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Am Zentralinstitut für Seelische Gesundheit
der Medizinischen Fakultät Mannheim
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Pathways contributing to the Risk of Substance Use Disorders after Adverse Childhood Experiences

Inauguraldissertation
zur Erlangung des Doctor scientiarum humanarum (Dr. sc. hum.)
der
Medizinischen Fakultät Mannheim
der Ruprecht-Karls-Universität
zu
Heidelberg

vorgelegt von
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aus
Saulgau, jetzt Bad Saulgau
2023

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PREFACE

This work is a cumulative dissertation based on empirical studies, and part of the results have already been published as peer-reviewed publications. Therefore, certain sections, tables, or figures of this thesis will be identical to these publications. Please find the list of peer-reviewed publications below.

Publikation 1

Gerhardt, S., Eidenmueller, K., Hoffmann, S., Bekier, N. K., Bach, P., Hermann, D., Koopmann, A., Sommer, W.H., Kiefer, F., Vollstädt-Klein, S. (2022). A History of Childhood Maltreatment Has Substance- and Sex-Specific Effects on Craving During Treatment for Substance Use Disorders. Frontier in Psychiatry, 13, 866019. Impact factor 5.435. Original research paper.

Publikation 2

Gerhardt, S.*, Berhe, O.*, Moessnang, C., Horning, M., Kiefer, F., Tost, H.*, & Vollstädt-Klein, S.* (2023). Lack of amygdala habituation to negative emotional faces in alcohol use disorder and the relation to adverse childhood experiences. Addiction Biology, 28(1), e13251. Impact factor 4.093. Original research paper. *These authors contributed equally.

For Publication 1, the corresponding chapter in the dissertation is ‘Chapter 2: Study 1’. For Publication 2, the corresponding chapter in the dissertation is ‘Chapter 3: Study 2’. The detailed description of the personal contribution to each of the publication are listed in the table below.

Work steps	**Publication 1**	**Publication 2**
Conceptualization (%)	100	50
Literature research (%)	95	60
Ethics application (%)	0	90
Animal experiment application (%)	n/a	n/a
Data collection (%)	0	100
Data analysis (%)	90	40
Interpretation of results (%)	85	45
Writing of manuscript text (%)	90	45
Revision (%)	95	45
State which figures/ tables are the results of this doctoral thesis	All figures and all tables	Figures S11/ S12/ S13 und Tables 6/ S7/ S8 derive from the dissertation of Sarah Gerhardt
Detail which data/ figure/ tables are based on research by others	n/a	Figures 7/ S8/ S9/ S10 derive from the dissertation of Oksana Berhe

"*Although there is no single risk factor that is dominant, the more vulnerabilities a person has, the more likely the person is to develop alcohol-related problems as a result of alcohol consumption."*

World Health Organization

TABLE OF CONTENTS

ABBREVIATIONS

AAL	Automated Anatomical Labelling
ACE	Adverse Childhood Experiences
ADS	Alcohol Dependence Scale
ANOVA	Analyses of Variance
APA	American Psychiatric Association
AUD	Alcohol Use Disorder
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BOLD	Blood Oxygenation Level Dependent
CIMH	Central Institute of Mental Health
CM	Childhood Maltreatment
CSUD	Cocaine and Stimulant Use Disorder
CUD	Cannabis Use Disorder
CRH	Corticotropin Releasing Hormone
CTQ	Childhood Trauma Questionnaire
DSM-5	5th Version of the Diagnostic and Statistical Manual of Mental Disorders
DSM-IV	4th Version of the Diagnostic and Statistical Manual of Mental Disorders
FDR	False Discovery Rate
(f)MRI	(Functional) Magnetic Resonance Imaging
FTND	Fagerstroem Test for Nicotine Dependence
FWE	Family Wise Error
GLM	General Linear Model
HC	Healthy Controls
HPA	Hypothalamic Pituitary Adrenal
ICD	International Classification of Disease

MACE	Maltreatment and Abuse Chronology of Exposure Scale
MACS	Mannheimer Craving Scale
MNI	Montreal Neurological Institute
MPRAGE	Magnetization Prepared-RApid Gradient Echo
MRI	Magnetic Resonance Imaging
NIDA	National Institute on Drug Abuse
OMT	Opioid Maintenance Treatment
OUD	Opioid Use Disorder
PSS	Perceived Stress Scale
PTSD	Post Traumatic Stress Disorder
ROI	Region of Interest
SCID	Structured Clinical Interview for DSM-IV
SHA	Sedative, Hypnotics, or Anxiolytic Use Disorders
SUD	Substance Use Disorders
UNODC	Unites Nations Office on Drug and Crime
WHO	World Health Organization

1 THEORETICAL BACKGROUND

While the modern world is changing at a rapid pace and is faced with new global threats, one constant can be observed throughout history: purposefully producing and consuming alcoholic beverages has been common practice for at least 10,000 years (Liu et al., 2018) and the use of (plant-based) psychotropic substances dates back even further (Sullivan & Hagen, 2002). The search for an experience of inebriation or altered mental state – for whatever individual or societal reasons – accompanied humankind for thousands of years (Sullivan & Hagen, 2002; Wang & Liu, 2022). Whereas the historical aspect of psychoactive substances could be an intriguing field of study for some, many substances' ability to excerpt an effect on emotional states withholds risks for individuals and may have detrimental consequences for society.

Among psychoactive substances, alcohol is the most widespread one in use (Degenhardt et al., 2018; Peacock et al., 2018). While high global prevalence was observed for smoking tobacco (15%), followed by consuming cannabis (4%), amphetamines, cocaine, and opioids (< 1%, respectively), approximately half of the global population over the age of 15 years reported drinking alcohol in 2015. Moreover, 40% of individuals drinking alcohol also reported heavy episodic drinking, which is defined as 40/60 (women/men[1]) or more grams of pure alcohol on one occasion, at least once per month (Peacock et al., 2018; World Health Organization (WHO), 2018). In Germany, in 2018, 72% of the adult population reported drinking alcohol during the last 30 days, and 43% of this cohort recounted episodes of heavy drinking. Furthermore, 23% of the German population consumed tobacco products within 30 days of the survey, while 7% used cannabis, 1% amphetamines, 1% cocaine, and < 1% opioids in the 12 months leading up to the survey (Atzendorf et al., 2019).

Consequently, the burden of disease represented by disability-adjusted life-years is extremely high for both, alcohol, as well as other psychotropic substances (Degenhardt et al., 2018). In 2016, alcohol use was associated with 2.8 million deaths worldwide. Aside from these health-related and social impacts, alcohol also poses a great burden on the economy. In the United States, for example, alcohol-related monetary losses were estimated to lie around 249 billion dollars, in 2010 (Sacks et al., 2015). In Germany, the annual economic costs associated with

[1] The terms women/ men and female/male will be used to describe sex and gender-related aspects.

alcohol, both direct and indirect, are estimated to be 39 billion euro on average (Effertz et al., 2017). This vastly exceeds the alcohol-related tax income, in Germany, which amounts to approximately 3 billion euro per year (Bundesfinanzministerium, 2022) further underlining the detrimental economic impact of alcohol consumption.

The somatic and mental health issues - as well as societal and economic consequences - stemming from substance use, may well be considered a persisting global threat with the ongoing urgent need of being addressed.

Ultimately, alcohol or substance use may cause a variety of physical and mental health is-sues in individuals, such as cancer, diabetes, cardiovascular diseases, as well as *substance use disorder (SUD).*

Bearing in mind that pathways leading to SUD are not yet fully understood, recent scientific discussions aim to illuminate the question of whether SUD can be considered a brain disorder within the concept of the brain disease model of addiction (Leshner, 1997). This view is publicly supported by the National Institute on Drug Abuse of the United States (National Institute on Drug Abuse (NIDA), 2020). While some scholars emphasize the high relevance of addressing neurobiological mechanisms and alterations in the context of SUD (Koob & Volkow, 2016; Volkow & Koob, 2015), others oppose a simplified, neurobiological view (Hall et al., 2015), or highlight the perspective of life-long neuroplasticity and mechanisms of learning (e.g., Wakefield, 2020), as well as societal and environmental factors (Borsboom et al., 2019; Field et al., 2019). While this controversial subject catalyzed the formation of scientific networks opposing the brain disease model (Heather et al., 2018), SUD will be considered a multifactorial disorder in this dissertation.

To contribute to the ongoing discussion regarding the complexities of SUD, this dissertation aims to link neurobiological and societal aspects of SUD. To this end, *adverse childhood experiences* (ACEs) will be explored in depth. Firstly, the introductory chapter will provide information on SUD and ACE, describe prevalence rates, and elaborate on neurobiological considerations. Secondly, two studies will be presented that examine potential pathways linking ACE to SUD. Thirdly, a concluding discussion will integrate these novel observations, illuminating the interplay between societal and neurobiological aspects of SUD. Finally, this dissertation will provide an outlook regarding further research as well as clinical care.

1.1 Diagnostic and Clinical Considerations of SUD

In addition to the aforementioned prevalence of overall substance consumption, globally, in 2019, 35 million individuals suffered from SUDs (i.e., cannabis, opioids, amphetamines, cocaine, and ecstasy; Unites Nations Office on Drug and Crime (UNODC), 2019). In 2016, alcohol use disorder (AUD) affected 5.1% of the global population (equivalent to 283 million individuals; World Health Organization (WHO), 2018). Other surveys reported a prevalence of 2.2% for SUDs with AUD being the most common type (1.5%), in 2019 (Castaldelli-Maia & Bhugra, 2022). However, prevalence rates seem to associate with sociodemographic status and income (Castaldelli-Maia & Bhugra, 2022). Furthermore, regional and cultural differences have also been reported (Degenhardt et al., 2018).
In Germany, in 2018, the 12-month prevalence for all SUDs was estimated at 3.0% (cannabis, cocaine, amphetamines, hypnotics and sedatives) and for AUD at 3.1% (Atzendorf et al., 2019). It is worth noting that prevalence rates should be scrutinized in depth due to different diagnostic systems. This makes cross-border or cross-regional comparisons difficult, as estimates might diverge, according to the diagnostic criteria used.

While terms such as “dependence”, “abuse”, and “substance use disorder” are found in the scientific literature, the current consensus is to refrain from stigmatizing terminology (e.g., "addict") in clinical diagnosis systems. Within the concept of unidimensional structure, as published in the *Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) by the American Psychiatric Association (American Psychiatric Association (APA), 2013), SUD is defined as a “problematic pattern of substance use leading to clinically significant impairments or distress”. For AUD, at least two out of eleven diagnostic criteria must met within a period of 12 months for a clinical diagnosis. The severity of the disorder is then defined by the number of criteria met (2-3 mild; 4-5 moderate; > 6 severe SUD; American Psychiatric Association (APA), 2013). While loss of control and compulsive consumption of a alcohol represent two aspects of this disorder, the occurrence of physical and/ or psychological problems or impairments in social interactions further demonstrate the significance of this disorder for the affected individual (e.g., Carvalho et al., 2019). It is worth noting that the diagnostic criteria of the Fourth Edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) are used in contemporary research and clinical treatment. Following DSM-IV, one or more symptoms out of four have to be met to fulfil the diagnosis of substance abuse and three or more out of seven for the diagnosis of a substance dependence, respectively during a 12-months

period (American Psychiatric Association (APA), 1994). Notably, the criteria of abuse and dependence largely overlap between DSM-IV and DSM-5 (American Psychiatric Association (APA), 1994, 2013; Dawson et al., 2013). According to the *International Classification of Diseases, Tenth Revision* by the World Health Organization (ICD-10), harmful substance use and substance dependence describe two primary diagnoses within the category of mental disorders (World Health Organization, 2004). The diagnosis of alcohol dependence is given when an individual meets three out of six diagnostic criteria during a 12-months period. Analogous to both DSM editions, compulsive consumption, impairment over consumption behavior, as well as physical and psychosocial aspects are addressed. The ICD-10 diagnosis of alcohol dependence might, therefore, translate to a moderate to severe AUD according to the DSM-5 (Hoffmann & Kopak, 2015).

1.1.1 Instances of Relapse

SUDs are often characterized by chronic progression and (re-) occurring relapse (Hasin et al., 2013; Heilig et al., 2010b; Koob, 2008, 2013; Koob & Volkow, 2010; Sinha, 2011). This common trajectory merits consideration regarding the treatment of SUD. *Instances of relapse* can be defined as the use of a substance after a period of abstinence, or when an individual returns to her or his previous substance use behavior in terms of quantity or frequency of use (Brownell et al., 1986). High relapse rates, amounting to approximately 80%, underline the complexity of treating SUD (Walitzer & Dearing, 2006). However, it should be noted that these prevalence estimates are subject to a considerable heterogeneity regarding the definition of relapse (Sliedrecht et al., 2022). Furthermore, inter-individual factors, such as stress, negative affect, or ACEs, are thought to condition an individual's relapse probability (Sinha, 2008; Walitzer & Dearing, 2006). Importantly, re-occurring instances of relapse and substance use may transpire into a vicious circle: exposure to substances or substance-associated cues might intensify an individual's experience of distress, anxiety, and substance craving, possibly leading to relapse or sustained substance use (Sinha, 2007). Moreover, on the one hand, neural stress and reward systems interact with an individual's experiences and facilitate relapse. While, on the other hand, relapse and continued use of a substance alter these neural systems even further, exacerbating the vicious circle (Sinha, 2007).

1.1.2 Craving and Cue-Reactivity

In this context, *substance craving*, as one diagnostic criterion following DSM-5 and ICD-10, deserves closer attention. Substance craving can be described as the "subjective experience

of wanting to use a substance" (Sayette, 2016; Tiffany & Wray, 2012), bearing in mind that terms like substance "desire", "urge", or "need" are also in use (Cavicchioli et al., 2020; Sayette, 2016). The phenomenon of *cue-reactivity* further contributes to the experience of craving, based on processes of conditioning. Cue-reactivity can be defined as a subjective, physiologically, or neurochemically conditioned response to substance-associated stimuli (Tiffany & Wray, 2012). Besides self-reports, an objective assessment might include changes in heart rate, sweat gland activity, and brain activity (e.g., observed via neuroimaging) in response to exposure to substance-associated stimuli (Carter & Tiffany, 1999; Courtney et al., 2016; Vollstädt-Klein et al., 2010). Craving and cue-reactivity are addressed by several therapeutic approaches, for example pharmacologically (e.g., Bach et al., 2020; Hendershot et al., 2017) or psychotherapeutically (e.g., mindfulness-based relapse prevention; Witkiewitz et al., 2013). These approaches address an individual's loss of control over substance use behavior and relapse (Tiffany & Wray, 2012), thus, contributing to treatment outcomes. Although cue-reactivity and craving have been shown to be positively associated, their influence on relapse is still under debate (Courtney et al., 2016). To date, research on the relation between craving and relapse has produced diverging results: while some researchers observed a strong association between craving and substance use or relapse, other studies found no association (for an overview, see Tiffany & Wray, 2012). Witteman et al. (2015), for instance, found that the mere presentation of alcohol-related cues led to physiological reactions and subjective reports of increased alcohol craving in patients with AUD, even after successful detoxification treatment. However, no relation was observed between cue-reactivity and craving, both measured at baseline, and later relapse. A recent meta-analytic review solely found a small association between craving and substance use behavior, including relapse (Cavicchioli et al., 2020). Interestingly, craving emerged as a modest risk factor for substance use, when considering the length of abstinence as, the association between craving and substance use increases in strength over time. This incubation has not only been observed with regards to craving but also cue-reactivity (Bach et al., 2020), indicating a dynamic relationship between cue-reactivity, craving, and relapse.

1.2 Neurobiology of SUD

Thanks to recent advances in neuroimaging methods, such as magnetic resonance imaging (MRI), neurobiological aspects of SUD can be explored, providing the basis for a deeper understanding of the disorder. As the majority of the human body consists of water, high static magnetic fields can align the protons of the hydrogen nuclei (McRobbie et al., 2017). Applying additional radiofrequency pulses stimulates these proton, which then spin out of alignment. In

the short phases between the applied radiofrequency pulses, the protons then, again, realign according to the static magnetic field. During this process, these protons release energy, which can be detected by MRI sensors, in addition to the time it takes the protons to realign. As the released energy and time differs according to the respective environments (e.g., liquor, gray matter structure) it is possible to reconstruct images depicting these various types of tissue. Therefore, MRI can be used to examine brain structures, such as cortical thickness or regional volumes, by generating full-brain images with a high spatial resolution, while posing a low risk for participating individuals. MRI, thus, allows examining pathophysiological aspects of mental disorders (D'Esposito, 2006).

Additionally, functional MRI (fMRI) provides the opportunity to estimate brain activity or connectivity between brain regions due to the technique's ability to assess changes in blood flow (Chen & Glover, 2015). During task performance, local changes in metabolic activity occur in the brain, leading to a disproportional increase in blood flow and volume to these "activated" areas. Using fMRI, increases in the local oxygenation of blood can be detected as oxygen-rich blood replaces the paramagnetic deoxygenated blood roughly two seconds after neuronal activity. This so-called Blood Oxygenation Level Dependent (BOLD) effect was first described by Seiji Ogawa (1990), thus, offering the astonishing opportunity to depict the close relation between neural activity and cerebral blood flow, which had been debated since the late 19th century. By using a hemodynamic response function to model the BOLD response and applying general linear models that best fit the data, researcher can calculate statistical approximations of time-dependent underlying neural correlates when performing specific tasks as well as during rest (Chen & Glover, 2015). However, high temporal resolution comes at the expense of lower spatial resolution as compared to structural MRI.

Major addiction theories define alterations in neural structure and functioning as an outcome of prolonged substance use - or as a risk factor thereof. In general, brain networks that are relevant in SUD, involve reward, habit, salience, executive, self-directed, and memory networks. Hence, cognitive and emotional impairments are acknowledged in SUD (for an overview, see Zilverstand et al., 2018).

In the following, AUD will be referenced as the most prominent type of SUD (Peacock et al., 2018), in order to outline mechanisms of interest. In their conceptual approach to SUD as a brain disease, Koob and Volkow (2010) suggested that processes of neuroplasticity occur along the pathway from occasional consumption of alcohol to severe AUD. These involve the following stages: (1) binge and intoxication, (2) withdrawal and negative affect, as well as (3) preoccupation and anticipation (see also, Koob & Volkow, 2016; Volkow et al., 2016).

The first stage of this circular model, the *binge and intoxication stage*, highlights dopaminergic processes and the role of the nucleus accumbens as part of the ventral striatum regarding the acute and reinforcing substance effect. Embedded in neurobiological functioning, learning in terms of stimulus-response associations leads to an increase in incentive salience of alcohol cues and might elicit substance craving even after periods of abstinence (Cavicchioli et al., 2020). Further, neuroplasticity processes and habit formation also affect the dorsal striatum. While neural alcohol cue-reactivity was observed in the ventral striatum in social drinkers, heavy drinkers elicited activation of the dorsal striatum when presented with alcohol cues (Vollstädt-Klein et al., 2011). In addition, obsessive and compulsive alcohol use was positively associated with dorsal striatal cue-reactivity, indicating a change in neural correlates of learning processes. These processes ultimately result in substance use motivated by an (expected) rewarding effect thereof, and may influence neural cue-reactivity. Likewise, reward craving might occur at this stage (Verheul et al., 1999).

The second stage, the *withdrawal and negative affect stage*, is closely related to the functioning of the extended amygdala, while projections to the hypothalamus and brainstem are described. Substance use is motivated by an (expected) relief from negative affect, such as symptoms of anxiety or depressiveness. In a large sample of individuals with AUD who completed detoxification, trait anxiety positively related to self-reported relief craving (Glöckner-Rist et al., 2013). During prolonged use of alcohol, alterations of the hypothalamic pituitary adrenal (HPA) axis as well as the brain stress system occur. As these systems are mediated by the corticotropin-releasing hormone (CRH), a peptide involved in stress behavior and physiology (Backström & Winberg, 2013), an imbalance in stress and reward systems might enhance susceptibility for relapse.

The third stage, the *preoccupation and anticipation stage*, is described as the stage of craving and marks the chronicity of the disorder. Here, a broad and distributed network including orbitofrontal, striatal, insular, and hippocampal regions as well as the amygdala are involved. As impairments in inhibitory control occur, regions such as the cingulate gyrus, dorsolateral prefrontal, and inferior frontal cortices are affected. Conditioned cues eliciting relapse, might be of diverse nature (i.e., substance, stress, or emotion-related), further underlining the salience of substance-associated cues that climax during this stage.

The model by Koob and Volkow (2010), therefore, concludes that the transition from none-SUD over mild to severe SUD is accompanied by alterations in neuroplasticity within these

structures. Alterations are suggested to commence in the mesolimbic dopamine system, followed by ventral then dorsal striatal region, finally leading to alterations in frontal, cingulate regions as well as in the amygdala.

Merely considering neural alterations as consequences of prolonged substance use and SUD does not do justice to the complexity of integrating neurobiological and societal aspects. Preceding conditions or experiences that might cause or facilitate the development of SUD - as well as interacting with neural functioning throughout the aforementioned stages of SUD - merit attention. As such, ACEs seem of great importance.

1.3 The Impact of ACE on Mental Health

ACEs encompass events a child might encounter until the age of 18. They include household dysfunctions, separation of parents, domestic violence, a parent's substance use or mental disorder, as well as childhood maltreatment (CM; Brown et al., 2009; Negriff, 2020; Teicher & Samson, 2013). Relating thereto, experiences of active, as well as passive CM, can be differentiated (Teicher & Samson, 2013): emotional abuse (including verbal aggression, emotional manipulation, witnessing domestic violence); physical abuse (including corporal punishment); and sexual abuse. These forms of abuse describe active maltreatment whereas emotional and physical neglect (i.e., failure to provide basic emotional and physical needs) are considered passive maltreatment (Teicher & Samson, 2013). Commonly, ACEs are assessed retrospectively, using questionnaires or interviews. The *Childhood Trauma Questionnaire* (CTQ), for example, is a validated self-report questionnaire that explores all five types of CMs up to the age of 18 years. Bernstein et al. (2003) have reported a good reliability of the CTQ ($0.87 < \text{alpha} < 0.95$) as well as good applicability in specific populations, such as individuals with mental disorders or SUDs (Bernstein et al., 1997; Thombs et al., 2007). The overall severity of CM, as well as specific subtypes, can be classified into: none/minimal; minimal/moderate; moderate/severe; and severe/extreme. This descriptive classification allows a dichotomous approach with regards to having experienced CM or not (Bernstein et al., 1994; Häuser et al., 2011; Witt et al., 2017). Further, the *Maltreatment and Abuse Chronology of Exposure Scale* (MACE) examines CM by way of an interview (Teicher & Parigger, 2015). A recently validated, shortened version of the MACE suggests ten subscales of CM, including, for example, emotional or physical abuse by peers or siblings (Seitz et al., 2022). In addition, the interview assesses the timing of CM and provides a duration score reflecting the number of years a child was exposed to ACE. Integrating the broader definition of ACE, several versions of the *Adverse Childhood Experiences Scale*

are in use (e.g., Felitti et al., 1998). Recently, the WHO suggested an international version to capture aspects of CM, experiences of violence, parental substance use or mental illness, incarceration or parental separation using a 31-item questionnaire (Gette et al., 2022).

The safety of children and the prevention of ACE is one of the goals as stipulated by the WHO (World Health Organization (WHO), 2016). At the same time, prevalence numbers of ACEs above 80% are reported (Merrick et al., 2017). This is highly concerning, as it documents the far-spread extent of ACE along with their detrimental consequences for individuals and society. Remarkably, in their systematic review and meta-analysis, Bellis et al. (2019) reported annual costs of 581 billion U.S. dollars for Europe and 748 billion U.S. dollars for the Northern Americas that were attributed to ACE-related health care costs. They were further able to ascribe 75% of these costs to individuals having experienced more than two ACEs.

Regarding CM, emotional neglect appears to be the most prevalent type globally (Africa 47%, Asia 42%, Northern Americas 37%; Stoltenborgh et al., 2015). However, this type of ACE seems to be underrepresented in research and large differences exist regarding sex/gender and region (Moody et al., 2018). In Europe, prevalence estimates acknowledge 29% for emotional abuse, followed by physical abuse (23%), emotional neglect (18%), physical neglect (16%), and sexual abuse (10%; Sethi et al., 2013). Similarly, in Germany, the overall prevalence of at least one subtype of CM was estimated at 31% with physical neglect (22%) being the most prevalent form (emotional neglect 13%; sexual abuse 8%; physical abuse 7%; emotional abuse 7%; Witt et al., 2017). Furthermore, generational effects were observed as 50% of individuals over the age of 70 experienced some form of CM, as compared to 26% in the age group 20-29 years. Overall, the prevalence of CM appears to differ with respect to subtype, sex/gender, age, and region of origin. Additionally, the heterogeneity in reported prevalence might derive from the variety of instruments measuring ACE and CM. This does not only impede generalizability of study results, but further highlights the need to examine and characterize specific populations.

It is well-known, that ACEs relate to a broad range of somatic and mental disorders and are considered a relevant factor for the emergence of such disorders (Gilbert et al., 2009; Heim & Binder, 2012). Somatic consequences of ACE include gastrointestinal, cardiovascular, metabolic, and respiratory diseases, as well as affecting pain, sleep, and function. They might expand to sociobehavioral aspects such as behavioral problems or being a victim of violence, and further encompass reduced mental health, depressiveness, anxiety, suicidal ideations - and illicit substance or alcohol use (Bellis et al., 2019; Dovran et al., 2016; Edwards et al., 2003; Hussey

et al., 2006; Petruccelli et al., 2019; Raabe & Spengler, 2013). Several studies also observed a dose-response relationship between the severity of ACE and increased likelihood of mental problems (e.g., Hughes et al., 2016; Merrick et al., 2017; Pietrek et al., 2013; Weber et al., 2008; Wilker et al., 2015), mental distress (Gilbert et al., 2015), and increased severity of mental health disorders, such as post-traumatic stress disorder (PTSD), borderline personality disorder, or depression (Greeson et al., 2013; Read & Bentall, 2012). Additionally, a relation between ACE and later substance use or SUD has also been observed.

1.4 ACEs and Co-occurring SUDs

Previous research suggests that ACEs are a risk factor in the etiopathology of SUD (Choi et al., 2016; Cutajar et al., 2010; Enoch, 2011; Gilbert et al., 2009; Kirsch et al., 2020; Leza et al., 2021; Moustafa et al., 2021; Schäfer et al., 2016).

However, studies on prevalence rates addressing specific types of SUDs or ACEs are sparse. In the United States, the prevalence of CM in a sample of patients currently in treatment for AUD was estimated at 55% upon conducting the CTQ (31% physical abuse; 24% sexual abuse; 21% emotional abuse; 20% emotional neglect; 20% physical neglect; Huang et al., 2012). In Spain, in a large sample of patients with SUDs (i.e., alcohol, cocaine, cannabis, opiates, or sedatives), 46% reported having experienced some form of abuse during childhood (emotional abuse 39%; physical abuse 22%; sexual abuse 14%; Daigre et al., 2015). Furthermore, these experiences were related to more severe SUD and increased comorbidity. In individuals with opioid use disorder, the prevalence of CM ranged between 43% (emotional abuse) and 16% (sexual abuse) (Santo et al., 2021). While no prevalence estimates are available for Germany for these specific cohorts, individuals with SUD reported higher severity of all five subtypes of CM compared to the general population (Klinitzke et al., 2012; Wingenfeld et al., 2010).

ACEs are not only highly prevalent in SUD. A history of ACE additionally increases the odds for later substance use or SUD (Afifi et al., 2012; Afifi et al., 2020; Anda et al., 2006; Choi et al., 2016; Cutajar et al., 2010; Dube et al., 2006; Pilowsky et al., 2009; Whitesell et al., 2009), associates with the age of onset and severity of SUD (Alvanzo et al., 2020; Oberleitner et al., 2015; Schückher et al., 2018; Schwandt et al., 2013), and hampers treatment success (Schückher et al., 2019).

While the association between ACE and substance use remained stable throughout birth cohorts dating back to 1900 (Dube et al., 2003), having experienced ACE increased the odds

for alcohol and cannabis consumption (e.g., by 2.0 and 2.51 for emotional abuse) in adolescents between 14 and 17 years (Afifi et al., 2020). In adults, experiences, such as parental divorce or living with foster parents, were also related to AUD in later life even when controlling for confounders for instance, sociodemographic aspects or a family history of alcohol problems (Pilowsky et al., 2009). Of note, a similar relation between ACE and increase risk for alcohol use was observed for both men and women (Lee & Chen, 2017). However, race/ethnicity served as a moderator between ACE and heavy drinking risk.

Interestingly, a cumulative effect of the number of ACEs was reported, which was confirmed by other researchers observing a two- to threefold fold increase for early substance consumption after having experienced several types of ACEs (Dube et al., 2006). Furthermore, studies focusing on CM have shown that individuals who experienced sexual abuse in their childhoods had a 5.88 higher risk for AUD and a 5.94 higher risk for SUD in their later lives (Cutajar et al., 2010). The strong relation between childhood sexual abuse and SUD was also observed in an epidemiological twin study, which reported an increase in the odds ratio of up to 3.3 for children affected by any form of sexual abuse, as compared to their non-affected twin (Kendler et al., 2000). Additionally, an increased risk for AUD was also observed regarding physical abuse in men (Choi et al., 2016). As reported for a sample of patients with AUD, the cumulative effect of having experienced CM was also observed regarding the risk for (multiple) comorbid mental disorders or suicide attempts (Huang et al., 2012). Interestingly, the authors reported that emotional abuse significantly predicted comorbid major depressive disorder and PTSD while physical abuse predicted suicide attempts.

In addition to an increased risk for SUD, the cumulative effect of having experienced several types of ACEs also relates to the severity of AUD (Alvanzo et al., 2020). By examining over 35,000 participants, Alvanzo et al. (2020) observed an increased likelihood of progressing from no to severe problem drinking in individuals who had experienced more than three ACEs (odds ratio of 4.78 and 3.81 for men and women, respectively). The authors further reported a decreased likelihood of returning to less problematic drinking in relation to ACE exposure. Regarding specific types of CM, a history of emotional abuse was the strongest predictor for the severity of AUD in treatment-seeking patients with AUD (Schwandt et al., 2013).

Oberleitner et al. (2015) observed an interaction between gender and the history of CM with regards to the timespan between alcohol initiation and the onset of AUD. Women with a history of CM developed an AUD one year earlier than women with no history of CM, as well as compared to men with and without a history of CM. Others reported that emotional abuse,

in particular, was related to an earlier onset of AUD (Schückher et al., 2018). CM also predicted the persistence of alcohol use over the course of three years in individuals with AUD even after controlling for demographic variables and other types of ACE, such as parental divorce (Elliott et al., 2014). Compared to women with no history of CM, women who had experienced CM were less likely to remain abstinent during a 12-month follow-up period after a treatment for AUD (Schückher et al., 2019).

Several mediating and moderating factors contributing to the increased risk of SUD after ACE are discussed in the literature and hint towards specific pathways. In their meta-analyses, Gruhn and Compas (2020) observed a significant impairment of emotion regulation following CM. Emotion dysregulation, in association with CM, has been related to several psychopathologies (Bradley et al., 2011). In children, emotion dysregulation due to neglect or physical and sexual abuse lead to increased externalizing behavior and peer rejection one year later (Kim & Cicchetti, 2010). Altogether, this highlights the role of emotion dysregulation, or the lack thereof, contributing to later psychopathologies, such as SUD.

1.4.1 Emotion Processing and Regulation

Since the late 19th century, the importance of emotion processing has been debated by the likes of Charles Darwin, who theorized that social cognition, interaction, and communication rely on the facial expression of emotions and the interpretation thereof (e.g., Ekman, 2009; Hess & Thibault, 2009). Generally, the perception and understanding of social interactions can be summarized as emotion processing (Frith, 2009). Adding to this, emotion regulation describes either an automatic and incidental or an intentional and effortful process of modifying one's emotional experience (Berkman & Lieberman, 2009; Gross, 2013). Since some argue that impairments in emotion processing might represent one main characteristic of SUD, it seems vitally important to address this aspect here (Le Berre, 2019). Indeed, it is known that deficits in emotion regulation occur in SUD (Oscar-Berman & Bowirrat, 2005; Volkow et al., 2012). Considering alcohol and AUD, inefficient emotion regulation was observed to underlie alcohol craving and consumption in patients with AUD (Petit et al., 2015). In treatment-seeking patients with AUD, impairments in describing feelings as well as identifying and regulating emotions were associated with drinking duration; the amount of alcohol consumed during the most recent heavy drinking episode; and prolonged heavy drinking (Kopera et al., 2015). Berking et al. (2011) reported a predictive value of emotion regulation skills (e.g., modification, acceptance, understanding or tolerating emotions) before treatment for AUD with regards to alcohol use

during treatment. Interestingly, deficits in tolerating negative emotions also predicted alcohol use during the subsequent three months following treatment (Berking et al., 2011) and deficits in emotional processing and social-cognitive functioning impair the initiation and maintenance of alcohol abstinence (Le Berre, 2019). In addition, others reported that impairments in emotion regulation were associated with negative consequences of alcohol use rather than with increased consumption per se (Dvorak et al., 2014). And, in healthy students, the mere expectancy of being able to cope with negative emotions predicted the use of alcohol as a coping strategy in healthy students (Kassel et al., 2000).

It has further been observed, that healthy students consumed alcohol to decrease social anxiety (Battista et al., 2015). Using ecological momentary assessment, Fatseas et al. (2018) observed an association between comorbid mood- and anxiety disorders and increased craving in individuals with SUD, which also seems to influence substance use. Additional findings using ecological momentary assessment supported a relation between stress reactivity and negative affect as well as substance craving (Neupert et al., 2017; Simons et al., 2010; Waters et al., 2020). In line with these findings, ineffective stress-regulation strategies enhanced substance craving in individuals with AUD, alcohol was used as a means to cope with negative feelings (Gąsior et al., 2016). Likewise, alcohol consumption following post-traumatic stress symptoms following rape was mediated by negative affect in a sample of non-treatment seeking women (Cohn et al., 2014).

Following a history of ACE, it seems likely that substance consumption fulfills the role of a coping mechanism, for instance, to deal with negative affect or to regulate stress (Afifi et al., 2012; Hien et al., 2005; Merrick et al., 2017; Rothman et al., 2008; Schmid et al., 2010; Sinha, 2008; Temmen & Crockett, 2020; Vilhena-Churchill & Goldstein, 2014). It has been observed, for example, that emotion dysregulation mediated the relation between childhood emotional and physical maltreatment and subsequent SUD (Wolff et al., 2016). Additionally, mood and anxiety disorders mediate the relation between ACE and SUD to some extent (Douglas et al., 2010). Using ecological momentary assessment, in individuals with both SUD and CM, increased substance use was observed in situations of shame and sadness (Holl et al., 2017). The authors interpreted their observations by hypothesizing that individuals drank alcohol to cope with negative emotions.

Due to the fact that emotion regulation abilities are a mediating factor in the relation between ACE and mental and physical health outcomes, a transdiagnostic approach in diagnosis

and treatment seems promising (Cloitre et al., 2019). While impairments in cognitive reappraisal skills and increased use of negative rumination are known to contribute to psychopathologies (Cludius et al., 2020), underlying causal explanations are still underway.
Endocrine and neurobiological alterations that occur after having experienced ACE might explain these observations (e.g., Andersen et al., 2008; Choi et al., 2016; Dannlowski et al., 2012; Gilbert et al., 2009; Hien et al., 2005; Lloyd & Turner, 2008; Pechtel et al., 2014; Pechtel & Pizzagalli, 2011; Riem et al., 2015; Vilhena-Churchill & Goldstein, 2014; Zorrilla et al., 2014).

1.4.2 Neurobiological Considerations

To date, it has been repeatedly observed that ACEs alter neural reward and stress circuitries and brain regions relevant for cognition or emotion processing (Enoch, 2011; Lee et al., 2018; McCrory et al., 2017). Specifically, function and structure of brain regions, such as the hippocampus, insula, medial prefrontal cortex, and anterior cingulate cortex are affected (Andersen et al., 2008; Ansell et al., 2012; Dannlowski et al., 2012; Herzog & Schmahl, 2018; Holz et al., 2020; Kirsch et al., 2020; McCrory et al., 2017; Pechtel et al., 2014; Riem et al., 2015; Teicher & Samson, 2016; Zhu et al., 2019). Likewise, chronic stress, such as ACE, is known to change amygdala structure, i.e. by remodelling dendrites and synaptic connections and altering neurotransmitter functioning (McEwen et al., 2016; Roozendaal et al., 2009). This leads to, for example, enhanced fear perception and hypersensitivity of corresponding networks, as observed in adolescents with ACE (Hart et al., 2018). In addition to effects on brain regions and networks, ACEs intervene with psychoneuroendocrine functioning, including the HPA axis (Kirsch et al., 2020; Moustafa et al., 2021). For example, chronic low levels of the glucocorticoid cortisol were found in hair samples of healthy adults with a history of ACE (Kalmakis et al., 2015). In this context, the CRH is noteworthy, as it both facilitates an immediate stress response as well as initiates the release of the adrenocorticotropin releasing hormone which, in turn, stimulates secretion of cortisol (Backström & Winberg, 2013; Makino et al., 2002). Interestingly, both the amygdala and hippocampus are sites where glucocorticoid receptors are occupied in case of increased cortisol availability, further providing inhibitory (hippocampus) or excitatory (amygdala) feedback to the HPA axis. In the case of chronic stress experiences, feedback loops of the HPA axis fail to regulate stress reactivity, which may lead to mood or anxiety disorders.

al'Absi et al. (2021) proposed, that ACE leads to a blunted stress reactivity, which then serves as a risk factor for early substance use. This impaired HPA axis functioning and, therefore, stress reactivity affects brain regions such as the nucleus accumbens, hippocampus, and

amygdala. The ensuing early and untimely substance use additionally alters neurobiological functioning, culminating in an increased risk for subsequent SUD. Similarly, Kirsch et al. (2020) summarized in their review that alterations of the HPA axis as well as neural stress, reward, and control circuitries might underlie the increased risk for SUD following ACE. As illustrated in Figure 1, the authors further discussed ACE as a shared risk factor for both SUD as well as mood disorders (Kirsch et al., 2020), as both disorders often co-occur (Grant et al., 2004). Also, ACE-related alterations of neurotransmitter systems, such as dopamine, glucocorticoids, and oxytocin were reported to be risk factors for later SUD (Kim et al., 2017). A moderating effect of genetics and environmental factors was also discussed in previous research (Enoch, 2011; Lee et al., 2018), as the interaction between specific polymorphisms and ACEs as stressors increased the odds for AUD (Keyes et al., 2012). Specifically, S-allele carriers of one serotonin transporter genotype polymorphism (5-HTTLPR) were observed to be at higher risk for early alcohol use (Kaufman et al., 2007).

Negative affect related to alcohol abstinence is one driving factor regarding alcohol craving and relapse (Heilig et al., 2010a; Koob & Volkow, 2010). To this end, several observations have been made in previous research: alterations in neuroplasticity following prolonged alcohol use impair neural responses to and the regulation of negative affect; these deficits remain even after long periods of abstinence (Heilig et al., 2010b). Eliminating an aversive state (i.e., experience of negative affect) by using alcohol becomes a learned behavior through negative reinforcement (i.e., relief craving). Additionally, an increased, stress-related risk for relapse has been postulated, and the amygdala has been suggested to mediate behavioral sensitization to stress (Heilig et al., 2010b). As described above - and besides its relevance with regards to the hypothalamic stress cascade (Backström & Winberg, 2013; Makino et al., 2002) - CRH modulates stress behavior, for instance, in the context of real or perceived social threat, neural targets of action involve the amygdala as well as.

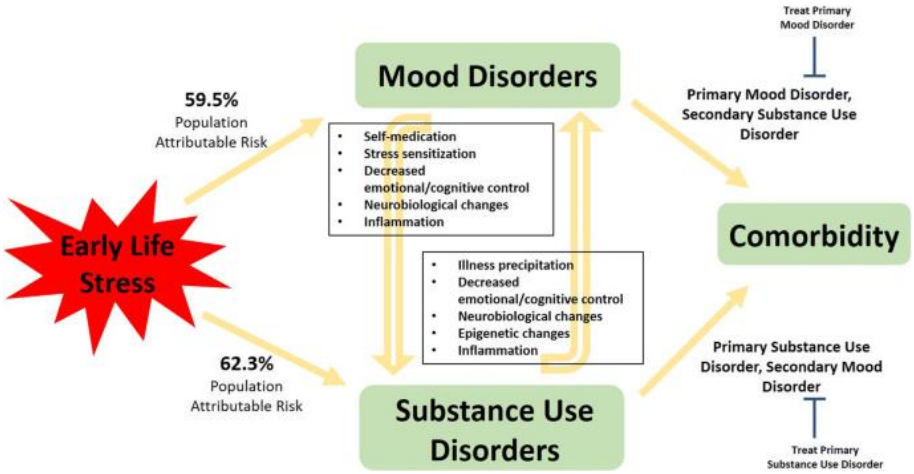


Figure 1: Early life stress, such as adverse childhood experiences, is considered a risk factor for substance use disorder. However, neurobiological changes and impairments in emotional functioning could also contribute to the high comorbidity of mood and substance use disorders. Taken from Kirsch, D., Nemeroff, C. M., and Lippard, E. T. C. (2020). Early Life Stress and Substance Use Disorders: Underlying Neurobiology and Pathways to Adverse Outcomes. Adversity and Resilience Science, 1(1), 29-47 with permission of Springer Nature.

In AUD, CRH receptor functioning relates not only to the experience of anxiety during alcohol withdrawal but also to the sensitized stress response during later stages of the disorder (Heilig et al., 2010b). To this end, some studies merit consideration: in individuals with cocaine use disorder, the interaction of stress-induced craving and CM related to decreased activation of the anterior cingulate cortex, while substance-induced craving in interaction with CM led to increased activation of visual and motor areas (Elton et al., 2015). The authors concluded that CM influences the appetitive anticipatory response to substance-cues, as well as regulatory processes during stress- or cue-induced craving. Furthermore, lifelong experiences of trauma were related to blunted cortisol levels at awakening and increased stress-responsivity of the amygdala (Seo et al., 2019). However, regarding AUD and ACE, previous studies were unable to clearly disentangle the effect of ACE and AUD on alterations of HPA axis functioning when examining individuals with AUD and healthy controls with or without ACE, respectively. It has been discussed that the masking effects of alcohol might conceal those of ACE (Muehlhan et al., 2020). Then again, subjective reports of anxiety were related to having experienced ACEs but not group allocation (AUD versus healthy controls) (Muehlhan et al., 2017). These diverging findings - psychological versus subjective stress responsiveness - hint at deficits in coping mechanisms and might explain the increased risk for relapse in stressful situations.

The aforementioned observations are intriguing because studies on SUD (or prolonged substance use) postulate alterations of brain regions relevant for emotional functioning, cognition, and reward and report sensitization of the brain stress system ,as well as high reactivity to

daily stress – even without considering ACE (Blaine & Sinha, 2017; Dvorak et al., 2014; Enoch, 2011; Koob, 2008; Koob & Volkow, 2010; Koob & Volkow, 2016; Kopera et al., 2015; Oscar-Berman & Bowirrat, 2005). Threatening stimuli, for instance, led to a decrease in activity of the posterior cingulate cortex and ventromedial prefrontal cortex in individuals with AUD (Wilcox et al., 2020). Furthermore, neural activation (anterior cingulate cortex, ventral, and medial prefrontal cortex) in relation to stress hormone levels predicted relapse rates (Sinha et al., 2011). In line with these findings, reduced efficiency of the mesocortico-limbic network was observed in individuals with AUD and associated with impaired processing of emotional stimuli (Dvorak et al., 2014). In long-term abstinent individuals with AUD, as compared to healthy controls, decreased connectivity between the amygdala and regions relevant for emotion and stress processing was observed during a stress task (Wade et al., 2017).

Essentially, the amygdala represents central neural hub that is involved in emotion perception and processing in general; but it also shapes our behavioral and physiological responses to stress, fear, and reward-associated stimuli, in terms of emotion regulation (Banks et al., 2007; Berboth & Morawetz, 2021; Davis & Whalen, 2001; Gilpin et al., 2015; Koob, 2003). In the context of threat, amygdala reactivity further predicts stress vulnerability (Swartz et al., 2015). Besides being involved in fear conditioning, this region also plays a role in stimulus-reward learning (Baxter & Murray, 2002; Everitt et al., 1999). Therefore, the amygdala represents one major region of interest, when considering neurobiological relations between ACE and AUD.

In healthy individuals, decreased activation of the amygdala predicted emotion regulation abilities, which, in turn, were modulated by habitual use of reappraisal strategies and openness to experience (Morawetz et al., 2017a). Furthermore, functional connectivity between prefrontal regions of the brain and regions relevant for emotion evaluation were observed to relate to the successful use of reappraisal strategies (Morawetz et al., 2017b).

In AUD, the amygdala serves as a central mechanism regarding negative affective symptoms; thus, it affects relapse (Centanni et al., 2019). In social drinkers, acute alcohol consumption reduced frontal-amygdala functional coupling in response to both negative and positive emotional faces, indicating altered emotion processing (Gorka et al., 2013). However, in individuals with a family history of AUD, no amygdala activation in response to emotional faces was observed (Glahn et al., 2007). It is noteworthy that in abstinent patients with AUD, amygdala reactivity to alcohol instead of emotional or stressful cues was negatively related to relapse - depending on genetic variations (Jorde et al., 2014). The latter finding is of interest, as is underlines the amygdala's role in the conditioned response to aversive or appetitive stimuli

(Balleine & Killcross, 2006), possibly leading to craving and relapse. This process is further paralleled by increased negative affect within the circular model of SUD, namely during the stage of withdrawal (Koob & Volkow, 2010). This, in turn, promotes a negative reinforcement of continued substance use in a rather impulsive and automated way (Crews & Boettiger, 2009).

Regarding ACE, reduced amygdala reactivity towards negative emotional faces was observed in children at risk for ACE (Taylor et al., 2006). Furthermore, adolescents with a history of ACE exhibited increased reactivity of the amygdala towards conflict-related stimuli as well as impaired emotion regulation (Marusak et al., 2015). Additionally, CM positively related to amygdala activity towards emotional faces in both healthy individuals and those reporting symptoms of depression and anxiety (van Harmelen et al., 2013). Dannlowski et al. (2012) reported an association between CM and hyperreactivity of the amygdala in response to threatening faces in healthy individuals. Summarizing previous studies, a meta-analysis observed hyperreactivity of the amygdala to emotional faces in individuals with a history of CM, which the authors interpreted as a neural basis for impaired emotional functioning following ACE (Hein & Monk, 2017).

Examining differential effects of abuse and neglect, childhood abuse has been related to increased amygdala reactivity to threatening stimuli, whereas neglect related to the activation of a widespread network including regions relevant for social and cognitive processing (Puetz et al., 2020). Interestingly, combined experiences of abuse and neglect resulted in reduced reactivity of the amygdala and further brain regions. Additionally, amygdala-hippocampal connectivity during stress conditions was related to emotional abuse in a healthy community sample (Fan et al., 2015). In adolescents with physical or sexual abuse, McLaughlin et al. (2015) observed hyperreactivity of the salience network (amygdala, putamen, insula) towards negative emotional stimuli. While those individuals were able to downregulate amygdala activity similarly to healthy controls, they relied on a broad network of brain regions relevant for cognitive control, implying an enhanced effort for those adolescents.

Besides amygdala reactivity to specific stimuli, amygdala habituation represents an interesting phenotype and can be regarded as one important mechanism of automatic emotion regulation (Berkman & Lieberman, 2009). Amygdala habituation can be considered a rapid decrease in amygdala reactivity to repeatedly presented stimuli, such as negative emotional faces (Plichta et al., 2014). Considered a mechanism of neuroplasticity, habituation is an everyday process where irrelevant, non-threatening, and repeatedly presented information needs to be filtered in a rapid and adaptive manner (Ramaswami, 2014). This ensures the allocation of

processing resources to where they are actually needed, for instance, for survival. Interestingly, it has been summarized that habituation, as one form of learning, is impaired in several mental disorders and, furthermore, predicts severity of such disorders (McDiarmid et al., 2017).
In adolescents suffering from PTSD following sexual abuse, a strong amygdala reactivity to emotional faces was observed which was followed by rapid amygdala habituation, indicting a neural marker of emotion processing (van den Bulk et al., 2016). Regarding adult traumatic events, PTSD was related to amygdala habituation in response to fearful faces (Kim et al., 2019). However, the association between having experienced CM and PTSD partly mediated these observations. Additionally, Bilek et al. (2019) observed a negative relation between severity of ACE and amygdala habituation.

While examining amygdala activation in the context of aversive stimuli yielded interesting results, reports of amygdala habituation are sparse. As habituation is broadly considered one of the simplest forms of learning - it is even observed in single cell organisms (Dussutour, 2021) - extending this neuroplasticity perspective to SUD and ACEs entails novel perspectives also with regards to possible treatment options.

Altogether, previous findings regarding emotion processing or regulation, and the involvement of stress mechanisms highlight the importance of amygdala functioning in AUD. Adding the societal aspect of ACE as an individual factor altering psychoneuroendocrine stress systems and affecting social interactions as well as emotional processing and regulation, amygdala functionality also represents a research target of interest. In this context, amygdala habituation gains importance.

1.5 Aim and Research Questions

In summary, the aforementioned neurobiological models of SUD, contribute to the understanding of the disorder and might inform treatment approaches. However, this view is limited, as psycho-social factors further contribute to the development and maintenance of SUD. Including the history of ACE - especially regarding specific types of CM – is a promising approach, as it facilitates the development of SUD. Possible pathways thereof include alterations targeting (neurobiological) stress, reward and emotion-processing. Therefore, the overarching goal of this dissertation is to gain a better understanding of this interplay. To this end, two studies will be presented.

The *first study* of this dissertation will shed light on the current status regarding CM in individuals in treatment for SUD, as the prevalence and severity of the five subtypes of CMs

are unknown - especially regarding different types of substances. As outlined above, sex/gender effects will be investigated, as these seem to play an important role. Additionally, current symptoms of depressiveness and anxiety as well as the subjective estimation of perceived stress will be incorporated in the analyses, since mood-and stress-disorders often co-occur in SUD. Lastly, the influence of the specific type of ACE with regards to substance craving will be addressed, as craving is conceived to be one important factor that contributes to treatment outcome and promotes relapse.

Research Questions Study 1:

(1) What is the prevalence and severity of CM in treatment-seeking individuals with SUD?
(2) Do types of SUDs differ with respect to prevalence and severity of CM?
(3) Does the type of CM affect substance craving during treatment?
(4) Do symptoms of stress, depressiveness and anxiety, as well as gender, influence substance craving during treatment?

Hypotheses Study 1:

(1) In individuals with SUD, the prevalence of all forms of CM is higher in individuals with opioid use disorder as compared to all other substances.
(2) The severity of CM is strongest in individuals with opioid use disorder compared to all other substances.
(3) For both prevalence and severity of CM, women are more severely affected than men.
(4) In SUD, the severity of CM is positively associated with the severity of depressive and anxious symptoms, as well as perceived stress.
(5) Emotional abuse followed by physical abuse are predictors for the severity of craving at admission to SUD treatment.
(6) Experiences of emotional abuse and physical abuse hamper the decrease in substance craving during SUD treatment.
(7) Sex/Gender and type of SUD exert an influence regarding hypotheses 5 and 6; however, ages does not.

The *second study* of this dissertation will examine neural habituation of the amygdala towards aversive emotional stimuli, as this region represents a hub involved in emotion perception and processing, and the regulation thereof. Previous studies observed deficits in such processes,

which were derived from a history of CM and affect amygdala functionality. Additionally, impairments were also observed in SUD and previous studies suggest that amygdala functioning is vastly involved during intermediate and later stages of the development of SUD. As AUD represents the largest share of individuals with SUD, individuals with varying severity of AUD and CM will be included in this neuroimaging study.

Research Questions Study 2:

(1) Does neural habituation of the amygdala to aversive emotional stimuli differ between individuals with AUD and healthy controls?
(2) Does CM influence this phenotype?

Hypotheses Study 2:

(1) Amygdala habituation to aversive emotional stimuli is reduced in individuals with AUD, as compared to healthy controls.
(2) Amygdala habituation is related to the severity of CM in individuals with AUD.

The dissertation will be concluded by a discussion of the findings of both studies and clinical implications will be elaborated. Lastly, an outlook on future research that might build upon the current studies will be provided.

2 STUDY 1: A HISTORY OF CHILDHOOD MALTREATMENT HAS SUBSTANCE- AND SEX-SPECIFIC EFFECTS ON CRAVING DURING TREATMENT FOR SUBSTANCE USE DISORDERS

An adapted version of this chapter has been published as "Gerhardt, S., Eidenmueller, K., Hoffmann, S., Bekier, N. K., Bach, P., Hermann, D., Koop-mann, A., Sommer, W.H., Kiefer, F., Vollstädt-Klein, S. (2022). A History of Childhood Maltreatment has Substance- and Sex-specific Effects on Craving during Treatment for Sub-stance Use Disorders. Frontier in Psychiatry, 13, 866019."

2.1 Abstract

Rationale: Childhood maltreatment (CM) leads to detrimental mental health outcomes, such as substance use disorders (SUD). This study examined prevalence and severity of all five types of CM with respect to specific substances and sex in treatment-seeking individuals with SUD. The influences of type of CM and symptoms of depressiveness, anxiety, and perceived stress on substance craving at admission as well as craving reduction during SUD treatment were examined.

Methods: N = 546 patients in treatment for SUD and N = 109 individuals in opioid maintenance treatment filled out questionnaires regarding CM (Childhood Trauma Questionnaire) and psychopathologies. Substance craving was assessed throughout treatment using the Mannheim Craving Scale. Group differences in CM, type of substance and sex were examined. General linear models were applied to examine influences on substance craving.

Results: Higher prevalence and severity of all five subtypes of CM were observed in individuals with SUD compared to the general population. Women were more severely affected by emotional and sexual abuse than men. Patients with cannabis use disorder reported more severe experiences of emotional abuse compared to all other substances. Craving at admission to treatment was influenced by emotional abuse, however, symptoms of depressiveness, anxiety, and perceived stress contributed to craving at admission or craving reduction during treatment.

Conclusion: CM relates to SUD and should be incorporated in prevention and treatment of SUD. Underlying mechanisms of the association might relate to impairments in processing and regulation of stress, emotions, and interpersonal relations following a history of CM.

2.2 Introduction

A variety of studies examined the consequences of adverse childhood experiences (ACE) that are related to the development of somatic and mental disorders (Gilbert et al., 2009). ACE are defined as household dysfunction but also childhood maltreatment (CM; Brown et al., 2009; Negriff, 2020). Specifically, CM is operationalized as emotional, physical, and sexual abuse as well as emotional and physical neglect (Teicher & Samson, 2013). A history of CM is related to the age of onset and severity of subsequent mental disorders, and reduces treatment response (Heim & Binder, 2012; Hughes et al., 2016; Hussey et al., 2006; Moustafa et al., 2021; Raabe & Spengler, 2013; Teicher & Samson, 2013).

In Europe, high prevalence rates of CM have been reported for the general population: 29.1% for emotional abuse, 22.9% for physical abuse, 13.4% (female) and 5.7% (male) for sexual abuse, 16.3% for physical neglect and 18.4% for emotional neglect (Sethi et al., 2013). Figures for Germany are comparable, between 6.5% for at least moderate emotional abuse and 22.4% for at least moderate physical neglect (Witt et al., 2017).

A history of CM is frequently observed in individuals with substance use disorders (SUD) (Choi et al., 2016; Cutajar et al., 2010; Hägele et al., 2014; Santo et al., 2021; Schafer et al., 2017). It increases the risk of developing a SUD (Afifi et al., 2020; Anda et al., 2006; Cutajar et al., 2010; Kirsch et al., 2020), and this extends also to non-substance use disorders such as problematic and pathological gambling (Felsher et al., 2010; Poole et al., 2017). Compared to the general population in Germany (Klinitzke et al., 2012), individuals with SUD have experienced more severe forms of CM (Wingenfeld et al., 2010). For example, the prevalence in individuals with opioid use disorder (OUD) ranges between 16% for sexual abuse in men and 43% for emotional abuse (Santo et al., 2021).

Since prevalence number of SUD and relapse rates after SUD treatment are high (e.g., Andersson et al., 2019; Moos & Moos, 2006; Peacock et al., 2018), examining factors contributing to the development and maintenance of SUD are still of importance. A stable, mostly correlational, relation has been observed between CM and different kinds of SUD even after correction for comorbid psychiatric disorders and sociodemographic variables (Afifi et al., 2012). The age of drinking onset was one year earlier in individuals with CM (Oberleitner et al., 2015). Furthermore, exposure to several CM predicted SUD in young adults, irrespectively of sociodemographic variables (e.g. sex or culture) and after controlling for prior mental disorders (Turner & Lloyd, 2003). Similarly, a cumulative effect of the number of types of CM

events was observed regarding the severity of alcohol use disorder (AUD) (Alvanzo et al., 2020). Regarding all five sub-types of CM, emotional abuse is the strongest predictor for the severity of AUD, followed by physical abuse (Schwandt et al., 2013). Further, women with CM, compared to women without CM or men, were observed to have a shorter timespan between onset of drinking and AUD and lower rates of abstinence after AUD treatment were associated with CM (Oberleitner et al., 2015; Schückher et al., 2018). Contributing to this relation, it has been observed, that the association between cumulative CM and SUD was partly mediated by mood- and anxiety disorders that preceded SUD (Douglas et al., 2010).

Besides CM being associated with SUD, substance craving contributes to relapse (Paliwal et al., 2008; Schneekloth et al., 2012; Stohs et al., 2019; Tsui et al., 2014) and, thus, maintenance of the disorder. Further, an effect of stress on substance craving was observed for methadone (Ilgen et al., 2008), cocaine (Sinha et al., 1999), or alcohol (Clay et al., 2018), possibly linking CM, if seen as early life stress, to craving and relapse (Berhe et al., 2021).

Despite the above-mentioned impact of CM on characteristics of SUD, to our knowledge no study examined CM in individuals seeking treatment for SUD while directly comparing different SUDs, investigating sex effects, or addressing the influence of the type of CM on substance craving.

Within the current project we hypothesized that (1) in individuals with SUD, prevalence of all forms of CM is higher in individuals with OUD compared to all other substances; that (2) the severity of CM is strongest in individuals with OUD compared to all other substances. For both (1) and (2) women are more severely affected than men. We further hypothesize that (3) in SUD, the severity of CM is positively associated to the severity of depressive and anxious symptoms, and perceived stress; that (4) emotional abuse followed by physical abuse are predictors for the severity of craving at admission to SUD treatment; and that (5) experiences of emotional abuse and physical abuse hamper the decrease of substance craving during SUD treatment while sex and type of SUD but not age exert an effect on the latter two relationships (hypotheses 4 and 5).

2.3 Materials and Methods

2.3.1 Procedure and Participants

The aggregated dataset (N = 655 individuals) derives from two sources. Firstly, between 2016 and 2020, individuals with different kinds of SUD (N = 546, sample 1) participated in a questionnaire-based examination during their treatment in the Clinic of Addictive Behaviour

and Addiction Medicine, Central Institute of Mental Health, Mannheim, Germany. In either an inpatient or a day care setting they received a detoxification and a psychological SUD-related treatment including motivational and cognitive behavioral elements with the goal of continuous abstinence (Mann et al., 2006). SUD patients filled out several questionnaires at admission and once weekly during the treatment period of 24 ± 9.7 days. In case of repeated admissions during the data collection period of 2016 and 2020, the most recent admission time point was chosen. Diagnoses of substance addiction and additional comorbid mental disorders were made by trained medical staff following the International Classification of Diseases, (ICD-10). Regarding SUD as described in the DSM-5 (Diagnostic and statistical manual of mental disorders, 5th version) (American Psychiatric Association (APA), 2013), substance addiction corresponds to moderate to severe SUD (Dawson et al., 2013).

Secondly, data (N = 109, sample 2) from a research project including outpatients of the opioid maintenance treatment (OMT) of the Central Institute of Mental Health, Mannheim, were included to enrich the first dataset with individuals suffering from OUD. Data collection and diagnostic procedures also were performed by trained medical staff and a senior psychiatrist. A study description of sample 2 has previously been published (Eidenmueller et al., 2021).

For all individuals (samples 1 and 2), general inclusion criteria were: age over 18 years, sufficient knowledge of the German language (oral and in writing), main diagnosis of SUD and availability of data regarding the CM. Please see Supplementary Figure S5 for details of the data collection, preparation and allocation process.

The local Ethics Committee of the Medical Faculty Mannheim, Heidelberg University, Germany, approved the here presented study procedures (approval number 2018-531N-MA and 2018-807R-MA). Information for the first dataset (sample 1) was collected during the patients' inpatient treatment for clinical purpose and later used for retrospective analyses. Following the recommendation of the ethics committee to protect data privacy the data set was anonymized. Regarding the second dataset (sample 2), in accordance with the Declaration of Helsinki, all participants provided written informed consent prior to study participation.

2.3.2 Measures

As the focus of this study, all five sub-types of CM, namely emotional, physical, and sexual abuse as well as emotional and physical neglect, were assessed retrospectively using the reliable (0.87 < alpha < 0.95) Childhood Trauma Questionnaire (CTQ), a previously validated self-report questionnaire that addresses the childhood up to the age of 18 years (Bernstein et al.,

2003). All items of the German version were answered on a 5-point Likert scale (‘not at all’ to ‘very often’) leading to sum scores between 5 (no CM) and 25 (severe form of CM) for each subscale, respectively (Wingenfeld et al., 2010). As reported by others (Bernstein et al., 1994; Häuser et al., 2011; Witt et al., 2017), the severity of each subscale of CM was additionally described by aggregating the CTQ score for each subscale separately into none-minimal, minimal-moderate, moderate-severe and severe-extreme. Further, prevalence was calculated following Witt et al. (2017). To do so, all subscales of the CTQ were dichotomized into ‘having experienced this form of CM’ including moderate to extreme CM and ‘not having experienced this form of CM’ including none to moderate CM. The number of overall CM was calculated by summing up affirmed, dichotomized CTQ subscales.

To characterize sample 1 (N = 546), besides assessing the main diagnosis of SUD and sociodemographic variables (e.g., age, gender, employment, marital status, education), additional questionnaires were administered. The CTQ, Perceived Stress Scale (PSS; Cohen et al., 1983), and Fagerstroem Test for Nicotine Dependence (FTND; Heatherton et al., 1991) were administered only once, at least one week after admission. The Beck Depression Inventory (BDI; Beck et al., 1961; Kühner et al., 2007), Beck Anxiety Inventory (BAI; Beck & Steer, 1988), and Mannheimer Craving Scale (MACS; Nakovics et al., 2009) were administered at admission and every seven days during treatment. The MACS retrospectively measures overall craving during the last seven days independent of the substance and has shown to be highly reliable ($0.87 < \text{alpha} < 0.93$). MACS was applied at admission, after one and two weeks (at T01, T07, T14), respectively. The reduction of craving after two weeks as the difference T01 minus T14 was used to address the course of the treatment. Regarding sample 2 of N = 109 OMT individuals, the same sociodemographic variables were assessed and the CTQ was administered.

2.3.3 Analyses and Statistics

The main SUD diagnosis was grouped into six categories: alcohol use disorder (AUD), cannabis use disorder (CUD), cocaine and stimulant use disorder (CSUD), sedative, hypnotics, or anxiolytic use disorders (SHA), opioid use disorder (OUD, sample 1 only), and opioid use disorder during opioid maintenance (OMT; sample 2 only). OMT and OUD samples were compared using independent samples t-tests and chi-square tests including available data for both samples to justify merging both data sets (sample 1 and 2, OUD+OMT) analyses including the CTQ (see Supplementary Material).

A sample description was created, and group differences were examined using analyses of variance (ANOVA) or Welch-Test for continuous data, and chi-square tests for dichotomous data. Post-hoc tests included Tukey or Games-Howell tests for ANOVAs and Welch-Tests. Adjusted z-scores and a transformation into p-values were performed using chi-square tests according to García-pérez and Núñez-antón (2003). Further, the total number of additional SUD diagnoses and a dichotomous item on comorbid mental disorders (yes/no) were calculated. Relevant clinical variables (i.e., CM, substance craving, and symptoms of depressiveness or anxiety, perceived stress) were correlated pairwise (Pearson correlation) to assess bi-directional relations within the overall sample and separated by sex. General linear models (GLM, univariate) were used to assess the influences of CM and clinical variables (i.e., symptoms of depressiveness or anxiety, perceived stress) as well as sociodemographic variables (i.e., age, sex) on the SUD outcome (i.e., substance craving at admission, reduction of craving over the first two weeks of treatment). Descriptive and statistical analyses were performed in SPSS (Statistics for Windows, Version 27.0. IBM Corp., Armonk, NY, USA). To counteract multiple testing problems and following Storey (2002) false discovery rate (FDR) using the Benjamini and Hochberg method was applied when adequate and results were reported when surviving the correction ($p < 0.05$).

2.4 Results

2.4.1 Sample Composition

Out of N = 1,599 data sets, N = 804 data sets with information regarding the CTQ questionnaire (50%) were available. After excluding duplicate data sets due to readmission (N = 78) and individuals without a main diagnosis of SUD (N = 72), N = 655 data sets were available for subsequent analyses (41%), see flow-chart in the Supplementary Material. Between January 2016 and December 2020, N = 655 individuals provided information regarding the CTQ and additional questionnaires. Data were collected from the day care clinic (N = 391), the inpatient treatment (N = 136) and the outpatient opioid maintenance program (N = 109).

Participants were between 18 and 86 years of age (mean = 42.0 ± 13.0). They were mostly male (73.3%), single (51.0%) and had no children (40.9%). They received primary and secondary education of 12.8 years, but more than half were currently not steadily employed (57.4%). The majority of participants were tobacco smokers (74.8%). In sample 1, 66.7% (N = 364) were diagnosed with AUD as the main diagnosis, 21.6% (N = 118) with CUD, 7.8% (N = 43) with CSUD, 2.2% (N = 12) with SHA, and 1.6% (N = 9) with OUD, respectively. Sociodemographic

and clinical variables differed between substance groups. See Table 1 and Table 2 for more details regarding sociodemographic and clinical information.

2.4.2 Prevalence and severity for all sub-types of CM with respect to different kinds of SUD

Over all substances, prevalence rates of CM were 19.1% for sexual abuse, 19.8% for physical abuse, 24.7% for emotional abuse, 54.7% for physical neglect, and 67.9% for emotional neglect. Individuals with SUD experienced on average 1.90 (1.46) of five types CM, and significant group differences between substances emerged ($F(4, 540) = 4.48$, $p = 0.001$). Post-hoc tests indicated a significant difference in the number of CM between AUD (on average 1.71 (1.42) CM) and CUD (on average 2.38 (1.44) CM).

Within the overall sample, severity of CM (mean of sum scores (standard deviation)) resulted in 6.2 (3.5) for sexual abuse, 7.7 (4.4) for physical abuse, 8.8 (3.6) for physical neglect, 10.0 (5.4) for emotional abuse, and 13.2 (5.7) for emotional neglect. Significant group differences with respect to the main diagnosis were observed for emotional abuse ($F(4, 622) = 14.29$, $p < 0.001$) and physical abuse ($F(4, 52.5) = 5.09$, $p = 0.001$). Post-hoc tests indicated significantly more severe experience of emotional abuse for CUD compared to AUD and OUD, and, additionally, of emotional neglect for CUD compared to AUD. See Table 3 for details regarding prevalence for and severity of specific subtypes of CM in different substances.

2.4.3 Sex differences in prevalence and severity of CM

Over all substances, females in comparison to males reported significantly more often having experienced emotional abuse ($\chi^2(1) = 26.31$, $p < 0.001$), physical abuse ($\chi^2(1) = 9.19$, $p = 0.002$) and sexual abuse ($\chi^2(1) = 37.71$, $p < 0.001$), but not emotional neglect ($\chi^2(1) = 0.46$, $p = 0.423$) or physical neglect ($\chi^2(1) = 1.66$, $p = 0.197$). Depending on the main diagnosis, significant sex differences to the detriment of women became apparent for alcohol and emotional abuse ($\chi^2(1) = 14.45$, $p < 0.001$), alcohol and physical abuse ($\chi^2(1) = 7.09$, $p = 0.008$), alcohol and sexual abuse ($\chi^2(1) = 12.38$, $p < 0.001$), cannabis and emotional abuse ($\chi^2(1) = 7.28$, $p = 0.007$), cannabis and physical abuse ($\chi^2(1) = 5.94$, $p = 0.015$), cannabis and sexual abuse ($\chi^2(1) = 11.15$, $p = 0.001$) and opioids and sexual abuse ($\chi^2(1) = 9.09$, $p = 0.003$).

Over all substances, females reported more severe experiences of CM compared to men, resulting in significant sex differences for emotional abuse ($t(242.3) = -4.14$, $p < 0.001$) and sexual abuse ($t(196.3) = -4.46$, $p < 0.001$; Figure 2). Sex differences regarding emotional neglect ($t(628) = -2.16$, $p = 0.034$) did not survive correction for multiple testing. Within each

Table 1: Sociodemographic data of the overall sample. Mean values (standard deviation) or percentage values are displayed. Group differences are highlighted.

	AUD	CUD	CSUD	SHA	OUD + OMT	Descriptive Statistics
N	364 (55.6 %)	118 (18.0 %)	43 (6.6 %)	12 (1.8 %)	118 (18.0 %)	655
Age	**47.23 (12.66)[1,2,3]**	**28.6 (7.5)[1,4,5,6]**	**33.3 (7.2)[2,4,7,8]**	**42.9 (9.7)[5,7]**	**42.1 (8.1) [3,6,8]**	**F(4, 68.6) = 103.59, p < .001**
Gender (male, %)	74.2	73.7	74.4	58.3	71.2	$\chi^2(4) = 0.90, p = .824$
Family status (single yes, %)	37.6	78.0	69.8	50.0	65.7	**$\chi^2(4) = 69.30, p < .001$[a]**
Children (yes, %)	42.0	22.9	32.6	28.6	46.5	$\chi^2(4) = 16.38, p < .001$[a]
Years of education	**13.5 (2.7)[1,2,3]**	**12.4 (2.6)[1,4]**	**12.2 (2.6)[2]**	13.8 (2.9)	**11.3 (2.4)[3,4]**	**F(4, 561) = 14.90, p < .001**
Employed (yes, %)	36.8	31.4	23.3	22.2	19.7	**$\chi^2(4) = 22.60, p < .001$[a]**

Note: n = total sample size; AUD = Alcohol Use Disorder; CSUD = Cocaine and Stimulant Use Disorders; CUD = Cannabis Use Disorder; SHA = Sedative, Hypnotics, or Anxiolytic use disorders; OUD+OMT = Opioid Use Disorders + Opioid Maintenance Treatment. [1,2,3,4,5,6,7,8]Superscripted numbers describe significant group differences following post-hoc tests. [a]Following post-hoc testing including correction for multiple comparison, no statistically significant group-differences emerged.

Table 2: Clinical data of sample 1. Mean values (standard deviation) or percentage values are displayed for the clinical sample only. Group differences are highlighted.

Sample 1	**AUD**	**CUD**	**CSUD**	**SHA**	**OUD**	**Descriptive Statistics**
N	364	118	43	12	9	546
Type of stay (inpatient:day care-clinic, %)	26.9:73.1	21.2:78.8	20.9:79.1	58.3:41.7	44.4:55.6	**$\chi^2(4) = 9.70$, p = .021[a]**
Mental comorbidities, current (yes, %)	47.5	51.7	48.8	66.7	88.9	$\chi^2(4) = 7.72$, p = .103
Mental comorbidities, lifetime (yes, %)	56.6	56.8	55.8	75.0	88.9	$\chi^2(4) = 5.33$, p = .255
Total number of SUD, current	**1.8 (0.9)[1,2]**	**2.5 (1.0)[1]**	**2.7 (1.2)[2]**	2.8 (1.3)	3.1 (1.4)	**F(4, 33.4) = 14.94, p < .000**
Total number of SUD, lifetime	**2.0 (1.0)[1,2]**	**2.7 (1.1)[1]**	**3.2 (1.4)[2]**	2.8 (1.5)	3.1 (1.4)	**F(4, 33.5) = 14.87, p < .001**
Smokers (yes, %)	59.6	79.7	65.1	75.0	93.2	**$\chi^2(4) = 54.62$, p < .001[a]**
FTND of smokers[b]	5.3 (2.4)	4.9 (2.2)	5.3 (2.0)	5.0 (1.8)	5.6 (1.4)	F(4, 359) = 0.494, p = .740
BDI at admission	**18.9 (11.8)[1]**	**25.2 (12.0)[1]**	21.1 (11.5)	29.2 (10.2)	25.2 (12.0)	**F(4, 466) = 6.94, p < .001**
BAI at admission	**16.9 (13.0)[1]**	19.4 (13.0)	**15.9 (10.2)[2]**	**31.5 (11.0)[1,2]**	19.4 (13.0)	**F(4, 459) = 3.49, p = .008**
PSS[b]	**20.8 (6.3)[1]**	**23.5 (5.4)[1]**	22.5 (5.8)	24.4 (5.4)	23.5 (5.4)	**F(4, 406) = 4.08, p = .003**
MACS at admission	**16.6 (9.8)[1,2]**	**20.4 (10.2)[1]**	**21.0 (9.4)[2]**	25.0 (8.9)	19.8 (7.7)	**F(4, 467) = 5.27, p < .001**

Note: n = sample size; AUD = Alcohol Use Disorder; BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CSUD = Cocaine and Stimulant Use Disorders; CUD = Cannabis Use Disorder; FTND = Fagerstroem Test for Nicotine Dependence; MACS = Mannheimer Craving Scale; SHA = Sedative, Hypnotics, or Anxiolytic use disorders; SUD = Substance Use Disorder; OUD = Opioid Use Disorders; PSS = Perceived Stress Scale. [1,2]Superscripted numbers describe significant group differences following post-hoc tests. [a]Following post-hoc testing including correction for multiple comparison, no statistically significant group-differences emerged. [b]Only administered once.

Table 3: Severity of childhood maltreatment. Mean values (standard deviation) or percentage values are displayed. Group differences are highlighted in bold.

	AUD	**CUD**	**CSUD**	**SHA**	**OUD+OMT**	**Statistics**
N	364	118	43	12	118	655
CTQ sum score	**43.2 (16.6)[1]**	**51.4 (17.5)[1]**	43.7 (15.2)	42.6 (13.7)	46.9 (17.7)	**F(4, 539) = 4.96, p = .001**
Number of types of CM	**1.71 (1.42)[1]**	**2.38 (1.44)[1]**	1.70 (1.41)	1.71 (1.98)	1.99 (1.48)	**F(4, 540) = 4.48, p = .001**
CTQ emotional abuse	**9.2 (5.2)[1]**	**12.8 (6.0)[1,2]**	10.4 (5.2)	9.4 (3.9)	**9.5 (4.7)[2]**	**F(4, 622) = 14.29, p < .001**
Prevalence (yes, %)	19 %	47 %	28 %	25 %	19 %	**χ^2(4) = 35.18, p < .001[a]**
CTQ emotional neglect	12.7 (5.6)[1]	14.5 (5.6)[1]	13.0 (6.1)	12.7 (5.7)	13.5 (5.9)	F(4, 625) = 2.16, p = .072
Prevalence (yes, %)	65 %	78 %	62 %	50 %	70 %	χ^2(4) = 6.48, p = .166
CTQ physical abuse	7.3 (4.0)	**8.2 (5.6)[1]**	7.9 (4.3)	**6.0 (1.5)[1,2]**	**8.7 (5.2)[2]**	**F(4, 52.5) = 5.09, p = .001**
Prevalence (yes, %)	16 %	24 %	26 %	8 %	27 %	**χ^2(4) = 10.58, p = .032[a]**
CTQ physical neglect	8.7 (3.4)	9.2 (4.0)	8.0 (3.1)	8.6 (2.8)	9.1 (3.8)	F(3, 627) = 1.37, p = .241
Prevalence (yes, %)	54 %	58 %	47 %	50 %	56 %	χ^2(4) = 2.413, p = .660
CTQ sexual abuse	6.0 (3.3)	6.6 (4.0)	5.5 (1.5)	6.5 (3.7)	6.7 (4.0)	F(4, 617) = 1.72, p = .144
Prevalence (yes, %)	15 %	28 %	12 %	25 %	25 %	**χ^2(4) = 13.093, p = .011[a]**

Note: n = sample size; AUD = Alcohol Use Disorder; CSUD = Cocaine and Stimulant Use Disorders; CTQ = Childhood Trauma Questionnaire; CUD = Cannabis Use Disorder; SHA = Sedative, Hypnotics, or Anxiolytic use disorders; OUD = Opioids Use Disorders + Opioid Maintenance Treatment. Prevalence numbers and the number of types of CM are reported for the dichotomized item 'having experiences CM' coding 'yes' for at least moderate experience of the respective subscale of CM. [1,2]Superscripted numbers describe significant group differences following post-hoc tests. [a]Following post-hoc testing including correction for multiple comparison, no statistically significant group-differences emerged.

main diagnosis, significant sex differences to the detriment of women became apparent following two-sided t-tests for alcohol and emotional abuse (t(123.0) = -3.05, p = 0.003), alcohol and sexual abuse (t(100.75) = -2.77, p = 0.007), alcohol and emotional neglect (t(155.49) = -2.24, p = 0.026), cannabis and emotional abuse (t(46.50) = -3.31, p = 0.002) and cannabis and sexual abuse (t(33.40) = 2.54, p < 0.001). Sex differences for physical neglect in individuals with CUD (t(38.22) = -2.24, p = 0.031) did not survive correction for multiple testing. See Figure 3 for more details.

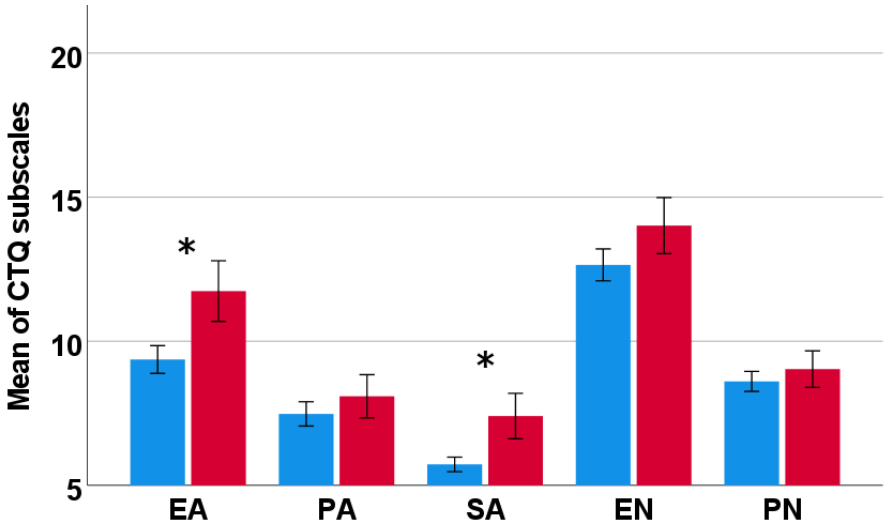


Figure 2: Significant sex differences for the overall sample regarding mean values of the sum scores per subscale of the CTQ. Females (red) reported significantly more severe CM for emotional and sexual abuse than males (blue). CTQ = Childhood Trauma Questionnaire.

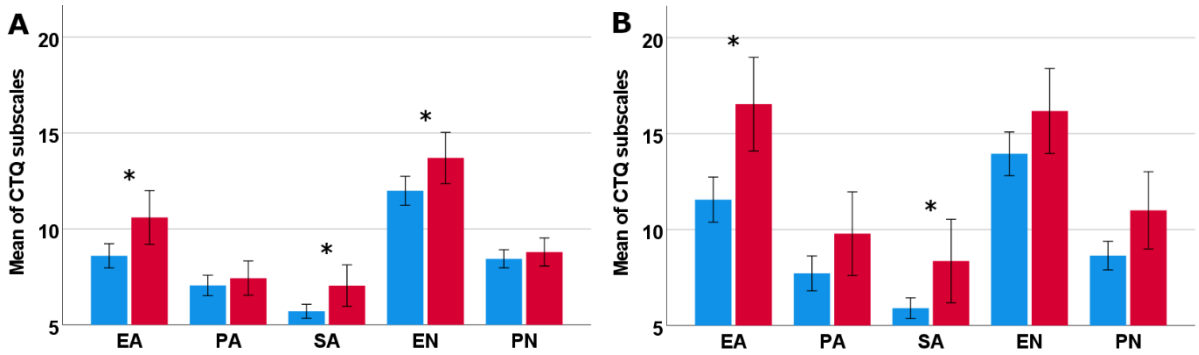


Figure 3: Significant sex differences for the main diagnoses AUD (left) and CUD (right) regarding mean values of the sum scores per subscale of the CTQ. A: In AUD (left), females (red) reported significantly more severe CM for emotional and sexual abuse, and emotional neglect. B: In CUD (right), females (red) reported significantly more severe CM for emotional and sexual abuse. CTQ = Childhood Trauma Questionnaire; EA = Emotional Abuse; PA = Physical Abuse, SA = Sexual Abuse, EN = Emotional Neglect; PN = Physical Neglect. Error bars are displayed at a 95-% confidence interval.

2.4.4 Severity of CM in relation to symptoms of anxiety, depressiveness and perceived stress in the overall patient sample

Statistically significant positive correlations between the severity of CM (CTQ sum score) and affective symptoms were observed in the overall sample. A positive correlation between the severity of CM and BDI sum score at admission was observed for males and females (males $r = 0.241$, $p < 0.001$; females $r = 0.251$, $p = 0.012$). The correlation between severity of CM and BAI sum score at admission and PSS sum score were significant for males (BAI $r = 0.248$, $p < 0.001$; PSS $r = 0.207$, $p = 0.012$), but not females (BAI $r = 0.188$, $p = 0.062$; PSS $r = 0.044$, $p = 0.679$). See Figure 4 and Table 4 for more details.

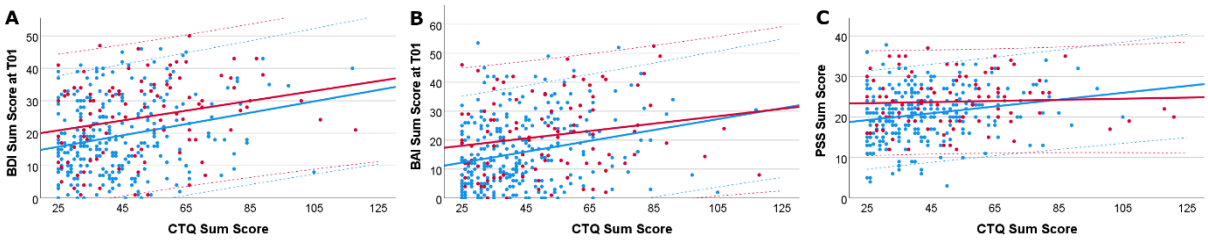


Figure 4: Correlation between CTQ sum score and A: depressiveness (BDI), B: anxiety (BAI) and C: perceived stress (PSS). In males (blue), a significant positive correlation was observed for all three clinical variables. In women (red), a significant positive correlation was observed only for depressiveness. BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CTQ = Childhood Trauma Questionnaire; PSS = Perceived Stress Scale. Dotted lines indicate 95-% confidence intervals.

2.4.5 The influences of different types of CM on substance craving at admission with respect to main diagnosis and sex

Craving at T01 (MACS T01) differed statistically significant for the different substance groups ($F(4, 381) = 2.622$, $p = 0.035$, $\eta^2 = 0.027$), and sex ($F(1, 381) = 6.771$, $p = 0.010$, $\eta^2 = 0.017$) after adjusting for all five subscores of the CTQ and age. Severity of emotional abuse ($F(1, 381) = 17.353$, $p < 0.001$, $\eta^2 = 0.044$) but none of the other subscales of CM or age did show a significant influence. After adjusting for before-mentioned covariates, Bonferroni-corrected post-hoc tests revealed significantly more severe craving for women ($p = 0.010$, MDiff = 2.92, 95%-CI[0.71, 5.12]). Post-hoc tests regarding substance group did not yield significant results following Bonferroni correction.

Table 4: Severity of childhood maltreatment in relation to symptoms of anxiety, depressiveness, and perceived stress for the overall patient group, and separately by sex. Pearson correlation coefficients, p-values (2-sided), and power estimates are displayed. Significant correlations are highlighted in bold.

CTQ	**BDI T01**	**BAI T01**	**PSS**
	Corr. Coeff. | p-value | 1−β | N	Corr. Coeff. | p-value | 1−β | N	Corr. Coeff. | p-value | 1−β | N
All	**0.277 | < 0.001 | > 0.9999 | 391**	**0.259 | < 0.001 | > 0.9961 | 388**	**0.191 | < 0.001 | > 0.8393 | 351**
Males	**0.241 | < 0.001 | > 0.9023 | 291**	**0.248 | < 0.001 | > 0.8981 | 288**	**0.207 | < 0.001 | > 0.8641 | 261**
Females	**0.251 | < 0.012 | > 0.3254 | 100**	0.188 | > 0.062 | - | 100	0.044 | < 0.679 | - | 90

Note: BAI = Beck Anxiety Inventory; BDI = Beck Depression Inventory; CTQ = Childhood Trauma Questionnaire, sum score; PSS = Perceived Stress Scale. All significant results survived correction for multiple testing ($p > 0.05$). Post-hoc power calculations were performed in G*Power (Faul et al., 2007).

After adjusting for all five subscores of the CTQ and age but also PSS, BDI (T01) and BAI (T01) sum scores, craving at T01 (MACS T01) did no longer differ statistically significant between the different substance groups ($F(4, 282) = 2.516$, $p = 0.107$, $\eta^2 = 0.027$) or sex ($F(1, 282) = 2.516$, $p = 0.114$, $\eta^2 = 0.009$). Severity of emotional abuse ($F(1, 282) = 1.282$, $p = 0.258$, $\eta^2 = 0.005$) did no longer show a significant influence, neither did the PSS sum score ($F(1, 282) = 0.735$, $p = 0.392$, $\eta^2 = 0.003$). BDI and BAI sum scores at admission, however, did show a significant influence ($F(1, 282) = 43.637$, $p < 0.001$, $\eta^2 = 0.134$; $F(1, 282) = 15.360$, $p < 0.001$, $\eta^2 = 0.052$).

2.4.6 The influences of different types of CM on the reduction of substance craving during the first two weeks of treatment with respect to main diagnosis and sex

Over all substances, craving diminished from 18.0 (10.0) at T01 to 11.0 (8.3) at T14 in the MACS questionnaire. However, no significant effect of substance group ($F(4, 306) = 0.836$, $p = 0.503$, $\eta^2 = 0.011$) or sex ($F(1, 306) = 3.516$, $p = 0.062$, $\eta^2 = 0.011$) was observed after adjusting for age and all five subscores of CM. There was no significant influence regarding all subscores of CM. Including PSS, BDI (T01) and BAI (T01), no significant effect of substance group ($F(4, 282) = 0.341$, $p = 0.850$, $\eta^2 = 0.005$) or sex ($F(1, 282) = 0.513$, $p = 0.475$, $\eta^2 = 0.002$) did emerge either. However, PSS and BDI (T01) sum scores excerpted a significant influence ($F(1, 282) = 14.433$, $p < 0.001$, $\eta^2 = 0.049$; $F(1, 282) = 21.050$, $p < .001$, $\eta^2 = 0.069$), so did age ($F(1, 282) = 5.095$, $p = 0.025$, $\eta^2 = 0.018$), but not the BAI (T01) sum score ($F(1, 282) = 2.807$, $p = 0.095$, $\eta^2 = 0.010$).

2.5 Discussion

To our knowledge, this study is the first to examine a broad range of CM, namely emotional and physical abuse, emotional and physical neglect as well as sexual abuse in patients undergoing treatment for SUD while including several substances, such as alcohol, cannabis, cocaine and stimulant, opioid and sedative use disorders. The most salient finding of the present study was the high prevalence and severity of experienced CM in patients with CUD compared to other SUDs and especially compared to AUD. This study expands previous work on the relevance of psychosocial and biographical aspects regarding SUD.

The association between CM and SUD is well known in literature (Afifi et al., 2020; Anda et al., 2006; Choi et al., 2016; Cutajar et al., 2010; Felsher et al., 2010; Hägele et al., 2014; Kirsch et al., 2020; Poole et al., 2017; Santo et al., 2021; Schafer et al., 2017). The prevalence

of moderate to extreme CM in our sample exceeded a previous estimation for the general German population ranging between 6.5% for emotional abuse and 22.4% for physical neglect (Witt et al., 2017). Similarly to the general population (Witt et al., 2017), women with SUD also reported higher prevalence rates for abuse but not neglect. Also, individuals with SUD suffered from significantly more severe experiences of CM for all subscales compared to the general German population (Klinitzke et al., 2012). Our findings are consistent with previous studies, reporting a high prevalence and strong severity of CM in individuals with SUD (Choi et al., 2016; Medrano et al., 1999; Santo et al., 2021; Wingenfeld et al., 2010). Compared to a previous study on the severity of CM in individuals with SUD (Wingenfeld et al., 2010), we observed significantly less severe experiences of all forms of abuse but a more severe experience of physical neglect. A higher percentage of women in the previously reported SUD sample (41.3% vs. 27%) might contribute to these differences, since women are known to report higher severities of CM, which was also observed in our sample regarding emotional and sexual abuse. Also, Wingenfeld et al. (2010) did not report on different substances. Depending on the composition of SUDs, group differences as we observed here might also contribute to the diverging observations.

Contrary to our hypothesis, individuals with OUD were not the most severely affected substance user group by CM in comparison to other SUD - although prevalence rates of OUD were comparable to previous studies (Medrano et al., 1999; Santo et al., 2021). This opposes previous research showing that individuals with OUD were more likely to report ACE in comparison to individuals with tobacco or cocaine use disorder (Lawson et al., 2013). Others observed similar prevalence numbers of CM in both, individuals with OUD and matched controls, which was explained by the control group also containing individuals with other SUD. Still, males with OUD experienced significantly more physical and emotional abuse than controls, and females sexual abuse, respectively (Conroy et al., 2009).

In our sample, patients with CUD showed both higher prevalence and more severe experiences of several subtypes of CM. Emotional abuse was significantly more severe in CUD compared to AUD. However, CUD compared to OUD did not reach significance. Individuals with CUD were similarly affected by comorbid mental disorders, i.e., schizophrenia, schizotypal and delusional disorders (F2), affective (F3), or neurotic, stress-related and somatoform disorders (F4) as AUD. Post-hoc analyses (see Supplementary Table S5) for CUD and AUD did not yield significant group differences. However, individuals with CUD were diagnosed

with more comorbid SUD compared to individuals with AUD. An explanation for our observation with respect to individuals with OUD might be three-fold. Firstly, an age effect cannot be ruled out regarding patients with CUD, since they were significantly younger. Post-hoc analyses (see Supplementary Material) revealed a negative correlation between age and overall CM severity. However, within each substance group, including CUD, this correlation did not reach significance. Discussing generational aspect when it comes to (not) reporting CM are relevant, but beyond the scope of this retrospective, observational study. Secondly, CM data for OUD mainly derived from OMT patients. In contrast to the other SUD patients of our study, OMT patients were not abstinent, but continuously treated with opioids. Therefore the daily opioid treatment may have an acute effect and memories of CM might be suppressed to a certain extent. This could have led to an underreporting of prevalence and severity of CM. Opposing to this and besides psychobiological mechanism of withdrawal, in-house patients might find themselves strongly confronted with current problematic psychosocial factors during our treatment. They might increase attention towards traumatic events as one potential factor within the biopsychosocial model of addiction that is regularly discussed during medical and psychotherapeutic treatment of SUD. Thirdly, endocannabinoids mediate the extinction of aversive memories and regulate fear, anxiety and stress. External cannabis might enhance these effects, and thus might be consumed as a self-medication (Lutz et al., 2015; Marsicano et al., 2002). A systematic review of cannabis use motives identified negative life events, trauma, and maladaptive coping being related to consumption (Hyman & Sinha, 2009). This was also confirmed for CM as origin of negative stress and influenced by impairments in emotion regulation, e.g., negative mood (Vilhena-Churchill & Goldstein, 2014). Cannabinoids are discussed as medical intervention for several anxiety- and trauma-related disorders by reason of their neuromodulator capacities in brain regions relevant for emotion and stress regulation (Kondev et al., 2021; Papagianni & Stevenson, 2019). Further research examined the hypothesis of a self-medication model of cannabis in posttraumatic stress disorder and revealed an acute, dose-dependent cannabis effect of a 51-67% symptom relief in more than 92% of cannabis users. However, a development of tolerance and therefore limited effects were observed (LaFrance et al., 2020).

Named considerations evoke the question of a causal origin of the association, namely whether CM is more frequent in SUD compared to the general population, because CM leads to SUD. Our analyses highlighted association between CM and SUD rather than causation. However, mechanisms identified in basic and animal research include a long lasting altered stress response after early life adversity. Further, perturbation of numerous neurodevelopmental processes, including the development and maturation of brain circuits involved in cognition and

emotion, finally result in diminished cognitive control and increased desire for drug effects, i.e., memory extinction and relief from negative affect. Mechanisms are reviewed in al'Absi et al. (2021) and Levis et al. (2021a). Recent basic research supported the contribution of CM to an increase in vulnerability for opioid addiction (Levis et al., 2021b), possibly mediated by the endogenous opioid system which is involved in pro-social behavior in mammals, including humans (Loseth et al., 2014). A recent review proposes "[…] based upon recent findings of opioid modulation of human social learning, bonding and empathy in relation to affiliative and protective tendencies. Fundamental to the model is that the mu-opioid system reinforces socially affiliative or protective behavior in response to positive and negative social experiences with long-term consequences for social behavior and health." (Meier et al., 2021). Lacking of pro-social touch, caring and protective behavior in childhood is a key feature of CM and may result in a long-term modification of the endogenous opioid system. On the emotional level this might result in an enhanced desire for social attachment and the pro-social effects of endogenous or external opioids. Not only opioids but all addictive substances share an activation of the opioid system, either by releasing endogenous opioids (alcohol, cannabis, amphetamines, cocaine) or by direct activation of opioid receptors (heroin and synthetic opioids; Charbogne et al., 2014; Mitchell et al., 2012; Olive et al., 2001; Valverde et al., 2001). Therefore, this opioid pathway also increases the risk for non-opioid SUD in individuals having experienced CM.

In our sample, a positive relation between the severity of the overall CM and depressiveness, anxiety and perceived stress was observed for males. However, in women, current perceived stress did not relate to a history of CM. The relation between ACE such as CM and a later SUD has been observed to be party mediated by mood and anxiety disorders (Douglas et al., 2010).

The influence of sex with regard to outcomes of CM has been discussed previously (White & Kaffman, 2019) and sex differences are commonly accepted. However, White and Kaffman (2019) argued that despite similar presentation, underlying mechanisms might differ. Also, impairments in mental health following CM are subject to effects of gender and CM subtype (Rehan et al., 2017). Potentially, physical abuse is more often related to internalizing mental disorders (e.g., affective disorders) in females subjects whereas in males physical abuse more often related to externalizing mental disorders (e.g., SUD) (Keyes et al., 2012). For women, but not men, several subtypes of CM were associated with an increased risk for cocaine relapse (Hyman et al., 2008). In cocaine, CM might increase the risk for relapses due to an increased

appetitive anticipatory response to drug cues. Further, regulatory and control mechanism regarding stress- and cocaine-induces craving might be reduced following CM (Elton et al., 2015).

Substance craving refers to a multifaceted construct, including internal and external factors as well as corresponding interactions, that results in the desire or urge for consumption (Tiffany & Wray, 2012). Further, within the diagnosis of SUD, craving is listed as a relevant item (American Psychiatric Association (APA), 2013). In our sample, substance craving at admission to treatment differed between sex and substance group and was influenced by emotional abuse, but not other types of CM. Higher craving at admission to SUD treatment was previously related to relapse, i.e., in individuals with AUD (Bottlender & Soyka, 2004; Schneekloth et al., 2012), indicating the importance of monitoring craving and examining influencing factors. Regarding a diverging influence of specific subtypes of CM, physical and emotional abuse, as well as emotional neglect were previously associated with drug use (Norman et al., 2012) and emotional abuse, followed by physical abuse, were the strongest predictors for the severity of AUD (Schwandt et al., 2013). However, depressiveness as a current affective state exerted a strong influence on craving at admission and on craving reduction over the course of treatment. The influence of anxiety on craving became apparent only at admission, whereas perceived stress significantly contributed to craving reduction. Within our sample, a positive correlations between CM and symptoms of depressiveness, anxiety, and perceived stress have been observed. Individuals with CM are at higher risk for psychopathologies related to anxiety and depressiveness (Teicher & Samson, 2013). At the same time, symptoms of depressiveness and anxiety are common for individuals entering treatment for SUD and negatively influence treatment outcome, i.e., increased risk for relapse (Charney et al., 2005). In AUD, inefficient emotion regulation is associated with increased alcohol craving and use (Petit et al., 2015). A history of CM was related to alcohol craving as a response to traumatic stimuli in healthy males. Further, physiological markers, such as cortisol reactivity, heart rate or skin conductance were also related to alcohol craving, CM or both (Trautmann et al., 2018).

2.5.1 Limitations

Limitation, that might reduce the generalizability of the results have to be mentioned. First, possible limitations include the study being based on retrospective self-report questionnaires. Especially, when retrospectively assessing CM as it is done with the CTQ, answers might be biased. When assessing CM, a great heterogeneity regarding the instruments can be

observed in the literature. Second, besides using questions defined by the authors, validated questionnaires, such as the CTQ, or interviews were used. When assessing ACE, CM has to be distinguished from a dysfunctional household (including divorce, substance use, observing intimate partner violence) per se. CM, abuse or neglect, account primarily for negative mental health outcomes in a study that examined individuals in their early and late adolescence (Negriff, 2020). Due to the design of the here presented analyses, we did not assess other ACE besides CM as defined by CTQ and did not collect information about income or family structures which might have added to the biographical burden that possibly contributes to the development of SUD. This hinders the integration of study results in previous literature. Third, only patients were included in the analyses. Therefore, the influence of CM on the transition from low-risk to high-risk consumption possibly leading to a substance use disorder as well as characteristics inherent to non-treatment seeking individuals with SUD could not be examined. Fourth, substances were grouped and only the main diagnosis was considered. The small sample size for individuals with OUD or SHA does not allow for a broader discussion of the influence of main diagnosis on craving at admission and the reduction of craving during treatment.

2.5.2 Clinical Implications

The here observed high prevalence and severity of CM in individuals with CUD, but also recent developments in the pattern of consumption and the potency of the available substances (Manthey, 2019) underline the need for screening for CM both during treatment for CUD and in prevention of CUD. This is backed up by previous studies in individuals with both a history of CM and cannabis use that indicated a higher risk for psychotic symptoms in adolescents (Harley et al., 2010) and a more severe symptomatology for bipolar disorder (Aas et al., 2014). Irrespective of the substance of use, a high prevalence and severity of CM was underlining the importance of assessing CM with suitable tools in all settings of SUD prevention and treatment. If CM can be ceased and a positive environment is installed including intact social networks, positive coping, self-esteem and optimism, the neuro-adaptive capacities of the human brain might allow for a positive outcome, even following CM (Holz et al., 2020). For example, low levels of mindfulness might link CM to alcohol use (Brett et al., 2018), therefore serving as a therapeutic target. Individuals with SUD and CM might benefit from integrative psychosocial interventions targeting both, trauma-related and SUD-related symptoms (Brady & Back, 2012), such as interpersonal psychotherapy (Markowitz et al., 2008) or trauma informed yoga (Esfeld et al., 2021; Macy et al., 2018).

2.6 Conclusion

Individuals with SUD experience various forms of CM more often and in a more severe manner than the general population. SUD group differences with regard to prevalence and severity of CM were observed. Sex differences to the detriment of women can be observed in several SUDs. CM, specifically emotional abuse, might be related to craving at admission to treatment. However, pathways of mediating factors, such as depressiveness, anxiety and stress still have to be examined in more depth. Also, underlying causal and explanatory mechanism such as impairments in processing of trauma history, emotional regulation, or neurobiological alterations following CM remain to be further examined. A history of CM should be assessed during treatment for SUD. A possible positive influence of trauma-related interventions during SUD treatment specifically addressing aspects of CM on treatment outcomes and relapse rates can be hypothesized.

2.7 Supplementary Material

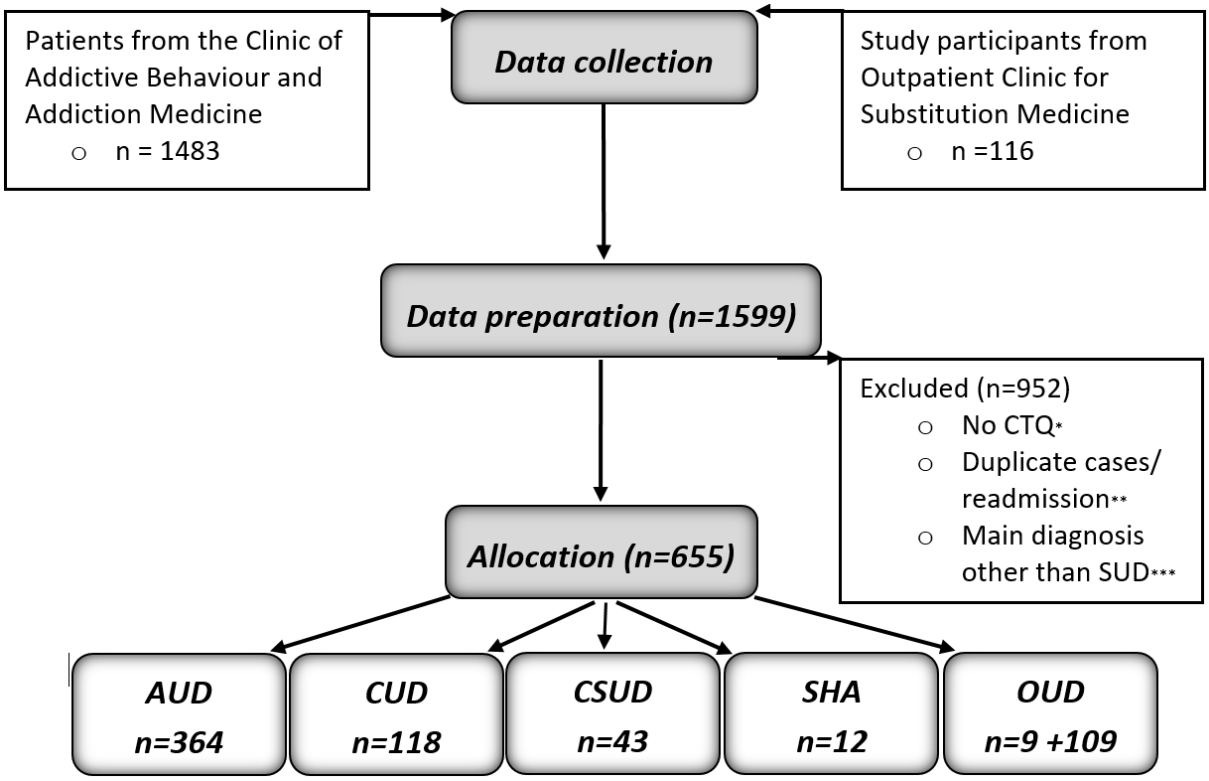


Figure S5: Flow-chart of data collection and preparation procedure. Note: n = sample size; AUD = Alcohol Use Disorder; CTQ = Childhood Trauma Questionnaire; CUD = Cannabis Use Disorder; OUD = Opioid Use Disorder (N = 9) including Opioid Maintenance Treatment (OUT, N = 109); SHA = Sedative, Hypnotics, or Anxiolytic Use Disorders; SUD = Substance Use Disorder

* Only individuals with at least one CTQ sub score were included, individuals without CTQ data were excluded (N = 794)

** The most recent dataset was used for patients with readmissions over the 5-year observation period, data results from repeated admissions was excluded (N = 78)

*** Only individuals with the main diagnosis of SUD were included. Other main diagnoses, such as personality disorders or other mental disorders were excluded from subsequent analyses (N = 72).

2.7.1 Supplementary Analyses

Comparison of individuals with opioid use disorder (OUD) between sample 1 and sample 2

Patients with OSUD (sample 1) and OMT (sample 2) did not differ in CTQ subscores, the dichotomous variable 'having experienced childhood maltreatment (CM), yes or no', and the total number of CM, as well as age, sex, family status, having children or employment status ($p > .1$, t-test 2-tailed; $p > .05$, chi-square tests). Because the two samples did not differ for the

main sociodemographic variables sex, age and CTQ subscores, both samples were merged for subsequent analyses regarding hypotheses one and two.

Correlation between CM and age

Correlation analyses between the severity of CM (CTQ sum score) and age revealed a significant association for the overall sample while controlling for sex (r = -0.169 p = 0.004). However, within each substance, this sex-controlled correlation did not reach significance (AUD (r = -0.037, p = 0.633), CUD (r = -0.024, p = 0.838), CSUD (r = 0.101, p =0.655), SHA (r = -0.043, p = 0.957), OUD (r = 0.473, p = 0.421).

Table S5: Comorbidities in AUD and CUD. Mean values (standard deviation) or percentage values are displayed.

	AUD	**CUD**	**Descriptive Statistics**
N	364	118	
F2 (% yes)	1.1	2.5	$\chi^2(1) = 1.288$, p = .256
F3 - current (% yes)	33.5	33.9	$\chi^2(1) = 0.003$, p = .954
F3 - lifetime (% yes)	39.3	37.3	$\chi^2(1) = 0.150$, p = .699
F4 – current (% yes)	13.5	12.7	$\chi^2(1) = 0.048$, p = .827
F4 – lifetime (% yes)	22.8	15.3	$\chi^2(1) = 3.065$, p = .080

Note: n = total sample size; AUD = Alcohol Use Disorder; CUD = Cannabis Use Disorder; F2 = Schizophrenia, Schizotypal and Delusional Disorders; F3 = Mood (Affective) Disorders; F4 = Neurotic, Stress-related and Somatoform Disorders.

Severity of different subtypes of CM in patients with SUD compared to the general population in Germany and a previous sample of individuals with SUD

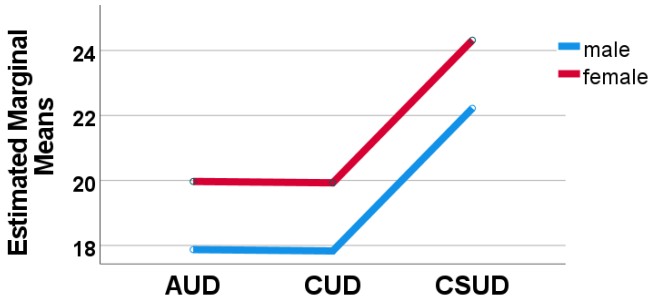
To compare the severity of CM in the present sample with a representative sample of the German population (Klinitzke et al., 2012), one sample t-tests were performed for all subscales of the CTQ separately, including the respective mean from the population-based study as test value. Similarly, the here presented data was compared to a German sample with SUD (Wingenfeld et al., 2010). Individuals with SUD reported higher severity for all subscales of CM compared to a German representative sample (Klinitzke et al., 2012), i.e., emotional abuse (t(626) = 16.374, p < 0.001), physical abuse (t(618) = 10.394, p < 0.001), sexual abuse (t(621) = 5.639, p < 0.001), emotional neglect (t(629) = 13.882, p < 0.001) and physical neglect (t(631) = 4.946, p < 0.001). Further, comparing the severity of CM to a previous study on SUD (Wingenfeld et al., 2010) our sample was less affected by emotional abuse (t(626) = -4.013, p < 0.001), physical abuse ((618) = -6.842, p < 0.001), and sexual abuse (t(621) = -3.905, p <

0.001), and more affected by physical neglect (t(631) = 2.122, p = 0.034). Emotional neglect did not yield significant differences (t(629) = 0.875, p = 0.382).

The influence of different types of CM on substance craving at admission

Craving at T01 (MACS T01) differed statistically significant for sex (F(1, 370) = 6.706, p = 0.010, η^2 = 0.018) but not the different substance groups (F(2, 370) = 3.027, p = 0.050, η^2 = 0.016) after adjusting for all five subscores of the CTQ and age. Emotional abuse (F(1, 370) = 16.482, p < 0.001, η^2 = 0.043) but none of the other subscales of CM or age did show a significant influence. After adjusting for before-mentioned covariates, Bonferroni-corrected post-hoc tests revealed significantly more severe craving for women (p = 0.010, MDiff = 2.98, 95%-CI[0.72, 5.25]). Post-hoc tests regarding substance group revealed significantly more severe craving for CSUD compared to AUD (p = 0.043, MDiff = 4.40, 95%-CI[0.093, 8.70]).

After adjusting for all five subscores of the CTQ and age but also PSS, BDI (T01) and BAI (T01) sum scores, craving at T01 (MACS T01) differed statistically significant between the different substance groups (F(2, 272) = 3.990, p = 0.020, η^2 = 0.029) and sex (F(1, 272) = 4.095, p = 0.044, η^2 = 0.015). Emotional abuse (F(1, 272) = 0.508, p = 0.477, η^2 = 0.002) did no longer show a significant influence, neither did the PSS sum score (F(1, 272) = 0.782, p = 0.377, η^2 = 0.003). BDI and BAI sum scores at admission, however, did show a significant influence (F(1, 272) = 47.825, p < 0.001, η^2 = 0.150; F(1, 272) = 17.697, p < 0.001, η^2 = 0.061). After adjusting for before-mentioned covariates, Bonferroni-corrected post-hoc tests revealed significantly more severe craving for women (p = 0.044, MDiff = 2.10, 95%-CI[0.06, 4.14]). Post-hoc tests regarding substance group revealed significantly more severe craving for CSUD compared to AUD (p = 0.025, MDiff = 4.35, 95%-CI[0.41, 8.30]) and CUD (p = 0.029, MDiff = 4.39, 95%-CI[0.34, 8.44]).



Covariates appearing in the model are evaluated at the following values: EA = 10,3088, PA = 7,6877, EN = 13,2035, PN = 8,8351, SA = 6,1789, PSS sum score = 21,3212, BDI sum score at T01 = 20,9713, BAI sum score at T01 = 17,2595, age = 40,77

Figure S6: Estimated marginal means of the MACS sum score (craving) at admission to treatment. After adjusting for all five subscores of CM, depressiveness, anxiety and perceived stress, as well as age, individuals with CSUD reported more severe craving at admission compared to AUD or CUD, so did females compared to males.

The influence of different types of CM on the reduction of substance craving

Over all three substance groups, craving diminished from 17.9 (10.0) at T01 to 11.0 (8.4) at T14 in the MACS questionnaire. A significant of sex ($F(1, 296) = 4.321$, $p = 0.039$, $\eta^2 = 0.014$) but not substance group ($F(2, 296) = 1.331$, $p = 0.266$, $\eta^2 = 0.009$) was observed after adjusting for age and all five subscores of CM. There was no significant influence regarding all subscores of CM. Post-hoc tests regarding sex revealed significantly higher reduction of craving in women compared to men ($p = 0.039$, MDiff = 2.30, 95%-CI[0.12, 4.47]).

Including PSS, BDI (T01) and BAI (T01), no significant effect of substance group ($F(2, 272) = 0.423$, $p = 0.656$, $\eta^2 = 0.003$) or sex ($F(1, 272) = 1.228$, $p = 0.269$, $\eta^2 = 0.004$) did emerge. However, PSS, BDI (T01), and BAI (T01) sum scores excerpted a significant influence ($F(1, 272) = 13.184$, $p < 0.001$, $\eta^2 = 0.046$; $F(1, 272) = 21.677$, $p < .001$, $\eta^2 = 0.074$; $F(1, 272) = 3.928$, $p = 0.048$, $\eta^2 = 0.014$), so did age ($F(1, 272) = 5.115$, $p = 0.025$, $\eta^2 = 0.018$).

3 STUDY 2: LACK OF AMYGDALA HABITUATION TO NEGATIVE EMOTIONAL FACES IN ALCOHOL USE DISORDER - AND THE RELATION TO ADVERSE CHILDHOOD EXPERIENCES

An adapted version of this chapter has been published as "Gerhardt, S.*, Berhe, O.*, Moessnang, C., Horning, M., Kiefer, F., Tost, H.*, & Vollstädt-Klein, S.* (2023). Lack of Amygdala Habituation to Negative Emotional Faces in Alcohol Use Disorder and the Relation to Adverse Childhood Experiences. Addiction Biology, 28(1), e13251."
*These authors contributed equally.

3.1 Abstract

Introduction: Aberrant limbic circuit reactivity to negative stimuli might be related to alterations in emotion processing and regulation in alcohol use disorder (AUD). The current study tested for the first time in AUD the hypothesis of aberrant amygdala habituation to repeated aversive stimuli – a robust and reliable neuroimaging marker for emotion processing. We explored the link between deficits in habituation to adverse childhood experience (ACE), a common risk factor for impaired emotion regulation and AUD.

Methods: AUD individuals (N=36) and healthy controls (HC; N=26) participated in an observational case-control functional magnetic resonance imaging (fMRI) study. An established habituation index was used to investigate processing of aversive emotional faces of the amygdala.

Results: AUD individuals showed an overall deficit in amygdala habituation (right: t=4.26, pFWE=0.004; left: t=4.79, pFWE≤0.001). Amygdala habituation was significantly related to increased exposure to ACE in HC (t=3.88, pFWE=0.012), whereas this association was not observed in AUD individuals (T=1.80, pFWE=0.662). Further, a significant association between higher alcohol consumption and reduced amygdala habituation (right: R2=-0.356, F=8.736, p=0.004; left: R2=-0.309, F=6.332, p=0.015) was observed.

Conclusion: We found novel evidence for neural alterations in emotion processing in AUD individuals, indexed by deficient amygdala habituation to negative emotional content. We replicated a prior report on a link between ACE and amygdala habituation, a well-established environmental risk factor for mental disorders and emotion dysregulation, in our control sample. Additionally, deficient amygdala habituation related to the amount of alcohol consumption in the overall sample might indicate a short-term substance effect.

3.2 Introduction

Alcohol use disorder (AUD) is a major health problem and socioeconomic burden (Peacock et al., 2018). Impairments in emotion processing and regulation play prominent roles in substance use disorders where negative emotional states, i.e., anxiety or dysphoria, might maintain the disorder through instances of relapse (Koob & Volkow, 2010). Impairments in emotion processing in AUD precede the development of the disorder (Kober, 2014; Le Berre, 2019; Petit et al., 2015) and compromise abstinence and treatment processes (Berking et al., 2011; Le Berre, 2019). The ability to tolerate negative emotions is one important predictor of relapse in AUD (Berking et al., 2011) and includes a process of habituation to such aversive experiences. Negative urgency, the impulsive risk-taking during extreme negative emotional states, is positively related to alcohol craving and negative emotional reactivity, which consequently leads to increased alcohol consumption (VanderVeen et al., 2016). Additionally, not only intra- but also interpersonal emotional problems might further contribute to the maintenance of the disorder (Kopera et al., 2018).

Another line of research has shown that adverse childhood experiences (ACE) are associated with an increased likelihood of substance use in adulthood (Afifi et al., 2012; Afifi et al., 2020; Anda et al., 2006; Cutajar et al., 2010; Kirsch et al., 2020; Oberleitner et al., 2015; Schückher et al., 2018; Turner & Lloyd, 2003). According to the stress coping model of addiction, high (early) life stress and lack of coping resources predispose an individual to use alcohol as a way of coping with negative emotions and traumatic events (Redman, 2008; Wills, 1990). Indeed, behavioral emotion dysregulation was observed to be a potential mediator between ACE and substance use disorder (Wolff et al., 2016). Further underlining the observed relation between ACE, emotion dysregulation, and SUD, attention and interpretation biases for negative emotional faces following ACE were reported (Gibb et al., 2009).

The amygdala as a central neural hub for the regulation of emotion perception and processing (Davis & Whalen, 2001; Gilpin et al., 2015; Swartz et al., 2015) is of particular relevance for both substance use disorder (Koob, 2003) and ACE. Reduced neural responses in the amygdala were not only reported in individuals with AUD (Marinkovic et al., 2009), but also in offspring of individuals with AUD (Glahn et al., 2007), which highlights the involvement of this brain region in AUD-driven emotion processing impairments. Likewise, neuroimaging studies in individuals with ACE have shown decreased amygdala volume, increased limbic connectivity at rest, hyperreactivity of the amygdala, and a deficit in amygdala habituation

(Bilek et al., 2019; Dean et al., 2014; Hanson et al., 2015; Marusak et al., 2015; Swartz et al., 2015; Tottenham et al., 2010).

In general, neural emotion regulation processes can involve both the use of intentional and learned strategies (e.g., through cognitive reappraisal) as well as innate, automatic, and neuroplastic adaptations of responses to repeated stimuli (e.g., repeated exposure to threatening stimuli without aversive consequences; Berkman & Lieberman, 2009). Amygdala habituation, the phenotype of interest in this work, belongs to the latter category of emotion regulation processes and describes the rapid and adaptive decline in amygdala responsiveness to repeated negative affective stimuli (Plichta et al., 2014). Habituation is a basic learning mechanism helping in rapidly and adaptively filtering irrelevant and repeated sensory information in the environment. Deficits to this end, however, lead to inappropriate allocation of processing resources to stimuli with no potential relevance for survival (Ramaswami, 2014). This trans-diagnostic risk factor for psychopathology further suggests a deficit in neural plasticity (Ramaswami, 2014). Aberrant amygdala habituation to emotional stimuli has been linked to various psychiatric conditions, such as social anxiety disorder, borderline personality disorder, autism spectrum disorder, schizophrenia, psychosis, and post-traumatic stress disorders (PTSD; Avery & Blackford, 2016; Avery et al., 2021; Blackford et al., 2013; Hare et al., 2008; Kim et al., 2019; Tam et al., 2017). It has also been linked to ACE (Bilek et al., 2019; Kim et al., 2019), which facilitates the development and modulates the course of subsequent mental disorders.

Despite the biological relevance of this phenomenon, this fundamental neural phenotype has not previously been studied in individuals with AUD, even though neural and neurobiological sensitization (Volkow et al., 2012) and failed habituation (Di Chiara, 2000) are known mechanisms in substance use disorder. Evidence of aberrant amygdala habituation in AUD could, however, provide an explanation of the biological underpinnings of disrupted emotion regulation in AUD and open an avenue to probe the link to environmental risk factors, such as ACE.

Consequently, this project aims (1) to examine neural habituation patterns in individuals with AUD when processing aversive emotional stimuli and (2) to investigate the potential relationship of the phenotype to ACE, a well-known risk factor for AUD. To this end, we examined individuals with varying levels of severity of AUD and ACE, as well as healthy controls (HC) with no or minimal consumption of alcohol and no or minimal severity of ACE. We hypothesize

(1) that amygdala habituation is reduced in individuals with AUD compared to HC. Additionally, we hypothesize (2) that this neural phenotype will be related to the severity of ACE in individuals with AUD.

3.3 Materials and Methods

3.3.1 Procedure and Participants

Data was collected at the Central Institute for Mental Health (CIMH) in Mannheim, Germany between January 2019 and March 2021. The overall study of which this data derived from was pre-registered at ClinicalTrials.gov (identifier NCT03758053). The local Ethics Committee of the Medical Faculty Mannheim, Heidelberg University, approved the study procedure (approval #2018-560N-MA). All participants provided written informed consent and received financial compensation.

HC as well as individuals with heavy drinking were recruited via public announcements within the local community of Mannheim, Germany. Additionally, AUD patients from our clinic were examined. Following a short telephone screening to assess study eligibility, data was acquired at two time points: at the first baseline appointment, written informed consent was obtained, a drug and pregnancy screening was performed, breath alcohol was measured, sociodemographic data was collected, and the Structured Clinical Interview (SCID-IV) for the fourth version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV; Wittchen et al., 1997) as well as a baseline drinking interview (FORM-90 interview; Miller & Del Boca, 1994) were conducted. Eleven AUD-criteria were assessed in an interview according to the DSM-5. Participants were between 18 and 65 years of age and had normal or corrected-to-normal vision. Individuals belonged to the AUD group if they fulfilled the clinical diagnosis of AUD following DSM-5 or reported heavy drinking (alcohol/day ≥ 40 g (female), 60 g (male) on min. 5 days/week), i.e. individuals with AUD and/or heavy drinking individuals. A maximum of 28 days of abstinence was tolerated. Participants were excluded from the study if they reported MRI exclusion criteria, had a severe mental disorder (e.g., bipolar disorder, schizophrenia; currently severe depression, PTSD, anxiety or eating disorder), a neurological condition, or a history of severe head trauma. They were also excluded in case of pregnancy, severe somatic condition or withdrawal symptoms, treatment with psychotropic medication (except for withdrawal medication until 3 days max prior to study inclusion; antidepressants) or positive drug urine screening. HC were excluded if they reported a risky amount of alcohol consumption (alcohol/day ≥ 12 g (female), 24 g (male) on up to 5 days/week). Regarding ACE severity, a

five-item screening questionnaire representing all five subtypes of ACE (Grabe et al., 2012) was applied (range 5 – 25). HC were excluded if they reported more than minimal severity of ACE (cut-off score of 8 (2 * 1 + 3 *2)).

Participants completed several questionnaires using the web-based software EvaSys (Electric Paper Evaluationssysteme GmbH, Lueneburg, Germany). These included the Beck Depression Inventory (BDI-II; Beck et al., 1961) Alcohol Dependence Scale (ADS; Doyle & Donovan, 2009) and Childhood Trauma Questionnaire (CTQ), a 28-item self-report questionnaire (Bernstein et al., 1998). The reliable (0.87 < alpha < 0.95) CTQ assesses five sub scales of ACE, namely emotional, physical, and sexual abuse as well as emotional and physical neglect. Items are answered on a 5-point Likert scale (‘not at all’ to ‘very often’) leading to sum scores between 5 (none) and 25 (severe) for each sub scale, respectively (Wingenfeld et al., 2010). For the functional magnetic resonance imaging (fMRI) assessment, all smokers had to abstain from cigarettes for at least 90 minutes. Drinking data since the baseline appointment (maximum 14 days before the fMRI assessment) was assessed using a short version of the Form-90 (Miller & Del Boca, 1994).

3.3.2 Neuroimaging Paradigm

Participants performed the well-established Face Matching paradigm, a passive emotion processing task suitable to elicit amygdala habituation, a basic neural plasticity mechanism subserving an innate and automatic form of affective regulation (Plichta et al., 2014). In brief, participants were asked to match a face or a shape (e.g., rectangle) to one of two additional faces or shapes, respectively (Supplementary Figure S8). The participants were instructed to select the corresponding face or shape as quickly and precisely as possible. All stimuli were presented in black and white. The Presentation® software (Version 18.1.0, Neurobehavioral Systems, Inc., Albany, CA, USA) was used to implement and present the paradigm and all participants responded using a four-button response box (Current Designs, Philadelphia, PA, USA) by pressing left or right with the thumb of their dominant hand. The paradigm consisted of one run of 4:44 minutes. A block design of alternating form (4 blocks à 6 trials) and aversive faces (4 blocks à 6 trials) conditions with a preceding announcement was used.

3.3.3 fMRI Acquisition and Preprocessing

Functional neuroimaging data was collected using a 3T whole-body tomograph (Prisma Fit, Erlangen, Germany). A total of 88 T2*-weighted transversal echo planar images (EPI) were acquired, covering the entire brain (TR = 3.1 s, TE = 30 ms, flip angle = 90°, 51 slices, slice

thickness: 2.5 mm, 0 mm gap, voxel size 2×2×2.5 mm, FOV 192×192 mm^2, 96×96 in-plane resolution, 64-channel head coil). Fieldmaps were acquired to correct for geometric distortions due to magnetic field inhomogeneities (TR = 520 ms, TE =4.92 ms / 7.38 ms, flip angle = 60°, voxel size = 2×2×2.5 mm). Additionally, a 4:42 min anatomical scan was performed (T1-weighted 3D MPRAGE (Magnetization Prepared- Rapid Gradient Echo) dataset, 192 sagittal slices, TR = 2 s, TE = 3.03 ms, TI = 900 ms, flip angle = 9°, slice thickness: 1 mm, 0.5 mm gap, voxel size 1×1×1.5 mm, FOV 256×256 mm^2, 256x256 in-plane resolution).

Preprocessing was performed using SPM12 (The Wellcome Centre for Human Neuroimaging, at University College, London, UK). The first 4 volumes of each run were excluded to avoid artefacts due to magnetic saturation effects. The remaining 84 scans were corrected for residual geometric distortion using the acquired magnetic field map. Slice timing, spatial realignment, and normalization to an MNI template (Montreal Neurological Institute, Quebec, Canada) were conducted. The resulting images were smoothed using an isotropic Gaussian kernel of 8 mm full width at half maximum.

Quality checks were performed and individuals with excessive head movement or other artefacts were excluded from subsequent analyses.

3.3.4 Statistical Analyses

In total, $N = 69$ participants participated in the study. Due to technical problems ($N = 2$), drop-outs ($N = 3$) and heavy movement in the scanner ($N = 1$), N = 27 healthy controls and N = 36 individuals with AUD were included in the final analyses.

Psychometric data was analyzed with SPSS (Statistics for Windows, Version 27.0. IBM Corp., Armonk, NY). Sum scores were computed for all questionnaires according to their manuals. Descriptive analyses and chi square tests or t-test were applied to describe the sample and perform statistical analyses regarding group differences. Behavioral performance in the face matching task was assessed as response time and accuracy (percentage of correct hits) for each condition.

The analyses of MRI data consisted of a two-level procedure. As a first-level analysis, a general linear model was fitted for each participant for both experimental conditions, faces and shapes, with each block as a regressor which was convolved with the standard SPM hemodynamic response function. Six head motion parameters from the realignment step were included as nuisance covariates. A high-pass filter with a cut-off frequency of 1/262 Hz was used and first-order autoregressive modeling was administered to correct for temporal autocorrelations. To estimate amygdala habituation, we employed an established habituation index, which is the

difference between the first and the second half of the experiment for the faces condition ([block 1 + block 2] > [block 3 + block 4]; Bilek et al., 2019; Wiggins et al., 2014).

The resulting contrast images were subjected to a second-level univariate analysis of variance (ANOVA) to assess the effect of group (HC, AUD) as a between-subject factor while correcting for sex. Further, we set up an analogous univariate ANOVA model with an additional interaction term (e.g., group x CTQ sum score) to test for potential group-specific associations between ACE and neural habituation. Exploratory analyses including CTQ sub scores can be found in the Supplemental. Based on our a priori hypothesis, we defined the bilateral amygdala as an a priori region of interest (ROI) by merging the left and right amygdala labels from the Automated Anatomical Labelling (AAL; Tzourio-Mazoyer et al., 2002). Statistical significance was assessed using small volume correction at a threshold of $p < 0.05$, family-wise error (FWE) corrected for multiple comparisons within the ROI.

3.4 Results

3.4.1 Sample, Sociodemographic and Psychological Data Assessment

HC (N = 27) and individuals with AUD (N = 36) did not differ significantly regarding age ($T(61) = 1.05$, $p = 0.299$), however, the percentage of males was higher in the AUD group (67 %) than in the HC group (41%; $\chi^2(1) = 4.20$, $p = 0.040$). As expected, the AUD group had a higher overall score of the CTQ ($p = 0.007$) and higher scores in the severity of AUD and the amount of alcohol consumed 12 weeks prior to examination. See Table 6 for details.

3.4.2 MRI

fMRI task performance

Participants' response data did not differ between conditions. No significant group differences were found in the percentage of correct responses ($p > 0.05$) and reaction time in the faces condition ($p > 0.05$) (see Table 6 and Supplementary Figure S12 for more details).

MRI results

Group comparison of AUD and HC revealed a lack of habituation in the AUD group within the right amygdala ($t = 4.26$, $pFWE = 0.004$; Figure 7A) and the left amygdala ($t = 4.79$, $pFWE \leq 0.001$, Supplementary Figure S9). Specifically, we observed a rapid decline in amygdala activation across time within the ROI in the HC group (right amygdala: $t = 3.97$, $pFWE = 0.009$, left amygdala $t = 3.89$, $pFWE = 0.011$), whereas the AUD group failed to habituate (for

left amygdala t = 1.31, pFWE = 0.854, and right amygdala t = 0.56, pFWE = 0.958). These opposing response patterns (see Figure 7A) were corroborated in an exploratory follow-up analysis in the AUD group using the inverse contrast ([block 1 + block 2] < [block 3 + block 4]; t = 3.43, pFWE = 0.039).

Table 6: Sample description of healthy individuals (HC) and individuals with AUD.

	HC Mean (SD)	**AUD Mean (SD)**	**Statistics**
N	27	36	
Sex (male:female)	11:16	24:12	**$\chi^2(1) = 4.20$, p = 0.040**
Age (years)	36.9 (12.5)	40.3 (12.6)	T(61) = 1.05, p = 0.299
Marital status (married/divorced/single)	6:3:18	5:8:23	$\chi^2(2) = 1.72$, p = 0.423
Living (alone:together with others)	6:21	15:21	$\chi^2(1) = 2.63$, p = 0.105
Years of education	15.7 (2.3)	14.4 (3.0)	T(61) = -1.84, p = 0.071
Smoker (yes:no)	4:23	10:26	$\chi^2(1) = 1.50$, p = 0.221
CTQ (sum score)	31.3 (7.7)	39.3 (14.4)	**T(56.1) = 2.82, p = 0.007**
ADS (sum score)	2.3 (2.4)	11.9 (6.6)	**T(46.4) = 7.97, p < 0.001**
DSM-5 criteria (sum score)	0.4 (0.8)	6.1 (2.7)	**T(42.7) = 11.91, p < 0.001**
BDI (sum score)	2.4 (4.7)	10.4 (8.8)	**T(54.1) = 4.56, p < 0.001**
FORM-90 at baseline			
Total amount of alcohol (g)	360 (367)	7231 (6690)	**T(35.3) = 6.15, p < 0.001**
fMRI emotional faces task			
Reaction-times faces (ms)	1089.2 (443)	1265.0 (308)	T(61) = 1.86, p = 0.068
Reaction-times forms (ms)	1212.8 (442)	1222.0 (265)	T(61) = 0.10, p = 0.919
Correct hits faces (%)	91.5 (27)	99.3 (2)	T(26.2) = 1.52, p = 0.139
Correct hits forms (%)	87.8 (24)	95.9 (5)	T(27.6) = 1.76, p = 0.090

Note: SD = Standard Deviation; g = grams; n = sample size; ms = milliseconds; AUD = alcohol use disorder; ADS = Alcohol Dependence Scale; BDI = Beck Depression Inventory-II; CTQ = Childhood Trauma Questionnaire; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th version; FORM-90 = amount of alcohol consumption over the last 90 days. Significant group differences are highlighted in bold.

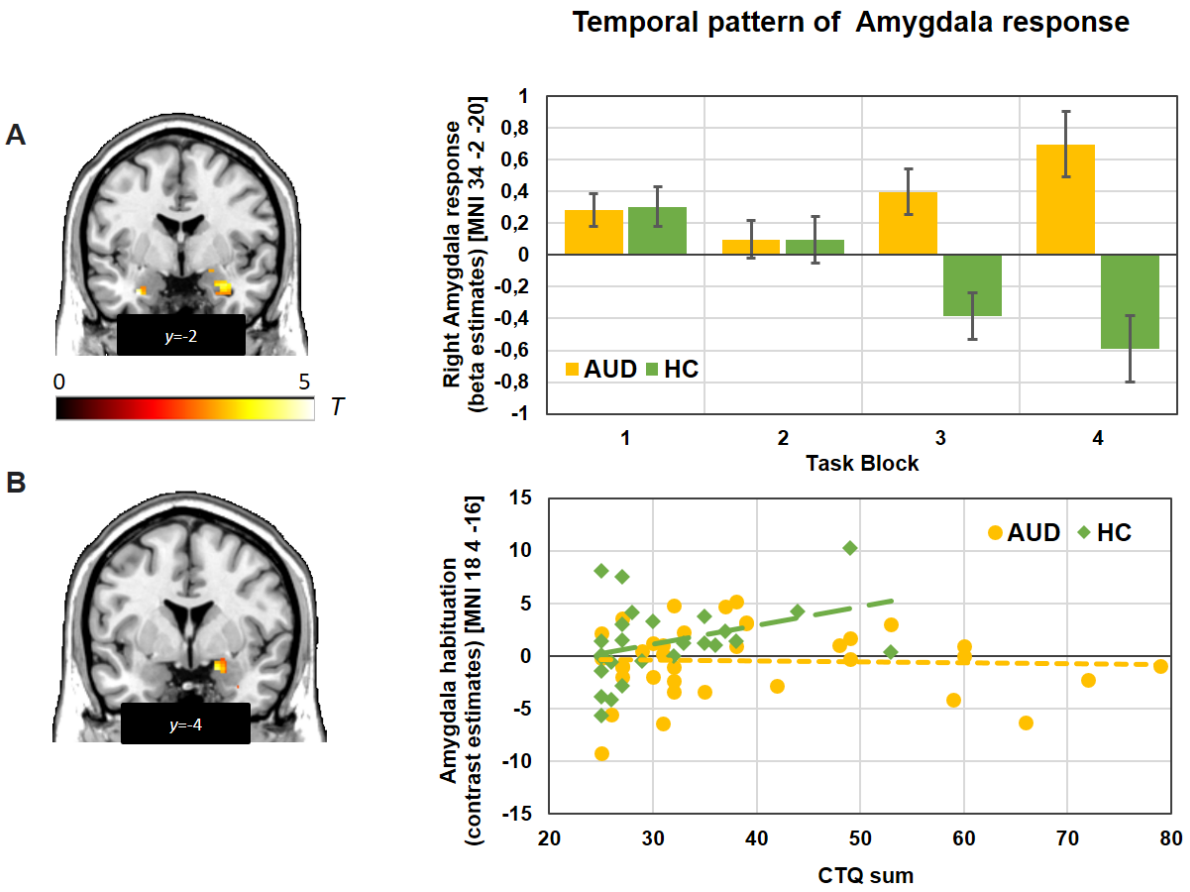


Figure 7: Group differences in Amygdala habituation to aversive stimuli. A: Decrease of amygdala activation over the course of the experiment for HC, whereas AUD group showed an increase (right amygdala (t = 4.26, pFWE = 0.004) and left amygdala (t = 4.79, pFWE ≤ 0.001)). Right: Plotted habituation estimates of the peak voxel in the right amygdala. B: Amygdala habituation relates to ACE differently: increased amygdala habituation is associated with higher CTQ sum score in HC, but not in AUD group (Interaction: T = 3.46, pFWE = 0.037; post hoc analysis: AUD: T = 1.80, pFWE = 0.662, HC: T = 3.88, pFWE = 0.012).
For illustration purposes, a significance threshold of $p_{uncorr} < .005$ was applied and displayed on the coronal section. HC: healthy control participants, AUD: alcohol use disorder, ACE: adverse childhood experience; FWE: familywise error; MNI: Montreal Neurological Institute. This figure derived from thee dissertation of Oksana Berhe, as specified in the preface on page III.

Inclusion of the CTQ sum score in an interaction model (Group x CTQ) as a predictor yielded a significant interaction effect within the right amygdala (T = 3.46, pFWE = 0.037). The subsequent post hoc analysis revealed an association between CTQ and amygdala habituation within the HC group (T = 3.88, pFWE = 0.012), but not in the AUD group (T = 1.80, pFWE = 0.662; Figure 7B). Exploratory analyses regarding the interaction of group and CTQ subscales are provided in the Supplemental.

Please also see the Supplementary Material for post-hoc analyses including the relation between alcohol consumption and amygdala habituation.

3.5 Discussion

Employing an established fMRI paradigm (Hariri et al., 2002) and a reliable amygdala habituation index (Bilek et al., 2019; Wiggins et al., 2014), the current study provides novel evidence for a neural emotion processing mechanism promoting our understanding of the AUD-related alterations in amygdala functioning. We report deficient amygdala habituation to repeated negative emotional stimuli in individuals with AUD relative to healthy controls. In our healthy sample, we replicated the finding of a link between amygdala habituation and ACE, an important environmental risk factor for mental disorders and deficient emotion regulation; however, this association was not observed in our AUD sample.

Alterations in amygdala activation in AUD are well documented (Koob, 2009). Some neuroimaging studies report blunted responses within the amygdala in relation to drinking or AUD (Glahn et al., 2007; Hur et al., 2018; Marinkovic et al., 2009; Stephens et al., 2005; Suzuki et al., 2020; Vollstädt-Klein et al., 2019). A positive relation between increased amygdala activation and AUD severity was also shown (Gowin et al., 2016). However, others observed no difference compared to healthy controls (Charlet et al., 2014; O'Daly et al., 2012). The (lack of) group difference in mean activation may be driven by either a dynamic or by sustained activation over time, and might therefore lead to false negative findings, and thus inferences (Phan et al., 2002; Plichta et al., 2014). Further, undifferentiated reactivity to faces (negative or positive) has been observed in AUD (Marinkovic et al., 2009). Our data suggest a robust activation of both groups at the beginning of the experiment. However, repeated presentation of the stimuli resulted in habituation only in our HC group, while amygdala activation rather increased in individuals with AUD. This pattern resembles neural sensitization (Ramaswami, 2014) and might reflect changes in neurotransmission in the brain emotion regulatory systems with the development of AUD (Robinson & Berridge, 1993). Indeed, the process of neural sensitization, or kindling, has been reported in relation to AUD (Breese et al., 2011; Gilpin & Koob, 2008), stress or negative affective stimuli (Heilig et al., 2010a), and can be discussed within the context of neural plasticity. However, due to experimental limitations (e.g., number of blocks, length of the paradigm), this interpretation needs further examination.

The observed deficit in habituation in individuals with AUD might reflect AUD-related alterations in fundamental neuroplasticity mechanisms (Lovinger & Kash, 2015; Seo & Sinha, 2015). These deficits and resulting inappropriate allocation of processing resources towards non-threatening or non-relevant stimuli (Ramaswami, 2014) might firstly indicate a failure in

emotion regulation, and therefore, secondly maintain the AUD. Impairments in emotion decoding in individuals with AUD might further be relevant (Foisy et al., 2005). However, these deficits might also be driven by chronic and enduring stress during childhood through an impact on neurodevelopment and physiological changes (Dube et al., 2006). We specifically tested this hypothesis by probing the relationship of the established habituation phenotype to ACE, measured by CTQ sum. Interestingly, in our sample amygdala habituation towards negative emotional faces was positively related to the severity of ACE in healthy individuals, but not in AUD. It might be that the impact of AUD or the consumption of high amounts of alcohol per se have masked the neurobiological effects of ACE, leading to the missing relationship between deficient amygdala habituation in the AUD group and ACE severity. Given that both, ACE and drinking behavior are associated with neuroadaptive brain responses in emotion processing circuitry, especially the amygdala (Gilpin et al., 2015; Puetz et al., 2020), we may assume that the observed disrupted amygdala habituation in individuals with AUD could be an effect of both. ACE may serve as a predisposing and maintaining factor for AUD through emotion dysregulation (Berking et al., 2011; Wilcox et al., 2016). In turn, acute administration of alcohol (Hur et al., 2018) as well as chronic alcohol consumption (Stephens et al., 2005) reduce amygdala reactivity, and thus contribute further to the ACE-caused behavioral and neural alterations. Indeed, deficient amygdala habituation in AUD may reflect both, a risk factor predisposing individuals for the development of the disorder and/or a functional marker of the consequence of previous hazardous alcohol consumption. While it is generally difficult to disentangle the effect of both above mentioned factors, we consider the interpretation of a functional marker more likely, since our supplemental analysis did detect an association between amygdala habituation estimates and the quantity of recent alcohol consumption (see Supplemental).

The observed deficit in habituation might also reflect alterations in amygdala functional connectivity across this brain circuitry, i.e., impaired prefrontal control function (Banks et al., 2007; Wilcox et al., 2016), as the amygdala shows widespread connections within the emotion regulation network (Berboth & Morawetz, 2021). Previously, the acute consumption of alcohol (Gorka et al., 2013) as well as having experienced ACE (Elton et al., 2015; McLaughlin et al., 2015; van Harmelen et al., 2013) were related to altered fronto-limbic coupling. In the present study, mild to moderate depression was not an exclusion criterion - comorbid depression could also in part explain the deficit in habituation in AUD. In a study by van den Bulk et al. (2016) participants with depression also demonstrated a lack of habituation. Further research is needed to reinforce this assumption.

The positive relationship between amygdala habituation and ACE severity in healthy controls could possibly be understood by the allostatic load and stress theory (Bower et al., 2008). Within the context of resilience, mild forms of ACE and a quick adaptation and habituation to repeated presentation of negative or aversive emotional cues could lead to a positive health outcome (McEwen et al., 2015). Previously, adaptive stress-dependent functioning of the amygdala has been discussed within the context of resilience towards psychopathologies (Holz et al., 2020). However, the distribution of ACE severity in our low-risk healthy control group was highly (positively) skewed. Thus, any inferences about the observed relationship should be made with caution and require refinement in future work.

3.5.1 Limitations

Possibly due to the recruitment procedure and the corresponding in- and exclusion criteria, we examined only individuals with AUD that had mild to moderate levels of ACE. Further, we only included HC that reported no ACE following our screening procedure. To overcome these methodological issues, future studies need to address the influence of ACE on amygdala habituation in individuals with AUD in larger study populations with a more normally distributed expression of ACE levels, while also including healthy controls with a wider range of ACE. Additionally, the proposed processes of sensitization need to be examined in a paradigm better suited for this purpose, e.g., by prolonging the current fMRI task. Lastly, longitudinal studies are needed to address amygdala habituation and causal relations of ACE as a major stressor in early life, the facilitating effect of ACE towards AUD, and finally the (neurotoxic) effect of alcohol.

3.5.2 Clinical implications

Following more recent developments in psychotherapy (i.e., modular, or process-based psychotherapy), emotion regulation is one of the core processes mediating symptom reduction and therapeutic outcome (Chambers et al., 2009; Kraiss et al., 2020; Pavlacic & Young, 2020). Our findings of a possible sensitization towards fearful and angry faces in individuals with AUD might serve as a neurobiological reinforcement for the fruitful use of interventions that aim to increase habituation to negative emotions (Berking et al., 2011; Garland et al., 2014). Mindfulness-based relapse prevention as therapy add-on shows a positive effect on craving, which is mediated by acceptance, awareness, and nonjudgment (Witkiewitz et al., 2013). Berking et al. (2011) observed a negative relation between emotion regulation skills and alcohol

use after standard treatment. In particular, tolerating negative emotions predicted alcohol consumption when controlling for other emotion regulation skills (Berking et al., 2011). Therefore, neural plasticity could also inversely be used to reduce sensitization and enhance habituation following before-mentioned interventions building a bridge from trans-diagnostic phenotypes to such therapeutic approaches.

3.6 Conclusion

The present study is the first to report a deficient amygdala habituation to repeated negative emotional stimuli in AUD. Our data suggests a lack of an association between amygdala habituation and adverse childhood experience in AUD. However, deficient amygdala habituation related to the amount of alcohol consumption in the overall sample might indicate a short-term substance effect. The findings of this study extend previous knowledge by suggesting a new neural mechanism for understanding the AUD-related alterations in amygdala functioning, and thus underlying emotion regulation, and thereby opening a new avenue for further research and treatment.

3.7 Supplementary Material

3.7.1 Adverse childhood experience

The ANOVA model with an additional interaction term (group x CTQ sub scores), to test for potential group-specific associations between severity of ACE and neural habituation was repeated for emotional neglect, emotional abuse, physical neglect, physical abuse, and sexual abuse. This exploratory analysis aimed to reveal the effect of specific sub scores potentially driving the effect of the CTQ sum score. Please see Supplementary Table S7 for details on ACE severity.

The exploratory analysis with CTQ sub scores testing the effect of different types of ACE (i.e. emotional neglect, emotional abuse, physical neglect, physical abuse, and sexual abuse) identified the similar associations for HC group for physical neglect ($t = 3.93$, $pFWE = 0.011$, see Supplementary Figure S10) and emotional neglect ($t = 3.71$, $pFWE = 0.019$). However, no effect of ACE on neural habituation within the amygdala was observed in the AUD group. No significant associations for other CTQ sub scores were observed in HC or AUD.

Alcohol consumption

To test the effect of previous alcohol exposure on amygdala habituation, we used the overall alcohol consumption in grams during the last three month prior to the experiment (Miller & Del Boca, 1994). For this we set up three separate regression models (with the left, right and bilateral amygdala habituation estimates) in SPSS, while including sex as a covariate. This analysis revealed a significant association between the higher alcohol consumption and reduced habituation in right amygdala (R^2 = -0.356, F = 8.736, p = 0.004) and left amygdala (R^2 = -0.309, F = 6.332, p = 0.015); not significant for bilateral amygdala (R^2 = 0.026, F = 0.041, p = 0.841). This association was detected across the full sample and thus was independent of the clinical status of the participants, as required from a neural risk marker.

To test a group-specific association, we set an additional model with group x alcohol consumption interaction term. However, we observed no significant interaction effect (right amygdala F = 1.524, p = 0.222; left amygdala: F = 0.622, p = 0.433, bilateral amygdala F = 0.069, p = 0.794).

Please see Supplementary Figure S11 for a scatterplot displaying the relation between amount of alcohol during the last three months prior to the experiment and amygdala habituation, separated by group.

3.7.2 Supplementary Tables

Table S7: Group differences in the severity of ACE between AUD and HC.

	HC Mean (SD)	AUD Mean (SD)	Statistics
N	27	36	
Sex (male:female)	11:16	24:12	**$\chi^2(1) = 4.20$, p = 0.040**
Age (years)	36.9 (12.5)	40.3 (12.6)	T(61) = 1.05, p = 0.299
CTQ			
Overall (sum score)	31.3 (7.7)	39.3 (14.4)	**T(56.1) = 2.82, p = 0.007**
Emotional abuse (sum score)	6.0 (1.8)	8.8 (4.9)	**T(47.5) = 3.12, p = 0.003**
Emotional neglect (sum score)	8.6 (4.8)	11.4 (5.4)	**T(60) = 2.13, p = 0.038**
Physical abuse (sum score)	5.3 (0.7)	6.3 (2.5)	**T(43.0) = 2.44, p = 0.019**
Physical neglect (sum score)	6.3 (2.1)	7.2 (3.3)	T(60) = 1.31, p = 0.195
Sexual abuse (sum score)	5.2 (0.5)	5.5 (1.9)	T(60) = 0.96, p = 0.339

Note: SD = Standard Deviation; n = sample size; AUD = alcohol use disorder; CTQ = Childhood Trauma Questionnaire. Significant group differences are highlighted in bold.

Table S8: Following a whole brain analyses using the individual first level statistics of habituation, a two-sample t-test including sex as a covariate revealed significant results. At pFWE < 0.05, one significant cluster emerged for the group contrast AUD < HC (cluster size 554 voxel, peak intensity of 4.308 at [x y z = 36 2 -22]). Supplementary Figure S13 is depicting this whole group comparison.

Side	Lobe	Brain Areas	Brodmann Area	Cluster Size	MNI Co-ordinates	t_{max}
Right	Temporal	Middle and superior temporal pole, middle temporal gyrus	21, 38	554	36 2 -22	4.308
Right	Limbic	Hippocampus, amygdala				

Note: MNI = Montreal Neurological Institute. A combined voxel-wise- [p < 0.001] and cluster-extent threshold [k >= 544 voxel] following the random-field theory in SPM12 was applied, corresponding to pFWE < 0.05.

3.7.3 Supplementary Figures

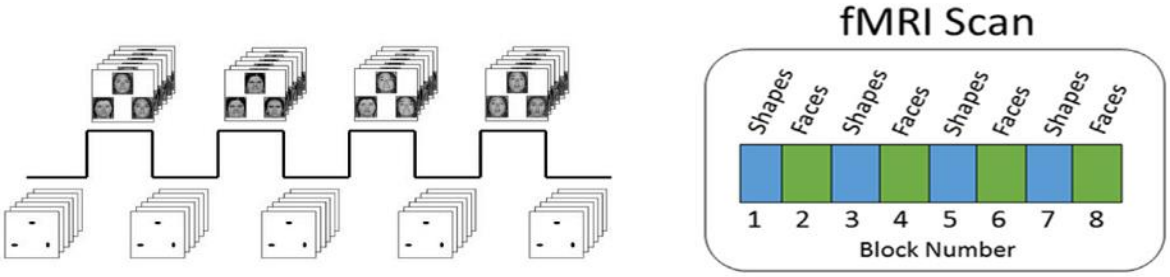


Figure S8: Face Matching paradigm. Faces with fearful or angry faces, as well as shapes were presented in a block design. All stimuli were presented in black and white. Participants were instructed to select the corresponding face or form according to the target as quickly and precisely as possible.
This figure derived from de dissertation of Oksana Berhe, as specified in the preface on page III.

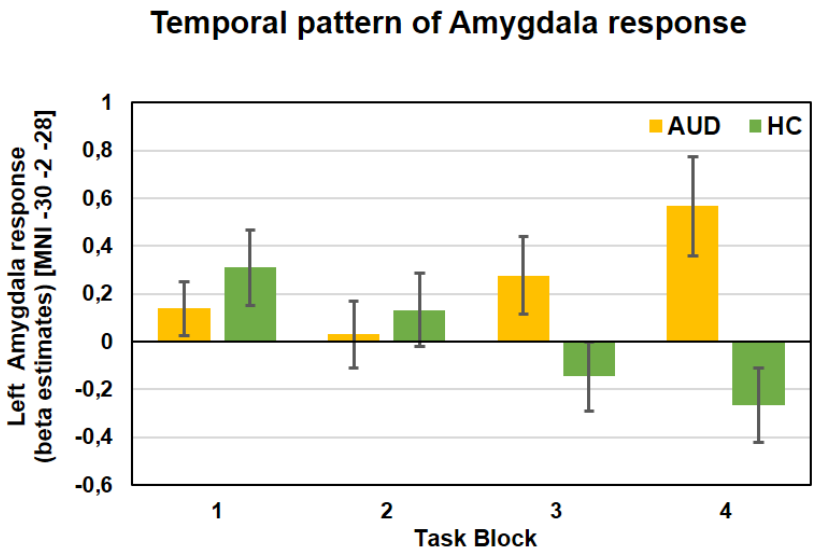


Figure S9: Amygdala habituation to aversive stimuli. Plotted habituation estimates of the peak voxel in the left amygdala are displayed.
This figure derived from the dissertation of Oksana Berhe, as specified in the preface on page III.

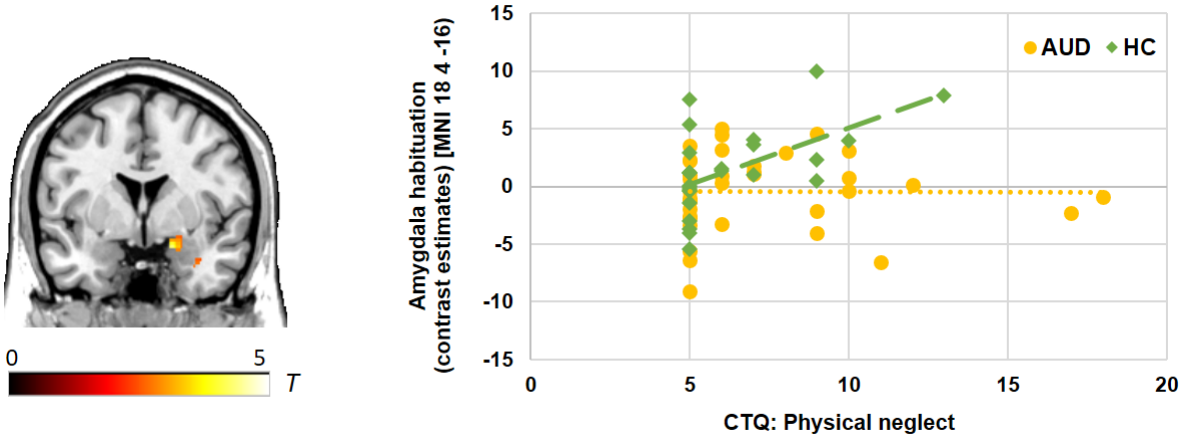


Figure S10: Amygdala habituation to aversive stimuli in relation to physical neglect. Amygdala habituation relates to ACE differently: increased amygdala habituation is associated with higher physical neglect sum score in HC, but not in AUD group (T = 3.93, pFWE = 0.011).

For illustration purposes, a significance threshold of $p_{uncorr} < .005$ was applied and displayed on the coronal section. HC: healthy control participants, AUD: alcohol used disorder, ACE: adverse childhood experience; FWE: familywise error; MNI: Montreal Neurological Institute.

This figure derived from the dissertation of Oksana Berhe, as specified in the preface on page III.

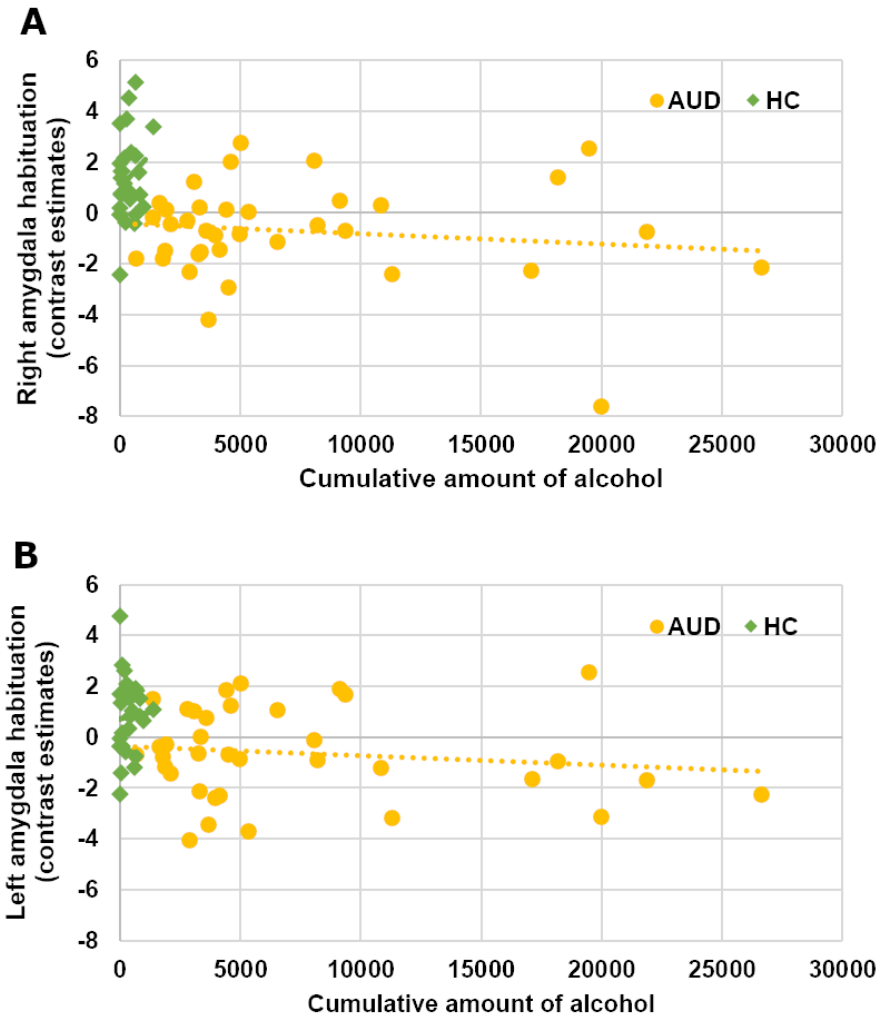


Figure S11: Relation between drinking and amygdala habituation. The relation between overall alcohol consumption in grams during the last three month prior to the experiment is displayed in relation to left or right amygdala habituation, separated by group (AUD, HC).
HC: healthy control subjects, AUD: alcohol used disorder

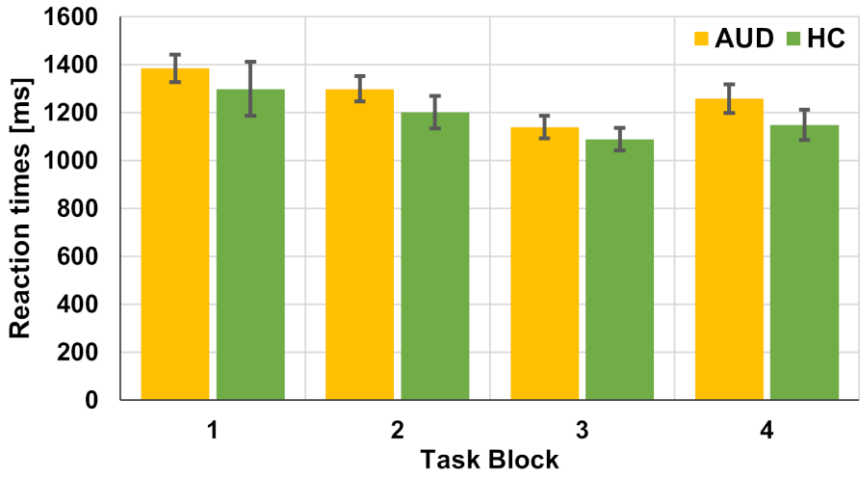


Figure S12: Plotted block wise mean reaction times to aversive stimuli. Both groups exhibited a reduction in mean reaction times from blocks 1+2 to blocks 3+4 (AUD: T = 4.79, p < 0.001; HC: T = 2.39, 9 = 0.025) . However, this reduction did not differ between HC and AUD (T = 0.14, p = 0.890).

HC: healthy control participants, AUD: alcohol used disorder, ACE: adverse childhood experience; FWE: familywise error; MNI: Montreal Neurological Institute.

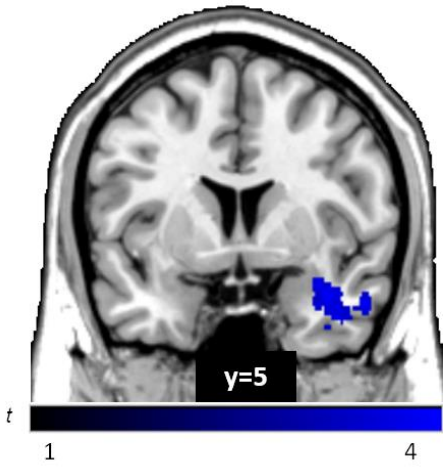


Figure S13: Whole brain group comparison using first level habituation index. Following a whole brain analyses including the individual first level statistics of habituation, a two-sample t-test including sex as a covariate revealed significant results. Using a FWE-corrected threshold of $p < 0.001$ in combination with a cluster-extend threshold 554 voxel of (following the random field theory in SPM), one significant cluster emerged for the group contrast AUD < HC (cluster size 554 voxel, peak intensity of 4.31 at [x y z = 36 2 -22]). This cluster encompasses voxels located in the right middle and superior temporal pole, the right amygdala, the right hippocampus and the right middle temporal gyrus.

HC: healthy control participants, AUD: alcohol used disorder, FWE: familywise error; MNI: Montreal Neurological Institute

4 DISCUSSION

ACEs represent one important risk factor regarding the etiology of SUDs. Despite the fact that ACEs and SUDs cause devastating harm to individuals and society, in terms of health and the economy, little is still known about specific pathways contributing to the risk of SUD after ACE. To date, the prevalence and severity of CM - one major aspect of ACE - have not yet been examined regarding the type of SUD. Further knowledge gaps need to be closed, for instance, regarding pathways related to stress, affective symptoms, or substance craving. Additionally, deficits in emotion processing and regulation have been discussed as a potential mediator between CM and SUD. The amygdala represents a target of interest for research, insofar as it is a central hub of the emotion circuitry. As outlined in Chapter 1, advances in neuroscience, i.e. within the model by Koob and Volkow (2010), contributed to a better understanding of neurobiological alterations in SUD; however, ACEs need to be integrated further into research as they are an important psycho-social factor that contribute to the development and maintenance of SUD. A deeper understanding of the prevalence and severity of those experiences in individuals seeking treatment for SUD, as well as possible underlying neural mechanisms of emotion processing, might provide insights regarding the etiopathological contribution of CM as well as possible treatment targets.

4.1 Integration of Study Results in Previous Findings

4.1.1 Prevalence and Severity of CM in SUD

Study 1 (Gerhardt et al., 2022a) demonstrated that treatment-seeking individuals with SUD are more often and more severely affected by all types of CM, as compared to the general population (Klinitzke et al., 2012; Witt et al., 2017). Contrary to Hypothesis 1 and 2, it is not individuals with OUD, but with CUD, who are the most affected - even though the prevalence of CM in included individuals with OUD was similarly high as in previous observations (Medrano et al., 1999; Santo et al., 2021). The first consideration relating hereto might be the use of cannabis for the purpose of self-medication. It is known that external cannabinoids can enhance the effect of endocannabinoids on the extinction of aversive memories or on the regulation of aversive affect and stress (Lutz et al., 2015; Marsicano et al., 2002). Furthermore, medical cannabis can be used to target neural circuitries relevant for emotion and stress regulation, for instance, in anxiety and trauma-related disorders (Kondev et al., 2021; Papagianni &

Stevenson, 2019). This neuromodulatory effect might explain why the use of cannabis was reported to be related to negative life events, trauma, maladaptive coping strategies, as well as emotion dysregulation (Hyman & Sinha, 2009; Vilhena-Churchill & Goldstein, 2014). Indeed, positive effects of cannabis intake on trauma symptoms were observed in individuals suffering from PTSD (LaFrance et al., 2020). Second, the OUD patient group mainly consisted of individuals currently in outpatient opioid maintenance therapy. Compared to in-house or day-clinic patients, this group was not abstinent and did not receive extensive therapeutic care throughout the day. An effect of this daily opioid intake might interfere with memory functioning and could hamper retrospective reporting of CM (Darke et al., 2012). Similarly, being intensely confronted with one's current situation, as is the case for patients in treatment for SUD, attention towards traumatic events could have been increased. However, these aspects require further examination.

In accordance with Hypothesis 3, higher prevalence of all types of abuse were observed in women and the severity of emotional and sexual abuse was significantly higher as compared to men. This confirms previous observations that women are more often and more strongly affected by ACEs. Studies also reported that the prevalence of emotional and sexual abuse was higher for women as compared to men, especially in Europe and North America (Moody et al., 2018). For the general population of Germany, sex/gender difference were also highest for emotional and sexual abuse (Witt et al., 2017). One opposing observation was made in Canada, where males reported a higher prevalence of physical abuse (Meng & D'Arcy, 2016). However, the authors also reported that women were more at risk for SUD after having experienced an ACE –despite the fact that the general risk for SUD was lower for women.

While a positive association between CM and depressiveness was observed for both men and women (Hypothesis 4), anxiety and perceived stress could only be related to CM in the male group. The likelihood for mood and anxiety disorders is higher following CM (Teicher & Samson, 2013), an association that was later confirmed by meta-analyses (Gallo et al., 2018; Gardner et al., 2019). However, the association between sexual and physical abuse and symptoms of depressiveness and anxiety was observed to be larger for women as compared to men (Gallo et al., 2018). In a sample of college students, CM related to specific drinking motivess such as coping with depression and anxiety as well as mood enhancement (Goldstein et al., 2010). In men, only the latter motive mediated the relation between CM and alcohol consequences, as measured using the Alcohol Use Disorder Identification Test. In contrast, coping

with depression and anxiety were observed to be significant mediators for women. In the present sample of individuals with SUD, a relation of these symptoms to CM also seems to be sex-specific, which needs to be elaborated in future studies.

Regarding Hypothesis 5, emotional abuse was the most important type of CM with respect to its influence on craving at admission to treatment. Previously, this subtype of CM was related to substance use (Norman et al., 2012) and was observed to be the strongest predictor for the severity of AUD (Schwandt et al., 2013). The relation that was observed between CM and craving at admission to treatment is of high interest as craving potentially excerpts an influence on relapse susceptibility (Bottlender & Soyka, 2004; Schneekloth et al., 2012). Being aware of the potential influence of CM on treatment outcomes could improve individual treatment strategies, possibly reducing relapse risk.

In this study, however, symptoms of depressiveness and anxiety, as well as perceived stress were observed to excerpt great influence on both craving at admission and craving reduction over the course of the treatment (Hypothesis 6). While CM might enhance the risk for future mood and anxiety disorders (Teicher & Samson, 2013), conversely, symptoms of depressiveness and anxiety were reported to facilitate relapse in patients with SUD (Charney et al., 2005). Kirsch et al. (2020) summarized the shared mechanisms that are relevant for this highly prevalent comorbidity (Kirsch et al., 2020). To this end, impairments in emotion-, stress- and reward regulation were reported, as well as underlying endocrine and neural alterations. Interestingly, Brady and Sinha (2005) reported that mood and anxiety disorders mediated the relation between ACE and increased risk for SUD (Brady & Sinha, 2005). This finding aligns with others (Salokangas et al., 2018), supporting this mediation. Furthermore, it has been concluded that SUD in association with ACE further increases the likelihood of mood and anxiety disorders (Kirsch et al., 2020). This is backed up by the observation that substance consumption alters the neurobiology implicated in the development of such comorbidities, for instance, on the level of neurotransmitters (Palomo et al., 2007). In the context of AUD and comorbid PTSD, Lee et al. (2018) found that a dysregulation of the HPA axis and glucocorticoid signaling following ACE in conjunction with (epi-)genetic effects on those mechanisms, contribute to the comorbidity (Lee et al., 2018). Finally, these observations underline the complexity by which ACE might influence mental health outcomes and highlight potentially diverging pathways from ACE to such comorbidities in terms of the temporal course of this interdependency.

Following Hypothesis 7, the present study observed that women (as compared to men) exhibited higher craving at admission to treatment – and that the severity of emotional abuse excerpted an influence. Trautmann et al. (2018) observed that, when exposing healthy individuals

with a history of ACE to traumatic stimuli, an increased craving for alcohol was observed in women, but not men. However, in men, the severity of ACE was positively associated with trauma-induced craving and further related to cortisol reactivity (Trautmann et al., 2018). In female rape victims, negative affect mediated the relation between PTSD and same-day alcohol drinking, especially in those women with AUD (Cohn et al., 2014). These findings further support the notion of sex-specificity in the context of ACE and SUD.

4.1.2 Amygdala Habituation in AUD and the Relation to CM

One potentially important mechanisms underlying the relation of ACE and SUD – and comorbid mental disorders such, as depression - are impairments in emotion processing and regulation, as well as alterations of neural correlates. To this end, amygdala habituation was examined in individuals with varying severity of AUD and CM, in Study 2.

Study 2 (Gerhardt et al., 2023) observed altered emotion processing in individuals with AUD as compared to healthy individuals and a relation to the severity of CM. While amygdala habituation to aversive emotional stimuli was not only reduced in individuals with AUD, as postulated in Hypothesis 1, data indicated a sensitization of amygdala reactivity towards such stimuli. Interestingly, a positive association between the severity of CM and amygdala habituation was observed only for healthy individuals, thus, opposing Hypothesis 2.

In individuals with SUD, deficits in emotion regulation are often cited and it has been observed that emotion dysregulation relates to the severity of the disorder and consumption frequency (Garke et al., 2021). Furthermore, higher use of response modulation and less frequent use of cognitive change were observed in individuals with AUD (Petit et al., 2015). Interestingly, the use of response modulation strategies was related to stronger alcohol craving while shorter rehabilitation duration were necessary for individuals with more frequent use of cognitive change.

The amygdala, as part of the neural emotion circuitry (LeDoux, 2003), is involved in emotion processing and regulation (Phelps & LeDoux, 2005). In their quantitative meta-analysis, Hein and Monk (2017) observed increased amygdala activation in individuals with a history of ACE, as compared to controls. Most paradigms applied aversive emotional stimuli, equal or similar to the stimulus material used in the present study. Likewise, alterations of amygdala functioning were repeatedly reported for individuals with AUD or in relation to alcohol consumption; however, researchers also observed a lack of differences between healthy individuals and individuals with AUD (Centanni et al., 2019; Glahn et al., 2007; Gorka et al., 2013). Approaching

amygdala reactivity by averaging neural activity per stimulus conditions throughout the task, as it is custom in many analyses, might reduce the interpretability of findings. Examining amygdala habituation, a proxy for the dynamic adaptation of amygdala activation, indeed, revealed such a dynamic change of activation to aversive emotional stimuli in Study 2. Previous studies observed reduced amygdala habituation in anxiety (Avery & Blackford, 2016; Hare et al., 2008), borderline personality disorder (Bilek et al., 2019), autism spectrum disorder (Tam et al., 2017), and psychosis (Avery et al., 2021). Interestingly, increased habituation was related to PTSD severity (Kim et al., 2019). In AUD, however, the results resembled a sensitization of amygdala activity towards aversive emotional stimuli, therefore, displaying a unique pattern compared to other mental disorders. Alterations in neural emotion processing and regulatory systems, regarding neurotransmission, for instance, following the development of AUD (Robinson & Berridge, 1993) could result in this novel observation of neural emotion processing in AUD, as compared to healthy controls. Plasticity mechanisms of the brain might cause this neural sensitization (Ramaswami, 2014) which previous studies have reported in AUD (Breese et al., 2011; Di Chiara, 2000; Gilpin et al., 2015; Heilig et al., 2010a; Heilig et al., 2010b; Volkow et al., 2012). This includes individuals with chronic AUD, for whom repeated episodes of abstinence and relapse result in a sensitization of withdrawal symptoms, ultimately leading to a prolonged experience of negative affect throughout abstinence (Heilig et al., 2010a). Neural correlates of the stress and emotion processing system suggest a sensitization to aversive or stressful stimuli, which then translates to the behavioral level.

In this context, additional thoughts merit consideration. Dannlowski et al. (2012) reported an association between CM and hyperreactivation of the amygdala in response to threatening faces in healthy individuals. The authors also observed underlying structural alterations, including reduced gray matter volume of the hippocampus, insula, caudate, orbitofrontal, and anterior cingulate cortices (Dannlowski et al., 2012). Interestingly, these findings were observed in healthy individuals, and survived correction for depressiveness, anxiety, age, recent stressful life events, and others. The authors discussed their observation in the light of a causal relationship between emotional disorders and ACE being moderated by those functional and structural alterations (Dannlowski et al., 2012).

While the amygdala and further limbic structures are commonly focused upon in SUD-related emotion processing research, hypoactivation of the frontal and anterior cingulate cortex were also observed in the context of emotion regulation (Wilcox et al., 2016). Furthermore, impaired prefrontal regulation, rather than hyperreactivity to emotional stimuli of the amygdala, was discussed with regards to SUD. Additionally, altered frontal-limbic pathways (Hart & Rubia,

2012) in relation to ACE were observed, and emotion regulation related to frontal-amygdala connectivity as well (Kim et al., 2011). Likewise, it has been observed that the emotional response to stress and the expression and regulation thereof seem to rely on prefrontal and amygdala functioning (Orem et al., 2019). Functional connectivity also gains importance in the case of successful emotion regulation strategies, such as reappraisal (Banks et al., 2007; Berboth & Morawetz, 2021). In abstinent methamphetamine users, connectivity of the amygdala to widespread brain regions during rest was positively related to CM, and amygdala-hippocampus connectivity was negatively related to mindfulness and positively to emotion dysregulation (Dean et al., 2014). This is significant because in patients with AUD, cognitive changes are related to rehabilitation duration and response modulation is related to craving severity, underscoring the differential consequences of adaptive or inefficient regulatory strategies (Petit et al., 2015).
Of note and with regards to the high comorbidity of AUD and anxiety and mood disorders, individuals (as compared to individuals with AUD only) experience even stronger difficulties in emotion regulation (Bradizza et al., 2018). Additionally, they report higher distress and more drinking due to negative affect, and impaired mindfulness skills.
While amygdala habituation represents a novel and interesting area of research in emotion processing, possible influences of comorbidities, structural alterations, and mechanisms of functional connectivity need to be considered in future research.

In the present study, a relation between CM and amygdala habituation was only observed in healthy individuals and, therefore, contradicted Hypothesis 2. While the ongoing alcohol consumption of the presented sample may have masked the effects of CM, as discussed in Chapter 3, this observation also initiates the discussion of resilience. While one aspect might be of environmental nature, epigenetic mechanisms could further contribute to the risk (or lack thereof) for mental health problems after ACE (for an overview, see Bellis et al., 2014; Herzog & Schmahl, 2018). Furthermore keeping in mind that the sample of Study 2 included healthy controls with only mild levels of CM, this somewhat less threatening environment could have contributed to a quick adaptation and habituation of amygdala reactivity to aversive emotional stimuli – and, thus, may have promoted positive health outcomes (McEwen et al., 2015). Resilience towards psychopathologies could be enhanced by an adaptive functioning of the amygdala during stressful situations. Interestingly, it has been observed that positive childhood experiences contribute to good mental health outcomes, possibly counteracting detrimental effects of ACE (Bethell et al., 2019). This is also backed up by biological mechanisms related to social bonding, as a positive family environment in interaction with a specific allele of the oxytocin receptor gene might buffer ACE effects (Bradley et al., 2013). Additionally, research has shown

that a supportive social environment strengthens neural correlates and might thus counteract detrimental influences of ACEs (Holz et al., 2020). How the aspect of positive childhood experiences might influence amygdala habituation in individuals with SUD remains to be examined in future studies.

4.1.3 Influence of Gender and Sex

In general, consumption of alcohol worldwide is quite high, which is reflected in the prevalence of AUD. In the past, observable sex/gender differences were attributed to biological and psychological aspects (Becker et al., 2017; Ceylan-Isik et al., 2010; Erol & Karpyak, 2015). In line with previous research, individuals with SUDs displayed a higher prevalence and severity of CMs. However, this was more pronounced for women in Study 1. Therefore, sex/gender differences merit attention - in addition to what has already been discussed above. Erol and Karpyak (2015) suggested in their review that gender differences might arise from psycho-socio-cultural factors, whereas sex differences might result from underlying biological factors. Whereas the gender aspect might relate to traditional gender roles and generational factors, the sex aspect may be associated with sex hormones, pharmacokinetics, and alcohol effects on the brain (Erol & Karpyak, 2015).

Approximately 85% of all European men over the age of 15 years reported drinking alcohol within the last 12 months in 2016. For women, only 61% stated to do so (World Health Organization (WHO), 2019). However, during the past decade, the overall increase in alcohol was greater for women (Grucza et al., 2018). Furthermore, if initiation of alcohol consumption occurs during early adolescence, young women are at higher risk for developing AUD (Cheng & Anthony, 2018).

Men were reported to use alcohol to increase positive affect or during social contact, while women tend to drink alcohol to regulate stress and negative emotions (Becker et al., 2017; Becker et al., 2012; Müller et al., 2021; Peltier et al., 2019). Women with AUD experience more intense alcohol craving than men (Boykoff et al., 2010), and exhibit a stronger relation between craving and negative affect during detoxification (Petit et al., 2017). In contrast, other researchers reported higher alcohol craving for non-dependent alcohol drinking men, as compared to women, even though participants' drinking behavior was comparable (Wang et al., 2019). The authors also observed that cue-reactivity of the thalamus mediated the relation between craving and the cue-induced skin conductance response in men, but not women. These findings are of high relevance, as craving was worse in women when examining the influence

of emotional abuse on craving at admission to treatment (see Study 1). Diverging findings between men and women could also derive from the severity of AUD, as mild versus severe courses of the disorder might reduce or inverse sex effects.

Sex differences were also observed during an fMRI imagery task using personalized scenarios of either stress or alcohol-cues or a neutral context (Seo et al., 2011). In men, stress-associated hyperactivation of medial prefrontal regions, the anterior cingulate, insula, hippocampus, and amygdala were reported (Seo et al., 2011). In women, however, alcohol-cue-associated hyperactivation of superior and middle frontal regions was observed. Additionally, activation in emotion-regulation brain regions in relation to stress-induced anxiety was observed in men; in women, however, an association with brain regions relevant for cognitive processes emerged. Finally, in men, an association between alcohol craving and the ventral and dorsal striatum was observed (Seo et al., 2011). In problematic alcohol drinkers, an fMRI task using visual alcohol cues elicited stronger activation of the nucleus accumbens (ventral striatum; Kaag et al., 2019). However, the examined sample consisted of socially drinking healthy individuals. Opposing this finding, in treatment-seeking patients with severe AUD, no sex differences in neural cue-reactivity were observed when being presented with visual alcoholic cues (Gerhardt et al., 2022b). Therefore, the stage of AUD, for example, in terms of severity, might diminish sex differences in AUD-related neural alterations.

Returning to the circular model of SUD, as described Chapter 1.2 (Koob & Volkow, 2010), Flores-Bonilla and Richardson (2020) integrated the aspect of sex into the neurobiological concept. During the binge and intoxication stage, in which men and women have displayed diverging prevalence, higher risk-taking and sensation-seeking tendencies of men as well as anxiety-reducing expectations of women were related to detrimental consumption patterns of alcohol. Furthermore, gonadal hormones interact with the brain reward system (i.e., meso-cortico-limbic, and dopaminergic system) in a sex-specific manner. Lastly, the anterior cingulate and dorsolateral prefrontal cortex were then shown to be relevant regions that are affected during this stage, especially in men. Regarding the withdrawal and negative affect stage, a dysregulation of stress hormone levels - but also experiences of negative affect and irritability - occur, which suggests that neural stress circuitries are altered. This arises, for instance, when negative reinforcement learning occurs, as individuals during alcohol to counterbalance aversive consequences of alcohol abstinence. In preclinical studies, male rats seem to display greater sensitivity towards aversive withdrawal symptoms. Furthermore, sex differences in hormonal and neural stress regulation have been postulated to be associated with the direct effect of alcohol on

the stress system, for instance, following prolonged alcohol consumption. Besides the amygdala, alterations of prefrontal regions, as well as the hippocampus, might be affected. Lastly, during the preoccupation and anticipation stage - during which compulsive drinking and experiences of strong craving occur - inflexibility regarding the drinking behavior and impaired executive functioning promote the continuance of drinking. While increased striatal activation in men was observed, there were no conclusive results regarding the (in-) flexibility of drinking behavior in women. In addition, a stronger negative association between prefrontal cortical thickness and heavy episodic drinking was observed in men, while functional and structural alterations (e.g., regarding medial prefrontal regions, the insula, the hippocampus, and the striatum) might be sex-dependent. Hippocampal impairments in females – as suggested by preclinical animal studies - may strongly interfere in stress regulation. This, in turn, could facilitate relapse via alcohol-cue reactivity and craving (Flores-Bonilla & Richardson, 2020).

In sum, sex/gender differences might contribute to the development and maintenance of SUD, either through psycho-socio-cultural aspects and/or neurobiological adaptation throughout an individual's history of SUD. Integrating the aspect of ACE and corresponding interactions, as discussed above, should be explored in future research.

In Study 1, sex differences regarding prevalence and severity of CM were observed in individuals with SUD. Additionally, a sex-specific influence regarding emotional abuse on craving at admission to treatment was revealed. In Study 2, sex-effects were not explicitly examined, as the small sample size imposed limitations in this regard. Therefore, sex was included as a covariate in those analyses. However, both studies are subject to additional limitations regarding the assessment of sex/gender, as is will be discussed in Chapter 4.5. Recently, Guinle and Sinha (2020) summarized that women who are more at risk for ACE, might also be more vulnerable to potential consequences such as SUD. Because exposure to ACE might impair emotion regulation, as well as executive functioning, and decision-making, it could also lead to early alcohol consumption to "cope" with these difficulties, ultimately fostering the development of AUD (Rothman et al., 2008). Interestingly, it has also been proposed that either enhanced or blunted (neuro-)endocrine stress reactivity in adolescence might mediate substance consumption (Chaplin et al., 2018). The authors suggested that young women are more likely to experience enhanced stress reactivity and might, therefore, use substances as a means to cope with resulting negative emotions. In contrast, young men might experience blunted stress reactivity, leading them to use substances to increase arousal or sensation. These hypotheses are crucial for understanding the effects of sex differences, as they acknowledge the observation that women report negative affect more frequently than men. This negative affect, in turn, has

been associated with impaired emotion regulation, for instance, through increased rumination in women (Thomsen et al., 2005). Lastly, the link between emotion dysregulation and substance use or SUD is equally well-established (Garke et al., 2021).

It is worth noting that ACEs' ambiguous influence neural endpoints might also be due to confounding factors like sex and gender. Sex-specific neurobiology (e.g., the influence of estrogen in women; Helpman et al., 2017), as well as gender aspects, should be acknowledged in future research. Ultimately, the interplay between women's higher risk for ACE, their differential neurobiological stress-reactivity, and their responsiveness to the effects of substances might increase the likelihood for women to engage in substance consumption or to attain severe SUD.

4.2 Additional Considerations Regarding the Pathway from ACE to SUD

4.2.1 Timing of ACE

Besides solely assessing whether or not an individual witnessed an ACE, the timing of ACE is also of great importance. By now, it is acknowledged that ACE interferes with brain development on a structural and functional level (Bick & Nelson, 2016). Time-specific sensitive periods of neural development (Cicchetti, 2015) might be one driving factor contributing to the heterogeneity of findings, when examining the sequelae of ACE. To date, results on the influence of ACE on neural structures are somewhat inconclusive. In some children with ACE, for instance, reduced amygdala volume was observed (Hanson et al., 2015). However, other children, who had spent long time periods in orphanages, displayed enlarged volumes of the amygdala as well as impaired emotional regulation (Tottenham et al., 2010). These diverging results could be due to the timing of ACEs, which previous researchers have found to have an effect on brain volume in individuals with ACE (Herzog et al., 2020; Pechtel et al., 2014). Pechtel et al. (2014) observed a peak sensitivity of the developing amygdala occurring between the ages of 10 and 11. During these years, ACE severity has the strongest influence on an individual's adult amygdala volume. Therefore, this time span might represent a critical period for the detrimental effects of ACEs (Pechtel et al., 2014). Additionally, random forest analyses revealed that ACE during the ages 10 and11 as well as 13 years had a time-specific impact on brain volume of the amygdala and hippocampus in later life (Herzog et al., 2020). Furthermore, it has been reported that stressful experiences, such as ACE or events leading to PTSD, do not only affect amygdala volume during childhood or adolescence but also amygdala reactivity to threatening stimuli during adulthood (Sicorello et al., 2021; Siehl et al., 2022). Consequently,

the authors recommended considering a longer period of time, as severe stress during adulthood could also affect brain structure and functioning—but potentially in opposing directions. For example, in a sample of women with ACE and PTSD or ACE and no mental disorder, larger amygdala volumes were associated with adulthood trauma, whereas smaller volumes were related to childhood trauma (Siehl et al., 2022). In SUD, relevant literature is even sparser. As reviewed by Andersen (2019), ACE does, in fact, influence brain development and possibly HPA axis functioning during sensitive periods, which then increases the risk for later SUD; and the review also confirmed differences regarding sex/gender. In cocaine use disorder, CM was associated with reduced gray matter volume of the orbitofrontal cortex (Bachi et al., 2018), a region highly relevant for SUD as it is involved in compulsive substance use (Volkow & Fowler, 2000). Regarding brain functioning, Zhu et al. (2019) observed differential amygdala reactivity to aversive emotional faces in individuals with ACE, depending on the timing of the ACE (Zhu et al., 2019). They reported an association between early ACE exposure and blunted amygdala reactivity, as well as between late ACE exposure and enhanced reactivity. These diverging associations might explain why compiling ACE, throughout 18 years of life might lead to inconclusive or even contradictory results. The time-sensitive influence of ACE could, therefore, also hamper interpretability of study results, as reported in Study 2, and needs further evaluation.

Despite the consensus in neuroscience that there are specific sensitive time periods in neural development, there is a research gap regarding the timing of ACEs. As observed in Study 1, the majority of individuals with CUD, as well as women with SUD, reported on having witnessed ACEs. Consequently, the question of timing needs to be explored in this population. Here, it seems that not only structural impairments of ACEs during sensitive time periods merit attention. Moreover, functional impairments must be examined, firstly, as a consequence of ACE during sensitive time periods, as well as, secondly, independent of ACEs during such time periods. For instance, amygdala habituation, as reported in Study 2, warrants further investigation. In this context, some thoughts are elaborated upon in Chapter 4.5 Limitations.

4.2.2 The Role of Cognitive Functioning

As discussed above, ACE does not only affect neurobiology related to emotion, stress, and reward processing. ACEs also alter cognitive functioning, such as memory, attention, or executive functioning (Edalati & Krank, 2016; Goltermann et al., 2021; Kavanaugh et al., 2017). Studies have shown, for instance, that a history of ACE is associated to impairments in memory functioning affecting both short and long-term memory in adults (Beers & De Bellis,

2002; Bremner et al., 2004; Majer et al., 2010; Navalta et al., 2006); working memory in children and adults (DePrince et al., 2009; Majer et al., 2010); as well as memory content. Dysfunctional self-associations (i.e., self-blame; Wright et al., 2009) and memory associations related to anxiety and depressiveness and oneself (van Harmelen et al., 2010) were reported. Interestingly, the latter study reported a stronger effect of emotional abuse and neglect as compared to physical or sexual abuse, which further demonstrates the differential effect of specific subtypes of CMs. Additionally, visual and auditory attention capacities and executive functioning, such as inhibitory control, are reduced following CM (Beers & De Bellis, 2002; DePrince et al., 2009). Strikingly, experiences of neglect related to reduced executive functioning in adulthood (Nikulina & Widom, 2013). It is also worth noting that a history of CM relates to impairments in inhibitory control throughout childhood, adolescence, and adulthood (Edalati & Krank, 2016). Impaired inhibitory control, in turn, is considered a risk factor for SUD (López-Caneda et al., 2013), and hampers treatment success, for instance, by promoting relapse (Czapla et al., 2016). Neural circuitries of inhibitory control also involve prefrontal brain regions; and the maturation of these regions proceeds until early adulthood (Rubia et al., 2006). Therefore, childhood and adolescence represent critical time spans for the effects of ACEs as well as substance use regarding the influence on inhibitory control. Based on these observations, the mediating impact of the pathway of cognitive control regarding ACE and subsequent SUD should explored in depth in future studies. Therefore, a follow-up study will address this topic to re-evaluate the individuals from Study 2. Türkmen et al. (2022) will incorporate a neuroimaging paradigm on response inhibition (stop-signal task) and working memory (n-back task), therefore, generating new insights into neurobiological aspects of cognitive functioning in the context of ACE and AUD.

4.2.3 Reciprocity and Intergenerational Transmission

While SUD as a consequence of ACE has been widely discussed, SUD is also considered a cause of ACE, as visualized in Figure 14. The literature predominantly considers ACE a transdiagnostic risk factor related to mental health outcomes, as it adds to the risk of developing a mental disorder irrespective of specific diagnostic pigeonholes (Ball & Links, 2009; Green et al., 2010).

Anda et al. (2002) observed that children growing up in a household with problematic parental alcohol use were more likely to experience ACE. However, Eiden and Leonard (2000), on the other hand, hypothesized that an inadequate parenting style (e.g., by behaving aggressively towards the child) could results from a parent suffering from SUD (Eiden & Leonard,

2000). Additionally, neural alterations in reward and stress systems in parents suffering from SUD might result in decreased salience of their child's cues (Rutherford & Mayes, 2017). A rather passive and disengaged behavior towards the child might, thus, result in experiences of neglect for the child. Furthermore, taking care of a child might be perceived as being stressful rather than rewarding. A recent meta-analysis observed an association between maternal ACE and child externalizing behavior, a risk factor for later substance use (Pedersen et al., 2018). This is likely mediated by child ACE and maternal depressive symptoms (Loheide-Niesmann et al., 2022). Interestingly, neurobiological changes due to SUD might also affect the interaction with a child. For example, the dopamine, oxytocin, and glucocorticoid systems are altered following ACE, which represents a risk factor for later SUD (Kim et al., 2017). Additionally, these circumstances might ease the intergenerational transmission of both ACE and SUD. Therefore, - and aside of biological factors - a parent-child transmission of SUD is possible due to adverse environmental factors, namely ACE resulting from a parent with SUD.

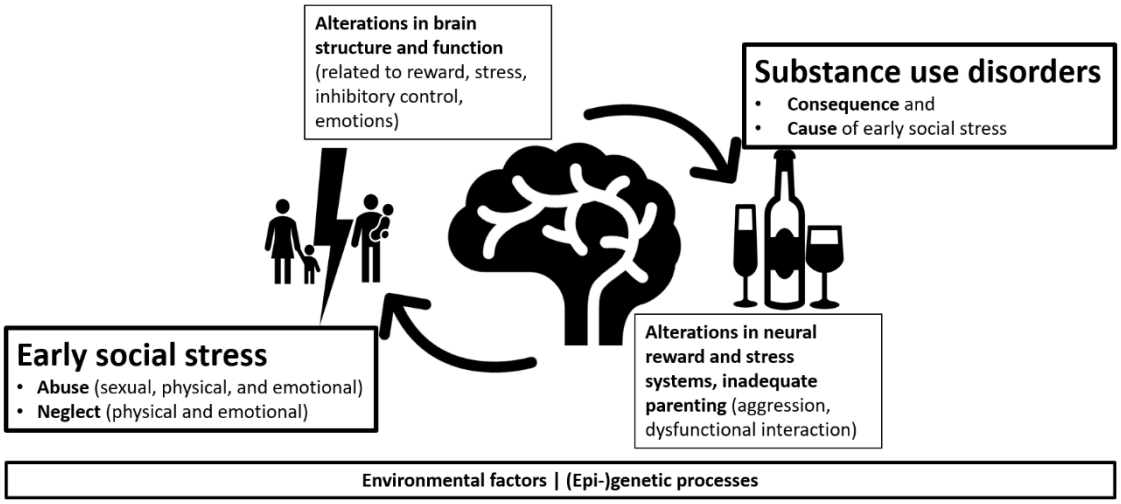


Figure 14: Substance use disorder represents cause and consequence of early social stress, such as adverse childhood experiences. The reciprocal relationship might be mediated by neurobiological alterations, for instance, neural circuitries of stress, reward, and emotion processing. Impairments in parenting styles could close this vicious circle. Lastly, environmental factors and (epi-)genetic processes might influence these effects. Taken with permission of Springer Nature from: Berhe, O., Gerhardt, S., Schmahl, C. (2022). Clinical Outcomes of Severe Forms of Early Social Stress. In: Miczek, K.A., Sinha, R. (eds) Neuroscience of Social Stress. Current Topics in Behavioral Neurosciences, vol 54. Springer.

4.3 Limitations

While the aspects of study sample size or study sample characterization were discussed in Chapters 2 and 3, further limitations need to be acknowledged.

First, retrospective assessments, which are easy to implement, are known to be subject to bias, such as recall problems or the influence of current mood or motivation. While test-retest reliability of retrospective measures (e.g., CTQ or MACE) are deemed to be good to excellent for in individuals with SUD (Bernstein et al., 1994; Seitz et al., 2022; Teicher & Parigger, 2015), other studies have shown moderate to good reliability in older adults (mean age 68.5 years) over a six-year follow-up period (Wielaard et al., 2018). Interestingly, in this older sample, yes-answers were reported to fluctuate more than no-answers. Furthermore, depressive symptoms influenced the reporting of emotional neglect. In their meta-analysis, Baldwin et al. (2019) observed diverging outcomes of mental health regarding ACEs, when prospectively examining children or, retrospectively, adults. They concluded that either measure identifies different individuals at risk, which relates to differential underlying risk mechanisms as well as potential intervention strategies (Baldwin et al., 2019). Importantly, the association between CM and SUD risk remained, although repeated measures of CM in a sample of young adults varied in the given responses (Fergusson et al., 2000). This supports the use of retrospective measurements, as biased reporting did not fully explain this association.

Nevertheless, generational aspects also play a role. Some studies reported increased ACE scores for younger generations (e.g., "Generation Z", birth years 1995 - 2010) as compared to older generations (e.g., "baby boomers", birth years 1946 - 1964; Hughes et al., 2022). However, another study observed that the relation between ACE and detrimental health outcomes (e.g., AUD) remained stable throughout the 20th century despite the broad societal changes that took place during this period (Dube et al., 2003). While the observations by Dube et al. (2003) have been replicated, in the meantime, other studies additionally reported that the type of ACE is dependent on the respective birth cohort (Damian et al., 2021): physical abuse, neglect, divorce, and household mental illness in relation to suicidal thoughts were more prevalent in the group of Baby Boomers.

Second, the region of origin and culture were observed to be driving factors behind the heterogeneity of results with regards to prevalence of both ACE and SUD. As the here presented samples included German-speaking individuals only - most of whom originated from Central and Eastern Europe (data not shown) - generalizability of the presented results is subject to these restrictions. Besides the inclusion criteria of German language skills, random sampling took place to this end. However, we lack knowledge regarding underlying mechanisms linking ACE and SUD that also consider the possible influence of region of origin and/or culture. To name one example, HPA-axis reactivity was three times more sensitive in male African Amer-

icans as compared to male White Americans. Furthermore, White Americans with AUD exhibited a blunted cortisol reactivity as compared to healthy controls, while African Americans with AUD displayed an increased cortisol reactivity (Price et al., 2019). Additional studies including individuals from a broad range of cultural backgrounds are, therefore, urgently needed.

Third, in addition to ACE, traumatic experiences in later life may also excerpt an influence on neurobiology and behavior. As recently reported, amygdala reactivity to negative stimuli (e.g., pictures of physical or sexual violence or mutilation) differed with regards to ACE during early childhood or PTSD (Sicorello et al., 2021). While higher severity of ACE related to reduced amygdala reactivity, PTSD was associated with increased amygdala reactivity when controlling for ACE. However, this study had several limitations, such as having examined only women and not having included a control group. Also, most individuals with PTSD exhibited high severity of ACE. Nevertheless, this aspect is of high interest and was not explicitly examined in the present studies. While comorbidities were assessed in Study 1, current PTSD was an exclusion criterion for Study 2. Therefore, the results of Study 1 and Study 2 do not shed light on possible converging effects of early and later life traumatic experiences. Similarly, the timing of ACE was not explored in depth in the present analyses. Using a structured interview to assess ACE throughout the first 18 years of life, such as the MACE interview (Teicher & Parigger, 2015), corresponding analyses are possible. During data collection for Study 2 an adapted, brief version of this interview was administered. In collaboration with other research groups, a validation study of this German interview was conducted, including data from Study 2 (Seitz et al., 2022). This raises the possibility for follow-up analyses, which could further explore ACE type and timing, as discussed in Chapter 4.4.1.

Fourth, the sample presented in Study 2 consisted of healthy controls with no to mild CM and individuals with AUD who had reported no to moderate CM. While the current data might have yielded interesting results regarding group differences, the influence of CM on amygdala habituation needs to be interpreted with caution. For both groups, namely the healthy controls and individuals with AUD a broad range of CM severity would have been necessary to better generalize results. The current data does not allow for the interpretation of the effects of moderate to severe ACE. Furthermore, the effects originating from either CM or the substance consumption by itself, were not clearly disentangled. Likewise, the interaction of both aspects was not examined in depth due to the distribution of severity of ACE in both groups.

Fifth, the aspect of sex/gender was assessed by means of a binary question in Study 1 and Study 2. As outlined in Chapter 4.3., both sex and gender might influence the development

and maintenance of SUD possibly via different pathways. It is therefore recommended that future studies assess both aspects, for example, using the Bem Sex-Role Inventory (Auster, 2020) to address masculine, feminine, and neutral personality characteristics.

Lastly, as it is apparent in the choice of study designs, one must not equate correlation with causality. The presented data derives from cross-sectional studies, which, in inherently, do not allow to draw causal conclusions. It is worth noting that previous longitudinal studies had already observed a causal relation between familial conflict, which potentially leads to ACE, and an increased risk for SUD during adolescence (Skeer et al., 2009). In a large sample of over 12,000 adolescents, CM was related to an increase in heavy episodic drinking even after controlling for other factors, such as parental AUD, age, or gender. The authors concluded that there is a robust and causal relation between CM and later alcohol-related problems (Shin et al., 2009). Longitudinal studies are, therefore, necessary to address mechanisms underlying the pathways between ACE and SUD (e.g., emotion, stress, or reward). In this regard, large-scale studies (e.g., the ABCD Study in the United States) are of high scientific value, as they assess early life stress in relation to neurobiological functioning (Hoffman et al., 2019). At the moment, participating children, aged 9 to 13 years, are initiating and continuing substance use (Sullivan et al., 2022). The scientific community expects to gain in-depth knowledge on the relation between ACE and SUD as well as underlying neurobiological functioning, thanks to these large-scale studies.

4.4 Clinical Implications and Treatment Approaches

Roughly three-quarters of children worldwide witness ACEs (World Health Organization (WHO), 2022), which increases the likelihood of developing a broad range of mental and somatic conditions (e.g., SUD) later in life. Importantly, recent trends report a closing gap between men and women regarding the prevalence of AUD (Grant et al., 2017; Slade et al., 2016; White, 2020). This might increase the overall prevalence of SUD. In a large national representative survey in the United States, 12% of males and 5% of females were observed to have AUD in 2001 and 2002. Approximately ten years later, these numbers increased by 35% for males (to 17% total) and by 84% for females (to 9% total; Grant et al., 2017). The authors of this study warned of an increase in alcohol-related health consequences, such as breast cancer, liver cirrhosis, or fetal alcohol spectrum disorder. White (2020) substantiated these findings and postulated that women suffered more severe consequences than men following a comparatively shorter drinking history compared as well as having to endure stronger side

effects of SUD treatment medication (Agabio et al., 2016). Because this trend in drinking behavior might continue, a deeper understanding of sex and gender-related mechanisms is necessary to inform preventive and therapeutic approaches (e.g., McCaul et al., 2019). Furthermore, the influence of ACE and possible therapeutic approaches to this end are of relevance.
This dissertation's findings are not only relevant for research, but also inform therapeutic approaches targeting SUD. It further supports the line of argument by which the prevention of ACE needs to receive more support through financing, research, and implementation in everyday life.

First, because ACE increases the risk for later SUD, prevention strategies targeting children and adults withhold the greatest opportunity. The high prevalence and severity of ACEs in patients with SUD - especially regarding cannabis as observed in Study 1 - are paralleled by developments in consumption behavior and increased potency of the substances on the market (Manthey, 2019). Detrimental health outcomes, regarding cannabis consumption in individuals with a history of ACE, also encompass a higher risk for psychotic symptoms in adolescents (Harley et al., 2010), as well as a more severe course of bipolar disorder (Aas et al., 2014). A study using a focus group approach demonstrated that poverty and social isolation contributed to the experience of CM (Maguire-Jack et al., 2018). The authors also identified intergenerational transmission of violence as well as substance use to be a significant cause of CM. Regarding interventional approaches, parent education was reported to be focused on often. Maguire-Jack et al. (2018), however, stipulated that poverty and substance use must be reduced too. These findings apply to other countries as well: according to the WHO, the current global prevention plan for ACEs also includes approaches to reduce poverty, sex/gender inequality, as well as supporting caregivers (World Health Organization (WHO), 2020). While ameliorating general societal aspects, such as poverty or providing parents with educational help, are promising, specific interventions, such as child-centered help for children from parents in treatment for SUD could also be fruitful, as they identify specific individuals at risk rather than providing help via a scattergun approach. Nevertheless, a routine screening for ACE during childhood and adolescence might also identify at-risk children at an earlier stage as advocated by McCrory et al. (2017), who encourage early identification and intervention for children affected by ACE. In their review, they summarized alterations of neural threat-, reward-, and emotion processing as well as cognitive control following ACE. This not only strongly demonstrates the extent to which the developing brain might be sensitive to early life stressors (e.g., ACE), it once more describes ACE as a risk factor for later SUD.

Second, an early identification of children witnessing ACEs could be followed by early and beneficial intervention directly targeting children. In this regard, cognitive-behavioral therapy has proven to be beneficial (Runyon et al., 2010). Furthermore, addressing specific domains affected by ACE seems promising, for instance, emotion processing and regulation (Loevaas et al., 2019), as well as cognitive functioning including inhibitory control (Robinson et al., 2014). A meta-analysis reported overall small effect sizes for interventions regarding prevention and curation (van der Put et al., 2018). Besides cognitive behavioral therapy, home visitations and systemic approaches are recommended. Likewise, interventions addressing self-confidence of parents or emotional support are effective. Early identification of children witnessing ACEs or at risk thereof, followed by prompt interventions, might, therefore, be an effective treatment strategy for reducing the risk of later mental disorders (e.g., SUD), as they might prevent detrimental neurobiological changes following ACE (McCrory et al., 2017).

Third, screening for ACE could also be applied to individuals already engaging in heavy episodic drinking or seeking treatment for SUD. As presented in Chapter 1 of this dissertation, these adverse experiences are associated with a faster progression from drinking alcohol to developing AUD (Oberleitner et al., 2015), as well as promoting a more severe course of the disorder (Alvanzo et al., 2020; Schwandt et al., 2013), or higher chance for relapse (Schückher et al., 2019). Identifying this risk factor could positively influence the course of the disorder through adequate treatment strategies.

Fourth, individual therapy strategies could be implemented based on early identification of ACE. These therapy strategies include emotion regulation skills, mindfulness, habituation, or trauma-informed approaches. Interestingly, it has been observed that mindful emotion regulation, which includes non-judgmental aspects of awareness, disrupts habitual reactions towards emotions (Chambers et al., 2009). Regarding neural correlates, mindfulness meditation reduced amygdala reactivity to emotional stimuli (Kral et al., 2018). The authors discussed their finding as one mechanism resulting in improved emotion regulation following mindfulness-based stress reduction. Because mindfulness-based treatment approaches often require time and commitment, Wu et al. (2019) implemented a brief mindfulness meditation that successfully improved emotion processing, by decreasing the intensity of emotions. In a sample of undergraduates, Brett et al. (2018) observed an increase in alcohol use in relation to the increased ACE, which was mediated by lower levels of mindfulness. Furthermore, mindfulness-based approaches positively influence the treatment of AUD, as they target, for example, emotion regulation skills, craving, cue-reactivity, and physiological stress (Garland et al., 2014).

Additionally, integrative psychosocial interventions are promising for individuals suffering from both, SUD and ACE. Both, interpersonal psychotherapy (Markowitz et al., 2008) and trauma-informed approaches (Covington, 2008), including yoga (Esfeld et al., 2021; Macy et al., 2018) are recommended. Integrating cognitive-behavioral and interpersonal elements in psychotherapy (i.e., Cognitive Behavioral Analysis Systems of Psychotherapy), as compared to supportive psychotherapy, resulted in a better treatment outcome for individuals with depression who experienced emotional abuse (Bausch et al., 2020). Study 1 revealed that emotional abuse is the most relevant subtype of CM regarding individuals with SUD. Applying this approach to patients with SUD, who experienced this specific type of CM, therefore, warrants urgent examination. Regarding cognitive impairments mediating ACE and SUD outcomes as described in Chapter 4.2.2, neurocognitive trainings alongside psychotherapeutic interventions seem plausible but has not been investigated to date (Kavanaugh et al., 2017).

Fifth, real-time neurofeedback training could be applied to target amygdala habituation, for example. In healthy adults, first findings suggest an influence of mindful attention training on amygdala reactivity to emotional faces, which was interpreted as a positive intervention effect on emotion processing (Desbordes et al., 2012). Others observed that real-time neurofeedback using electroencephalography could be used to target amygdala-based reactivity, when examining individuals undergoing stressful military training (Keynan et al., 2019). The authors argued that this approach might even prevent stress-induced psychopathology. This workgroup later published a study using this approach in a small sample of individuals with PTSD (Fruchtman-Steinbok et al., 2021). The individuals successfully learned to downregulate amygdala activation, which further supports the idea that neural modulation could be trained and willingly applied. A successful modulation of amygdala activation through fMRI neurofeedback training was also reported for healthy individuals (Zotev et al., 2011). Applying this technique in individuals with borderline personality disorder resulted in successful downregulation of amygdala activity as well (Zaehringer et al., 2019). The latter study also discussed a positive effect on emotion regulation. As confirmed in a review, individuals can successfully learn to regulate neural activity in regions relevant for emotion, using real-time neurofeedback (Linhartová et al., 2019). These studies, therefore, provide a sound basis for exploring this technique regarding its effectiveness in individuals with SUD and a history of ACE, for instance, by increasing habituation of the amygdala to aversive emotional stimuli.

Lastly, it is worth noting that medical interventions also yield promising results for affected individuals. For example, amygdala-hippocampal connectivity during stress was related to emotional abuse in a healthy community sample (Fan et al., 2015). The authors were able to

alter this relation by administering the peptide hormone oxytocin, which is known for its stress-reducing effects. In SUD, the application of oxytocin is still under investigation, for example, regarding the management of withdrawal symptoms (Lee et al., 2016). Possibly, its mechanism of action could alter the dopaminergic or glutamatergic reward systems (Sundar et al., 2021). In regards to naltrexone, an opioid receptor antagonist used in AUD treatment, ACE influenced cortico-limbic reactivity to aversive emotional stimuli in individuals with AUD (Savulich et al., 2017). The authors observed that with more severe ACE, the desired effect of naltrexone became greater. Additionally, an effect on amygdala functioning was observed in individuals with AUD and comorbid SUD. Of note, this observation further supports the hypothesis of an interaction between neural and environmental factors in SUD, which is also relevant for individualized treatment.

Overall, a broad range of clinical interventions could benefit from the current knowledge regarding ACE and its influence on SUD. While some approaches might relate to the prevention of ACE, others could target the identification of ACE-related impairments (e.g., regarding emotion processing) to buffer the subsequent risk for the development of SUD. Likewise, behavioral therapy approaches could counteract mediating factors, such as emotion regulation, as such impairments potentially maintain an already developed SUD. Lastly, recent developments in neuroscience could not only be used for research but therapy as well, as is the case for real-time neurofeedback.

As many studies on ACE and subsequent mental health problems were conducted in adults with borderline personality disorder, PTSD, or depression, a deeper understanding of further mental disorders is needed. Study 1 demonstrated a high prevalence and severity of CM in individuals with SUD and indicated a relation thereof with substance craving, symptoms of stress, depressiveness and anxiety. Regarding amygdala habituation following ACE, a new approach of identifying therapy targets could be possible. Instead of focusing on diagnosis-specific deficits and symptoms, biology-based therapy approaches could be focused on. While some individuals with mental disorders might not differ from healthy individuals, others might exhibit increased amygdala habituation (e.g., in PTSD; Kim et al., 2019), impaired habituation (e.g., in anxiety, borderline personality disorder, psychosis, Avery & Blackford, 2016; Avery et al., 2021; Bilek et al., 2019; Hare et al., 2008), or even sensitization as observed in Study 2 for AUD. As a variety of mental and somatic disorders are considered an outcome of ACE, underlying deficits in neurobiological and behavioral functioning, such as stres- and emotion (dys-)regulation could be focused on during treatment.

5 SUMMARY

Substance use disorders are a major global health problem. Worldwide, over 35 million individuals suffer from substance use disorders, adding to 283 million individuals who are affected by alcohol use disorder. Being both a risk factor and consequence of substance use, alterations in the structure and function of the brain take place, for example, in regions relevant for reward, stress, and emotion processing.

However, merely considering neurobiological aspects does not do justice to the complexity of the disorder. Previous research suggests that adverse childhood experiences, for instance, childhood maltreatment (i.e., emotional, physical, and sexual abuse, as well as emotional and physical neglect), are an important risk factor in the etiopathology of substance use disorders.

As such, these experiences also affect the neurobiology of an individual, which might just as well lead to alterations in reward, stress, and emotion processing – and, thus, result in an earlier onset of substance use disorders or hamper treatment success. In this context, substance craving and impaired emotion processing are of importance as they may facilitate relapse, which, in turn, maintains a substance use disorder.

This dissertation, therefore, integrates neurobiological and societal aspects to address pathways contributing to the risk of substance use disorders. To this end, an individual's history of childhood maltreatment – one major aspect of adverse childhood experience – will be explored in depth.

Study 1 examined 655 treatment-seeking individuals with substance use disorders and revealed high prevalence and severity of all subtypes of childhood maltreatment. In this sample, women and individuals with cannabis use disorder were most severely affected, especially by emotional abuse. Emotional abuse, but not other subtypes of childhood maltreatment, positively related to substance craving at admission to treatment. However, symptoms of depressiveness, anxiety, and perceived stress influenced craving severity at admission and craving reduction during treatment rather than childhood maltreatment severity. The results revealed a subtype-specific influence of childhood maltreatment, and, furthermore, demonstrated the significance of type of substance and sex/gender. This study illustrated the importance of including the aspect of childhood maltreatment in individualized treatment approaches.

Study 2 addressed neural correlates of emotion processing and expanded previous findings of altered amygdala functioning in individuals with alcohol use disorder by applying a habituation index. Further, the relation between amygdala habituation to repeated aversive emotional stimuli and childhood maltreatment was examined. Individuals with alcohol use disorder exhibited not only deficient amygdala habituation, compared to healthy individuals. Beyond that, the temporal pattern of habituation resembled neural sensitization, thus, showing a unique amygdala habituation pattern compared to other mental disorders such as post-traumatic stress disorder. While no relation between childhood maltreatment and amygdala habituation was observed for individuals with alcohol use disorder, healthy individuals exhibited increase habituation in relation to more severe physical and emotional neglect. Lastly, a significant relation between higher alcohol intake and reduced amygdala habituation was observed to be independent of the clinical status of the participants, which might indicate short-term substance effects. The study revealed, thus, novel evidence regarding alterations in emotion processing in alcohol use disorder that might open a new avenue for treatment targets.

Taken together, the two studies demonstrated the relevance of addressing adverse childhood experiences, and informed about pathways leading to substance use disorders. Integrating this societal aspect into neurobiological research reveals new opportunities for treatment strategies.

6 ZUSAMMENFASSUNG

Substanzgebrauchsstörungen sind ein bedeutendes Gesundheitsproblem. Weltweit leiden mehr als 35 Millionen Menschen an einer Substanzgebrauchsstörung; weitere 283 Millionen sind von einer Alkoholgebrauchsstörung betroffen. Veränderungen in der Struktur und Funktion des Gehirns, beispielsweise in Regionen die relevant für Belohnungs- Stress- und Emotionsverarbeitung sind, können dabei sowohl Risikofaktor für als auch eine Folge von Substanzkonsum sein.

Die alleinige Berücksichtigung neurobiologischer Aspekte wird jedoch der Komplexität der Substanzgebrauchsstörung nicht gerecht. Bisherige Forschung deutet darauf hin, dass aversive Kindheitserfahrungen, wie beispielsweise Kindesmisshandlung (emotionale und körperliche Misshandlung und Vernachlässigung, sowie sexueller Missbrauch), ein wichtiger Risikofaktor für die Ätiopathogenese der Substanzgebrauchsstörung sind.

Diese Erfahrungen wirken sich zudem auch auf die Neurobiologie einer Person aus, was ebenso zu Veränderung in der Belohnungs- Stress- und Emotionsverarbeitung führen kann. Dadurch kann ein früherer Beginn der Substanzgebrauchsstörung begünstigt oder der Behandlungserfolg verringert werden. Auch ist in diesem Zusammenhang ein spezifisches Substanzverlangen und eine beeinträchtigte Emotionsverarbeitung von Bedeutung, da hierdurch ein Rückfall begünstigt werden kann, der wiederum zur Aufrechterhaltung der Substanzgebrauchsstörung beiträgt.

Die vorliegende Dissertation werden daher neurobiologische und gesellschaftliche Aspekte integriert, welche zum Risiko einer Substanzgebrauchsstörung beitragen. Es wird daher die individuelle Erfahrung von Kindesmisshandlung, ein wichtiger Aspekt aversiver Kindheitserfahrungen, eingehend untersucht.

In Studie 1 wurden 655 Personen mit einer Substanzgebrauchsstörung untersucht, welche sich zum Zeitpunkt der Datenerhebung in Behandlung befanden. Es konnte eine hohe Prävalenz und ein hoher Schweregrad aller Subtypen von Kindesmisshandlung aufgedeckt werden. Zudem zeigte sich in dieser Stichprobe, dass Frauen und Personen mit einer Cannabisgebrauchsstörung insbesondere von emotionalen Misshandlungen am stärksten betroffen waren. Auch stand die Schwere emotionaler Misshandlungen in einem positiven Zusammenhang mit der Stärke des Substanzverlangens bei Behandlungsbeginn. Jedoch beeinflussten Depressivität, Ängstlichkeit und wahrgenommener Stress eher das Substanzverlangen bei Behandlungsbeginn und dessen Abnahme im Verlauf der Behandlung, als Kindesmisshandlungen. Die Ergebnisse

zeigten einen subtypspezifischen Einfluss von Kindesmisshandlungen und belegten darüber hinaus die Bedeutung der Art der Substanz und des Geschlechts in diesem Zusammenhang. Diese Studie verdeutlichte auch, wie wichtig es ist, den Aspekt Kindesmisshandlungen in individualisierte Behandlungsansätze einzubeziehen.

Studie 2 befasste sich mit neuronalen Korrelaten der Emotionsverarbeitung und ergänzte vorherige Erkenntnisse über eine veränderte Funktion der Amygdala bei Personen mit Alkoholgebrauchsstörung. Mittels eines Habituationsmarkers wurde zudem der Zusammenhang zwischen der Aktivität der Amygdala während wiederholter Darbietung aversiver emotionaler Reize und Kindesmisshandlungen untersucht. Personen mit einer Alkoholgebrauchsstörung wiesen im Vergleich zu gesunden Personen nicht nur eine reduzierte Amygdala-Habituation auf. Darüber hinaus ähnelte das zeitliche Muster der Habituation dem einer neuronalen Sensibilisierung. Diese Beobachtung steht im Gegensatz zu anderen psychischen Erkrankungen, wie der posttraumatischen Belastungsstörung. Während bei Personen mit Alkoholgebrauchsstörung kein Zusammenhang zwischen bei der Aufnahme in die Behandlung und Amygdala-Habituation festgestellt werden konnte, führte bei gesunden Personen die Schwere der körperlichen und emotionalen Vernachlässigung zu einer erhöhten Habituation. Es wurde zudem ein signifikanter Zusammenhang zwischen höherem Alkoholkonsum und verringerter Amygdala-Habituation unabhängig vom klinischen Status beobachtet, was auf kurzfristige Substanzeffekte hinweisen könnte. Die Studie lieferte somit neue Erkenntnisse über Veränderungen in der Emotionsverarbeitung bei Alkoholgebrauchsstörungen, welche einen neuen Weg für Behandlungsmöglichkeiten eröffnen können.

Zusammengefasst zeigten beiden Studien auf, dass der Aspekt aversiver Kindheitserfahrungen bei der Untersuchung von Entstehungswegen einer Substanzgebrauchsstörung wesentlich ist. Die Einbeziehung dieses gesellschaftlichen Aspekts in die neurobiologische Forschung eröffnet auch neue Möglichkeiten für Behandlungsstrategien.

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8 LIST OF TABLES

9 LIST OF FIGURES

10 CURRICULUM VITAE

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April 2018 – Juni 2021	**Universität Heidelberg** Graduiertenkolleg 2350 zu ‚*Einfluss von Traumatisierung im Kindes- und Jugendalter auf psychosoziale und somatische Erkrankungen über die Lebensspanne'*
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Seit Febr. 2023	**Frontiers in Psychiatry** Reviewer-Tätigkeit

STIPENDIEN

2022: Gleichstellungsmittel des Sonderforschungsbereichs TRR 265 für einen Mentoring- und Forschungs-Besuch (1.100€)

2022: Kollaborations-Preis des Graduiertenkollegs GRK 2350 für die Veröffentlichung '*Lack of amygdala habituation to negative emotional faces in alcohol use disorder - and the relation to adverse childhood experiences'* in Zusammenarbeit mit Oksana Berhe (1.000 €)

2019: Reise- und Teilnahmestipendium für das Wissenschaftliche Gespräch der DG Sucht für einen Vortrag zu *Der Einfluss aversiver Kindheitserfahrungen auf die Entstehung einer Alkoholgebrauchsstörung: Neue Chancen für die Behandlung von Suchterkrankungen* im Rahmen der Nachwuchsförderung (200 €, Teilnahmegebühren, Reisekosten)

2018: Reise- und Teilnahmestipendium für den Deutschen Suchtkongress der Nachwuchsgruppe der DG Sucht für den Beitrag '*Strukturelle und funktionelle neuronale Konnektivität bei Personen mit Alkoholgebrauchsstörung ohne Behandlungswunsch*' (150 €, Kongressgebühren)

11 PUBLICATION LIST

*The authors contributed equally.

Berhe, O.*, Gerhardt, S.*, & Schmahl, C*. (2022). Clinical Outcomes of Severe Forms of Early Social Stress. In K. A. Miczek & R. Sinha (Eds.), *Neuroscience of Social Stress* (pp. 417-438). Springer International Publishing. 10.1007/7854_2021_261

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Gerhardt, S.*, Berhe, O.*, Moessnang, C., Horning, M., Kiefer, F., Tost, H.*, & Vollstädt-Klein, S.* (2023). Lack of amygdala habituation to negative emotional faces in alcohol use disorder and the relation to adverse childhood experiences. *Addict Biol, 28*(1), e13251. 10.1111/adb.13251

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12 ACKNOWLEDGEMENTS

First of all, I would like to thank Prof. (apl.) Dr. **Sabine Vollstädt-Klein and** Prof. Dr. **Falk Kiefer** for the opportunity to work in this remarkable research department. I further thank Prof. (apl.) Dr. **Sabine Vollstädt-Klein** for her inspirational guidance, her trust in my abilities, and the freedom of research and thought she provided the environment for. I also gratefully acknowledge her wholehearted support not only in challenging professional but also in personal situations.

Further, I want to thank **Julian Wasmuth** and **Maibritt Horning**, who greatly supported me in data collection during their time as student research assistants.

Over the last years, I was privileged to work with PD Dr. **Fungi Gerchen** who is always willing to share his extensive knowledge on neuroimaging (and how to socialize at conferences) with incredible and never ending patience. I further want to thank PD Dr. Dr. **Patrick Bach**, **Haoye Tan**, and **Sabine Hoffmann** for their great support regarding data management and analysis and from whom I learned a lot for my own work. I highly appreciate to have worked with Prof. Dr. **Uli Frischknecht** and Prof. (apl.) Dr. **Derik Hermann** who were always open to interesting, controversial and fun discussions regarding our field and above. I gratefully thank Prof. Dr. **Bernd Lenz** for his support in finding my work activities and for the freedom of thought that he provides the environment for. I also thank PD. Dr. **Anne Koopmann**, PD. Dr. **Malte Bumb**, and **Christian Wisch** from whom I also learned a lot about treating substance use disorders.

I also want to thank **Birgit Freudenberger**, who is a great colleague and whom I want to consider a friend by now. In her presence, life seems always full of exciting opportunities (especially region wise, considering the many leisure options the Palatine regions has to offer). I highly appreciate all the support by **Birgit Hrinkow**, who, with enduring patience and a good sense of humor, resolves any organizational struggle. I further want to thank **Uli Gründling** for her lightheartedness that, as a neighbor to my office, helped be through some strenuous days. I am also grateful for the support by Dr. **Julia Herzog** and Dr. **Sylvia Steinmann**, who - in their roles as scientific and administrative coordinators of the research training group I was part of - continuously supported me during the last years regarding my academic career.

I am grateful for meeting **Katharina Eidenmüller**, **Alisa Riegler**, and Dr. **Mirjam Deffaa** with whom I did not only do clinical work with but who continued to be dear colleagues and friends throughout the last years. I want to thank them for their friendship and support.

What would life be without good food? I highly appreciated your company during lunch breaks, Dr. **Ruben Vonderlin** and **Alfred Wieland**, and for making my (work-) life way more palatable.

Amongst others, I want to thank my friends **Pia Trübenbach**, **Maria Häberlein, André Orwaldi, Ines Timler, Christoph Götsch, and Elisa Blaser** - who not only provided moral support throughout school or university but also greatly and repeatedly encouraged me to pursue my dissertation project.

I further want to thank my **parents, grand parents, sisters, and friends** for their continuous support.

Most importantly, I want to thank **Martin Weissgerber** for his unconditional support and love – and for his accompaniment during this and upcoming adventures.