symptoms yields new insights into the biological underpinnings of symptoms, including the

genetics, epigenetics and neural circuits of stress-related neuropsychiatric disorders. By identifying more biomarkers of PTSD and trauma-related disorders, current diagnostic tools and treatment options can be improved as part of precision medicine. Developing individual treatment plans for disorders following trauma will also allow to address the heterogeneity of trauma-related disorders and lead to more effective multidisciplinary treatments.

6. Record of achievement

The studies in this thesis were realized in cooperation with a number of colleagues. The author´s independent research contribution is mentioned below.

Study 1: Symptoms of ADHD and PTSD following adverse childhood experiences. A study with adolescents.

Authors: Johanna Sill, Veronika Müller, Maggie Schauer, Thomas Elbert.

My contributions:

I coordinated the study, recruited study participants and carried out a large number of clinical interviews and supervised further data collection. I performed the statistical analysis and drafted the manuscript.

Study 2: Rapid brain responses to affective pictures indicate dimensions of trauma-related psychopathology in adolescents.

Authors: Johanna Sill, Tzvetan Popov, Maggie Schauer, Thomas Elbert.

Published: 2020, Psychophysiology, 57(1), doi: 10.1111/psyp.13353

My contributions:

I coordinated the study, recruited study participants and carried out a large number of clinical interviews and EEG measurements, supervised further data collection and developed the study concept. In cooperation with Tzvetan Popov I processed the EEG data and conducted the statistical analyses. I prepared the first draft of the manuscript with later adjustments by the co-authors and myself.

Study 3: Post-traumatic stress accelerates epigenetic aging.

Authors: Johanna Sill*, Hannah Weiland*, Eva Unternaehrer, Vanja Vukojevic, Jens Pruessner, Thomas Elbert.

* Equally contributing.

My contributions:

I coordinated the study, including DNA analyses, recruited study participants and carried out a large number of clinical interviews, supervised further data collection and developed the study concept. I conducted the statistical analyses and drafted the manuscript together with my co-authors.

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