Dissertation

Trauma, Personality and Substance Use Disorder: A Neuropsychodynamic Model of Addiction Etiology

submitted by

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Statutory Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all of those individuals and organisations that have contributed to the research for this thesis. Due acknowledgement has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the “Standards of Good Scientific Practice and Ombuds Committee at the Medical University of Graz“.

Vienna, September 2019 Jürgen Fuchshuber

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Abbreviations

ACC = Anterior cingulate cortex

alpha-MSH = alpha-melanocyte stimulating hormone

AN = Affective neuroscience

BNST = Bed nucleus of the stria terminalis

CCK = Cholecystokinin

CMA = Cortico-medial amygdala

CRF = Corticotropin releasing factor

DBI = Diazepam binding inhibitor

DMD = Dorso-medial diencephalon

DTI = Diffusion tensor imaging

FA = Fractional anisotropy

ICSA = Intracranial drug self-administration

LA = Lateral amygdala

LH = Lateral hypothalamus

LH-RH = Human luteinizing hormone-releasing hormone

MFB = Medial forebrain bundle

MH = Medial hypothalamus

ML-DA = Mesolimbic dopamine system

NAcc = Nucleus accumbens

NPY = neuropeptide Y

PA = Parafascicular area

PAG = Periaqueductal gray

PFC = Prefrontal cortex

POA = Preoptic area

SCR = Superior corona radiata

SLF = Superior longitudinal fasciculus

SUD = Substance use disorder

VMH = Ventromedial hypothalamus

vmPFC = Ventromedial prefrontal cortex

VTA = Ventral tegmental area

Abstract in German

Mit Hinblick auf die hohe Prävalenz von Substanzgebrauchsstörungen (SUD), ihre vergleichsweise schlechte Behandelbarkeit und ihre katastrophalen Auswirkungen auf die individuelle Gesundheit und die gesamte Gesellschaft, gibt es gewichtige Argumente dafür die psychologische Erforschung dieser Störung zu intensivieren. Während die Methoden der traditionellen Psychoanalyse als unzureichend für den Umgang mit dieser Störung kritisiert wurden, haben die jüngsten Fortschritte auf dem Gebiet der Neuropsychoanalyse neue und vielversprechend Hypothesen bezüglich dieser Erkrankung hervorgebracht. Bisher wurden diese jedoch kaum empirisch getestet.

Daher wurden im Zuge dieses Forschungsprojekts sieben Studien durchgeführt, die sich mit der Beziehung zwischen SUD, Kindheitstrauma, Primäremotionen, Persönlichkeitsstruktur, Bindung und neurophysiologischen Parametern befassen.

Die Ergebnisse zeigen, dass SUDs signifikant mit Kindheitstraumata und bestimmten psychodynamischen Persönlichkeitskonzepten, einschließlich unsicherer Bindung, verminderter Persönlichkeitsorganisation und vermindertem emotionalen Funktionieren, zusammenhängen. Berechnungen mit Strukturgleichungsmodellen und Pfadanalysen legen nahe, dass der pathogene Effekt von Kindheitstraumata durch seine Beziehung zu einer beeinträchtigten Persönlichkeitsstruktur mediiert wird. Auf einer neurowissenschaftlichen Ebene zeigten männliche SUD Patienten zudem deutliche Abweichungen hinsichtlich ihrer Faserstrukturen der Weißen Masse sowie eine reduzierte kortikale Dicke innerhalb der linken Insula und des linken lateral-orbitofrontalen Kortex. Zudem zeigte sich eine reduzierte Oxytocin Reaktivität bei diesen Patienten.

Die Ergebnisse betonen nicht nur die quantitativ-empirische Validität des neuropsychoanalytischen Ansatzes zur Erforschung der ätiologischen Hintergründe von SUDs, sondern es konnten auch erste Hinweise auf die neurophysiologische Korrelate dieser psychodynamischen Konzepte nachgewiesen werden. Zudem unterstreichen die Ergebnisse insbesondere die Konzeptualisierung von SUD als Störung, die mit dysfunktionalen Affektregulations- und Bindungsfähigkeiten zusammenhängt. Diese Defizite werden ihrerseits von Abweichungen in subkortikalen und neokortikalen Strukturen sowie neurophysiologischen Prozessen reflektiert. Ziel zukünftiger Forschung sollte es sein, diese Beziehung noch detaillierter zu kartographieren.

Abstract in English

Considering the high prevalence, the poor treatment outcome and the catastrophic health-related and socioeconomic consequences associated with substance use disorder (SUD), there is a strong case for intensified research on this subject. Therefore, the present thesis aims at developing a neuroscientifically informed psychodynamic framework regarding the etiology of SUD, in order to path new ways for the understanding and treatment of this potentially life-threatening condition. While traditional psychoanalysis has been criticized as insufficient for the treatment of SUD, recent progress in the field of neuropsychoanalysis has generated new and promising hypotheses regarding its etiology. However, empirical research applying this framework has been sparse. In order to fill this gap, the original research presented in this thesis consists of seven studies investigating connections between childhood trauma, primary emotions, personality structure, attachment and neurophysiological parameters as well as their relation to addiction development and treatment.

Studies indicate that SUDs are significantly associated with childhood trauma and a variety of psychodynamic personality concepts including insecure attachment, decreased personality organization and decreased primary emotion functioning. In correspondence to this, structural equation modeling and path analysis estimations suggest that the pathogenic effect of childhood trauma is mediated by its relation to impaired personality structure. On a neuroscientific level, these results are paralleled by evidence for neurological alterations associated with SUD, especially pronounced in widespread deviations in white matter fiber tracts and decreased cortical thickness predominately affecting the left insula and lateral orbitofrontal cortex. Furthermore, SUD patients showed decreased oxytocin reactivity in response to an attachment-based intervention.

The results not only highlight the empirical validity of the neuropsychoanalytic approach towards SUD etiology but also present tentative evidence for the neurophysiological correlates of psychodynamic concepts. In particular, the findings underscore the conceptualization of addiction as a disorder related to dysfunctional attachment and affect regulation abilities, often caused by traumatic childhood relationships. In turn, these deficits seem to be reflected by alterations in subcortical and neocortical structures as well as reduced oxytocin reactivity. Future research should aim at mapping this relationship and in more detail.

Chapter I: Introduction

General Introduction

Substance use disorders (SUD), commonly referred to as addictions, are generally defined as chronic, pathological and compelling urges to consume one or more psychoactive substances, notwithstanding harmful effects for oneself and others (Bilitza, 2008). Despite a "war on drugs", which has raged for almost 50 years with the aim of achieving a drug-free society, SUDs are still one of the most common psychiatric disorders worldwide. According to the World Drug Report 2017, problematic substance use and SUD currently affects about 29.5 million people (UNODC, 2017). The consequences of this syndrome not only impact individual health but also significantly burden the public health systems and society as a whole. In order to improve the understanding of this disorder, this thesis tries to analyze and empirically test the different paths SUDs take to manifest in subjects. Thereby, it aims at developing an integrative and neuroscientifically informed psychoanalytic approach, with the goal of improving treatment options based on empirical research.

The word "addiction", used as a synonym for SUD in this thesis, derives from the Roman and medieval legal term "addictus", which can be translated as debt slave, describing a person who was sold to slavery, due to his inability to pay back his debts (Crocq, 2007). According to the Oxford English Dictionary (1989), the term "addict" has been in use since the 16th century, initially describing a person devoted to a practice. However, the use of addiction in its current medical meaning, describing a disorder characterized by chronic and harmful use of psychoactive substances, evolved over time. Its widespread application dates back to the 20th century and replaced older terms like "inebriety". In addition, the German equivalent "Sucht", descended from the Middle High German term "siech", can be translated as sick or diseased. Interestingly, in its contemporary use "Sucht" is strongly associated with "suchen" (meaning "seeking" or "searching"); this is intriguing as a central characteristic of patients suffering from addiction is their constant "search" for their drug of choice (Paetzold, 2006).

A Brief History of Substance Use Disorder Diagnosis

The consumption of potentially addictive psychoactive substances dates back to ancient times and since the beginning the relationship between humans and drugs could have

been said to be an ambivalent one. Their use can be schematically differentiated into socially appropriate forms, including consumption in a spiritual/religious context, and use for medical and hedonistic purposes. However, even early written records mention their potential for abuse and warn of its danger (Crocq, 2007). Already at 10,000 B.C. the intoxicating effects of fermented fruits were discovered in China and hence their consumption in the form of alcoholic beverages (Nathan et al., 2016). Furthermore, archeological records indicate Sumerian use of opium at 3000 B.C. (Brownstein, 1993) and the consumption of alcohol in the pre-Vedic Indus high culture at ca. 2030 B.C. (Sharma et al., 2010).

Early written records are found in the Rigveda, which describes the consumption of soma (an ambiguous and not clearly defined psychoactive substance) and cannabis (Nathan et al., 2016). In addition, the Old Testament describes a magnitude of anecdotes involving the use of wine. While moderate consumption of wine is valued rather favorably, alcohol intoxication is strictly condemned: “Do not look on the wine when it is red, When it sparkles in the cup, When it swirls around smoothly; At the last it bites like a serpent, And stings like a viper” (Proverbs 23: 31-32; Revised Standard Version, 1952). Moreover, important figures like Noah, Samson or Lot pay the severe consequences of alcohol excess. The New Testament assesses alcohol in a similar fashion. Jesus is attributed with moderate consumption of wine, however he is critical of its intoxicating effect. St. Paul recommends wine for medical purposes. Nevertheless, people who are unable to drink in moderation are advised to stay in abstinence (Ephesians 5:18; Revised Standard Version, 1952).

The ambivalent evaluation of alcohol in the Torah and Bible is contrasted by the writings of Islam and Buddhism, which are fundamentally opposed. For example, the Surah 5:90 (Qu'ran, 1977) warns of the dangers of both intoxication and gambling: “Believers! Intoxicants, games of chance, idolatrous sacrifices at altars, and divining arrows are all abominations, the handiwork of Satan. So turn wholly away from it that you may attain to true success.” Buddha condemned alcohol as a poison, which dims the clear light of consciousness, fosters ignorance and consequently keeps the human soul caught up in the entanglements of the cycle of death and rebirth (Sarao and Long, 2017).

In ancient Greece, wine and winemaking were known since ca. 2000 B.C. and played an important social role (Schott and Tölle, 2006). In the ancient world, drinking sessions called symposia served as events to create a sense of community and acted as a framework to

facilitate philosophical and scientific discourse (Schott and Tölle, 2006). What is more, within the Dionysus and Bacchus cults wine was religiously worshipped. However, ancient physicians like Celsus and Pliny, as well as philosophers like Aristotle, not only described the medicinal effects of alcohol but also warned of the harmful consequences of excessive alcohol consumption (Crocq, 2007). Nevertheless, within a moderate attitude wine was an important component of felicitous dietetics in the ancient societies of Greece and Rome.

Similarly, in medieval Europe alcoholic beverages played an integral part in the diet of the general population, especially due to the lack of clean drinking water (Schott and Tölle, 2006). While the aristocracy still preferred wine, low-alcohol beer was popular with the lower social classes. This was in accordance with the opinion of many physicians who evaluated water as bad for digestion - possibly due to its widespread contamination - while moderately consumed alcohol was deemed as a means of strengthening and stimulation. In contrast, drunkenness was seen as a moral transgression or sin. Thereby, the self-indulgence of chronic intoxication was associated with the deadly sin of "gula" (gluttony) (Warner, 1992). For example, the painting "The Seven Deadly Sins and the Four Last Things", attributed to Hieronymus Bosch, illustrates a haggard drinker next to a morbidly obese man, both embodying the vice of gluttony. The religiously inspired concept of addiction as a consequence of bad character was dominant until the modern era and threads of the discourse linking addiction predominantly to aspects of morality instead of medicine can be traced to this day (Schlösser, 1990; Schott and Tölle, 2006).

With the rise of the industrialization and international trade in the course of colonization in the 18th century, the phenomena of substance abuse became a global health issue. While China was affected by the epidemic spread of opium addiction, fostered by Great Britain's aggressive trading policies, the increased availability of hard liquor in interaction with the socioeconomic upheavals of the industrial revolution led to the spread of chronic alcohol abuse in Europe (Crocq, 2007). Paralleled by the formation of the first psychiatric institutions at the end of the 18th and beginning of the 19th century, the view of chronic substance abuse started to change gradually from a moral misconduct to a medical disorder. In this context, the writings of French psychiatrist Phillipe Pinel (1754-1826) and the American physician Benjamin Rush (1745-1813) play an important role, as both influentially advocated the treatment of alcoholism as a life-threatening disease (Watzl and Singer, 1999). Moreover,

in 1841 the first specialist institution for the treatment of alcoholism was founded in Boston, Massachusetts (Schott and Tölle, 2006). This was followed by the foundation of medical journals dedicated to research on chronic substance abuse in 1876 (The Journal of Inebriety) and 1885 (British Journal of Addiction) (Crocq, 2007). At the end of the 19th century many prominent physicians and psychiatrists became fierce opponents of alcohol, including Anton Delbrück, Emil Kraepelin, Paul Julius Möbius and Eugen Bleuler (Bergman, 1907). Thereby, the medical discourse surrounding addiction became increasingly influenced by the eugenics movement and social Darwinism. This led to the stigmatization of patients as "degenerates", whose influence on humanity was deemed as genetically harmful. Finally, this development climaxed in the time of national socialism with the attempted extermination of all "unworthy life", including addicts (Schott and Tölle, 2006).

Even after the second world war SUDs were treated as moral disorders. In both DSM-I and DSM-II SUDs were classified as subcategories of sociopathic personality disorders, which also included "antisocial and dissocial reactions" and "sexual deviations" (American Psychiatric Association, 1952, 1975). According to the American Psychiatric Association, which was strongly influenced by the psychiatrist and eugenics movement supporter Adolf Meyer (1866-1950), these disorders shared a common deviant lifestyle or social environment, which is characterized by attacks against the moral order of society (Lidz, 1966). Furthermore, originating from the predominantly Anglo-American psychodynamic discourse, it was assumed that these disorders share a common etiology (Bilitza, 2008). This categorization, which was criticized for being stigmatizing and unempirical, gradually changed since the 1980s with the publication of the DSM-III. There, SUDs were described as an independent category, with a focus on the description of symptoms and biological markers rather than etiology or transgression of social norms (American Psychiatric Association, 1980). The DSM-III differentiated between substance use, substance abuse and substance dependence. Furthermore, the DSM-III included five substance classes (alcohol, barbiturates, opioids, amphetamines and cannabis). Substance abuse was defined by three criteria: Pathological substance use, functional impairment in work and social life due to substance consumption and persisting consumption for more than one month. Substance dependence was defined by the occurrence of physical dependence, like increased tolerance or withdrawal symptoms. The DSM-IV describes SUDs in the chapter "Substance-Related Disorders" and extended the

classes of drugs involved in addiction development to eleven, adding SUDs involving caffeine, hallucinogens, medications, inhalants, nicotine, phencyclidine, other or unknown substances and multiple substances (Frances, 1994). Furthermore, the category substance-related disorder included the diagnostic groups "Substance Induced Disorders" comprised of "withdrawal symptoms", "intoxication" and "substance induced psychosis".

Current Diagnostic Criteria of SUD in ICD-10 and DSM-5

The current DSM-5 describes SUDs in the chapter "Substance-Related and Addictive Disorders", which consists of disorders related to ten classes of drugs as well as gambling (American Psychiatric Association, 2013). In contrast to previous issues, the description of these disorders is more oriented towards their biology, which is outlined at the beginning of this chapter: "All drugs that are taken in excess have in common direct activation of the brain reward system, which is involved in the reinforcement of behaviors and the production of memories [...] individuals with lower levels of self-control, which may reflect impairments of brain inhibitory mechanisms, may be particularly disposed to develop substance use disorders" (American Psychiatric Association, 2013, p. 481). Moreover, the DSM-5 abolished the dichotomy between substance abuse and substance dependence. In DSM-5, SUDs are categorized according to the number of observable symptoms, persisting for at least 12 months. It differentiates between "mild" (two to three symptoms), "moderate" (four to five symptoms) and "severe" (more than five symptoms) SUDs. Altogether, the DSM-5 lists eleven symptoms characterizing SUDs. These include persistent desire to cut down or regulate substance use, often without success; spending a great deal of time obtaining the substance, using it and recovering from its effect; almost all activities revolve around the substance; craving; social problems due to substance consumption; neglect of important tasks at school, home or work; withdrawing from family activities and hobbies in order to consume the substance; persisting use despite knowledge of physical and psychological problems caused by substance consumption; increasing tolerance; and withdrawal symptoms (American Psychiatric Association, 2013; Hasin et al., 2013).

While still differentiating between "harmful use" and "dependence syndrome", the ICD-10, which is published by the World Health Organization (WHO), defines the diagnostic category of "dependence syndrome" largely in accordance with the DSM-5. The diagnostic criteria include: A strong desire to consume the substance (craving); reduced control over

substance use; increasing tolerance; persisting use despite harmful consequences; higher priority given to substance consumption in contrast to other activities and obligations; and physical withdrawal symptoms (World Health Organization, 1992).

Epidemiology

Epidemiologic studies concerned with SUD show that these disorders are one of the most common psychiatric diseases worldwide. Estimates of lifetime prevalence range from 5 to 15% (Kessler et al., 2005; Möller et al., 2007). According to the WHO the most frequent SUD within the USA is alcohol use disorder, with a lifetime prevalence rate of 8%. Illicit drug use disorders are less widespread, exhibiting a prevalence of 2% (World Health Organization, 2010; Merikangas and McClair, 2012). In Germany, this pattern remains similar but shows a lower incident rate, with a prevalence of 6% alcohol use disorder and 1% of drug use disorders (World Health Organization, 2014, 2010). In addition, literature consistently shows significant gender differences in SUD prevalence, with men being 2 to 3 times more likely to be affected by SUDs than women (Grant et al., 2015; Grant et al., 2016; Brady and Randall, 1999; Becker and Hu, 2008). The age of onset for SUDs is typically in the early adult years, with a peak manifestation between 18-27 years and a decrease with age (Kessler et al., 2005; Jackson and Sartor, 2016).

Furthermore, SUDs show substantial comorbidities with a wide range of psychiatric and somatic diseases. Results of recent epidemiological surveys by Grant et al. (2016; 2015) indicate significant associations between SUDs and major depression, dysthymia, bipolar I, posttraumatic stress disorder, generalized anxiety disorder, panic disorder, social phobia, other SUDs, increased risk of suicide as well as antisocial, borderline and schizotypal personality disorders. In fact, the literature suggests that for nearly every psychiatric disorder there are significant ties to SUDs. Additionally, this includes relationships between eating disorders and SUDs (Dawe and Loxton, 2004; Bulik et al., 2004), obsessive-compulsive disorder (Am Ruscio et al., 2010) and schizophrenia (Regier et al., 1990; Dixon, 1999). An exceptionally prevalent relationship seems to exist in regards to mood disorders like depression and bipolar I as well as anxiety disorders. Findings indicate that about 20% of individuals with a SUD were diagnosed with at least one independent mood disorder and 18% with at least one independent anxiety disorder (Grant et al., 2004). Moreover studies continuously link SUDs to infectious diseases like HIV and hepatitis, due to intravenous consumption and an increase in risky

sexual behavior (Swendsen and Merikangas, 2000). Other somatic illnesses like neurological deficits and organ damage can result from the toxicity of consumed substances (Swendsen and Merikangas, 2000; Whiteford et al., 2013; Rosenberg et al., 2001).

Likewise, SUDs diminish not only the individual's health and quality of life but also burdens society, through its relation to unemployment, crime, incarceration, poverty and homelessness (Degenhardt and Hall, 2012). Economic and health costs associated with SUDs are estimated to be $249 billion regarding alcohol and $193 billion for illegal drug use disorders in the USA alone (Center, 2010; Prevention, 2016).

Another characteristic of this disease is the high percentage of affected individuals not receiving appropriate treatment (Grant et al., 2016). This phenomenon can be partly explained by the strong stigmatizing societal bias regarding this disease but is also connected to a disease-specific individual reluctance to accept the steadily worsening effects of chronic substance abuse on the consumer´s life (Bühringer and Ferstl, 2005).

Etiological Models of Substance Use Disorders

There is a broad consensus that the development of SUDs is caused by a complex interaction of biological, social and psychological factors (Hawkins et al., 1992; Shaffer et al., 2004; Griffiths, 2005; Kendler et al., 2003b). Consequently, studies engaged in risk factor analysis identified a wide range of bio-psycho-social factors linked to an increased likelihood of occurrence. The emergence of SUDs is often associated with socioeconomically disadvantaged and highly traumatizing environments. Research on socioeconomic factors was able to establish a stable connection between economic decline and unemployment with SUDs (Henkel, 2011). Thereby, SUDs do not only increase the risk of becoming unemployed, but also unemployment significantly predicts the risk of substance use, dependence and relapse after treatments. Likewise, studies have documented the significant impact of violence, abuse and consecutively PTSD on the development of SUDs (Hawkins et al., 1992; Kendler et al., 2003b; Kilpatrick et al., 2000; Perkonigg et al., 2000). In this context, it is hypothesized that substance abuse may be a compelling but dysfunctional coping strategy, used to reduce the distressing emotional and psychopathological consequences of experienced assault. Further risk factors include a lack of social bonds and alienation from society (Hawkins et al., 1992). Empirical evidence also indicates that family dysfunction, substance related problems within the family environment and early initiation of drug use pose a high risk for developing an

addiction in later life (Sher et al., 1991; Hawkins et al., 1992; DeWit et al., 2000; Kendler and Prescott, 2007). Finally, genetic and neurobiological factors seem to play a relevant role in the development of addictions as well (Kendler and Prescott, 2007; Panksepp, 2004).

Because the present work deals with the development of an integrative neuropsychoanalytic approach to SUD etiology, the following will first give a brief overview of the pharmacodynamics and behavioral effects of the most common drugs of abuse, including tobacco, alcohol, sedatives and hypnotics, opioids, cocaine, amphetamine-like stimulants, cannabis, hallucinogens and inhalants (Humeniuk et al., 2008; World Health Organization, 2004). Furthermore, it will present neurobiological models of SUD development. Finally, psychodynamic concepts and contemporary neuropsychoanalytic approaches towards SUD etiology will also be reviewed.

Neurobiology of Addiction

Behavioral and Neurobiological Aspects of Drugs of Abuse

Tobacco

Tobacco use disorder is the most prevalent psychiatric disorder related to psychoactive substance consumption worldwide (Grant et al., 2016). Although several other potentially psychoactive substances have been identified in tobacco, including monoamine oxidase inhibitors and nornicotine, there is a vast consensus that the psychoactive and addictive effect of tobacco predominantly relies on nicotine ($C_{10}H_{14}N_2$) (Harrison et al., 2002). Nicotine is a potent alkaloid, naturally produced in a variety of plants belonging to the nightshade family (Rätsch, 2005). Tobacco is usually smoked, however other forms of consumption are known, including chewing or nasal insulflation. With an estimated 6 million annual deaths related to tobacco smoking, nicotine addiction is the primary cause of preventable mortality in the world (Zhao-Shea et al., 2013).

In animal studies nicotine serves as a potent reinforcer, inducing intravenous self-application and conditioned place preference, highlighting the intense addictive potential of this substance (Di Chiara, 2000). In humans, nicotine acts as both relaxant and stimulant. Acute effects of tobacco include reduction of appetite, increased blood pressure and heart rate, reduction of anxiety, mild euphoria, dizziness, light-headedness and enhanced task performance due to increased attention and concentration (Rätsch, 2005; World Health

Organization, 2004). Furthermore, it enhances the reward value of other stimuli, which might play an important part in the addictive properties of nicotine (Harrison et al., 2002).

Nicotine acts as a potent agonist at several nicotinic acetylcholine receptor (nAChRs) subtypes, which are widespread within the sympathetic, parasympathetic and central nervous system (Paterson and Nordberg, 2000). These nicotinic receptors are predominantly situated in presynaptic terminals, modulating neurotransmitter release (Sargent, 1993). In correspondence to this, the effect of nicotine is hypothesized to be related to various neurotransmitter systems (Markou, 2008). What is more, due to decreased effectiveness of acetylcholinesterase in nicotine breakdown, nicotine occupies nAChRs for longer periods than endogenous acetylcholine, blocking the stimulation of these receptors (Schandry, 2007). This is compensated by upregulation of nAChRs, which in turn might cause the increased irritability associated with nicotine withdrawal. Furthermore, nicotine is related to increased dopamine synthesis and release in the nigrostriatal and mesolimbic dopamine pathway (Harrison et al., 2002). The rewarding/addictive effects of nicotine might be particularly related to its association with increased dopamine transmission in the Nucleus accumbens (NAcc) shell and extended amygdala (World Health Organization, 2004; Volkow et al., 2017).

While physical withdrawal symptoms related to nicotine are rather mild, nicotine is known to produce pronounced psychological withdrawal symptoms including intense craving, irritability, hostility, dysphoric and depressed mood, anxiety and increased appetite (World Health Organization, 2004).

Alcohol (Ethanol)

Ethanol (chemical formula C_2H_5OH) is the most commonly consumed psychoactive substance (UNODC, 2017). It is produced by fermentation processes and usually taken orally. According to epidemiological data, alcohol use disorder is the second most frequent psychiatric disorder related to psychoactive substances (Grant et al., 2015).

In humans, ethanol has a two-phase behavioral effect, which includes both stimulation and sedation (Holdstock and Wit, 1998). In correspondence to this, effects depend on the time after ingestion, dose and interindividual differences. Typically, low doses cause increased activity and general disinhibition, while higher doses increasingly trigger impairments of cognitive, perceptual and motor functions (World Health Organization, 2004). Furthermore, there are significant interpersonal differences between its effect on mood and emotions

(Jacobs and Fehr, 1987). In general, alcohol consumption is associated with increased feelings of euphoria, elation, emotional expression, loquacity, aggression, risk taking behavior and anxiolytic effects as well as reduced pain perception (Holdstock and Wit, 1998). Thereby, the sedative and anesthetic effects increase over time after ingestion and dose rate (Hendler et al., 2011).

The behavioral effects of alcohol are primarily mediated by its agonistic effect on GABA-A receptors and to a lesser extent to its antagonistic effect on glutamate receptors (Davis and Wu, 2001; Mihic et al., 1997). Specifically, alcohol increases the inhibitory activity of GABA-A and decreases the excitatory activity of glutamate receptors, particularly in NMDA receptors. These mechanisms account for the most acute behavioral effects, including anxiolysis, sedation and motor incoordination (Grobin et al., 1998). Furthermore, as a secondary consequence of GABA-A receptor activation and glutamate inhibition, alcohol is related to increased firing of dopamine neurons in the ventral tegmental area (VTA) and NAcc, as well as increased availability of endogenous opioids (Di Chiara et al., 1996). However, increased dopamine firing only occurs in relation to the rising blood concentration of ethanol (World Health Organization, 2004).

Moreover, ethanol is known to produce severe physical withdrawal symptoms, which might be fatal if untreated (Bayard et al., 2004). Signs of alcohol withdrawal syndrome include shaking, rapid heart rate, sweating, agitation, weakness, nausea, vomiting, headache, and seizures (World Health Organization, 2004). In addition, withdrawal can be accompanied by a state known as “delirium tremens”, which is characterized by autonomic hyperactivity, severe agitation, delusions and hallucinations (Erwin et al., 1998). Without medical treatment, alcohol withdrawal syndrome usually lasts between 5 and 7 days.

Sedatives and Hypnotics

Due to their overlapping pharmacological properties, alcohol is often seen as a subcategory of the broader sedative and hypnotics group, which includes frequently abused tranquilizers like benzodiazepines and barbiturates (World Health Organization, 2004). However, in line with recent guidelines by the world health organization (Humeniuk et al., 2008), alcohol and sedatives/hypnotics will be described individually in this overview. It is known from animal studies that both benzodiazepines and barbiturates show strong reinforcement properties in mammals (Meisch, 2001).

The acute effects of sedatives/hypnotics are drowsiness, motor incoordination, memory loss, cognitive impairment, increased euphoria, fatigue and anxiolysis (Buffett-Jerrott and Stewart, 2002). Regarding benzodiazepines, these effects are mediated by their binding on the GABA-A receptor complex, increasing the effectiveness of GABA in the opening of the chloride channel (World Health Organization, 2004). In contrast, barbiturates - like ethanol - bind to a separate site on the GABA-A receptor, which directly opens the chloride channel (Nutt and Malizia, 2001). This mechanism leads to a hyperpolarization of the cell, decreasing its excitability. Furthermore, like all other addictive drugs, sedatives/hypnotics increase dopaminergic transmission within the mesolimbic dopamine system (Tan et al., 2010).

The withdrawal syndrome caused by prolonged tranquilizer abuse is as severe as alcohol withdrawal and might last between 10 - 14 days. Symptoms of tranquilizer withdrawal include restlessness, insomnia, anxiety, increased excitability, psychotic reactions and severe seizures (Petursson, 1994; World Health Organization, 2004). Moreover, tranquilizer withdrawal can be fatal if left untreated (Lann and Molina, 2009).

Opioids

The umbrella term "opioids" refers to compounds extracted from the poppy plant - which are called "opiates" (e. g. morphine) - as well as to semisynthetic (e. g. heroin) and synthetic substances (e. g. fentanyl) with similar pharmacological and behavioral properties (Karow and Lang-Roth, 2003). Pharmacological studies suggest the existence of three distinct opioid receptor classes within the brain, which are referred to as mu-, delta- and kappa-receptors. Each receptor class has its corresponding class of ligands, including endorphin (mu-receptor ligand), enkephalin (delta-receptor ligand) and dynorphins (kappa-receptor ligand). Furthermore, each receptor and ligand class is comprised of several subtypes (Kieffer and Gavériaux-Ruff, 2002). In addition, opioid receptors are widespread in the central nervous system, essentially involved in pain processing and strongly expressed in the mesolimbic dopamine path (Le Merrer et al., 2009).

Regarding their behavioral effects, opioids produce feelings of warmth, euphoria, drowsiness, analgesia and sedation. Common side effects include nausea, vomiting and respiratory depression (Rätsch, 2005). Pharmacological studies suggest that the rewarding effects of opioids are primarily mediated by their agonistic effects on mu- and delta-receptors (van Ree et al., 1999). However, molecular studies involving genetic inactivation of mu- and

delta-receptors suggest that mu-receptors might play a more important role in the analgesic, rewarding and addictive effects of opioids than delta-receptors (Le Merrer et al., 2009). By contrast substances acting as kappa-receptor agonists (e. g. Salvinorin A and U69,593) show not only analgesic but also potent hallucinatory properties in animal models and humans (Le Merrer et al., 2009; Yan and Roth, 2004). These hallucinatory effects of kappa-receptor agonists are often described as aversive, paranoid, anxiogenic, alienating, dissociative and bizarre (Culverhouse, 2016; Hutton et al., 2016; Rätsch, 2005). Therefore, the kappa-receptor system is assumed to oppose mu-receptors in the regulation of hedonic homeostasis (Bruchas et al., 2010; Nestler and Carlezon, 2006). Furthermore, the cessation of chronic consumption of opioids - acting as mu- and delta-receptor agonists - is known to produce severe physical withdrawal syndromes, which might last between 8-10 days (Trescot et al., 2008). Symptoms include intense dysphoria, watering eyes, runny nose, yawning, sweating, irritability, restlessness, tremor, nausea, vomiting, diarrhea, increased blood pressure and heart rate, cramps and muscle aches. In contrast, until now there have been no reports of withdrawal symptoms associated with kappa-receptor agonists. In fact, these compounds have shown anti-addiction properties in preclinical studies (Darcq and Kieffer, 2018; Simonson et al., 2015). However, due to their aversive and hallucinatory side effects, the therapeutic use of kappa-receptor agonists is severely limited. Therefore, currently none of the existing compounds have succeeded in clinical trials (Darcq and Kieffer, 2018).

Cocaine (Hydrochloride and Crack)

Cocaine is produced from the leaves of the *Erythroxylon coca* tree, a plant which is indigenous to Bolivia and Peru (Rätsch, 2005). It is a powerful stimulant, which is applied intranasally or intravenously. Crack is a free base form of cocaine which is smoked.

Cocaine activates the sympathetic nervous system and produces feelings of well-being, euphoria, increased alertness, energy and motor activity, feelings of self-competence and sexual desire (World Health Organization, 2004). Furthermore, common side effects include anxiety, restlessness, increased aggressiveness and paranoia. Overdoses are associated with tremor, convulsions, increased body temperature, tachycardia, hypertension, myocardial infarct and cerebrovascular hemorrhages. In animal models, cocaine shows strong reinforcing properties (Markou et al., 1993).

Cocaine produces its psychoactive properties by its ability to act as a monoamine transporter blocker, affecting dopamine, serotonin as well as norepinephrine transporters (Pomara et al., 2012; Ritz et al., 1990). This mechanism results in increased availability of monoaminergic neurotransmitters in the synaptic cleft, which act upon presynaptic and postsynaptic receptors. In particular, the exceptional affinity of cocaine to the dopamine transporter is assumed to be the main cause of its psychomotoric and rewarding properties (Pomara et al., 2012; World Health Organization, 2004). In correspondence to this, pharmacological studies suggest that the activation of both D_1 and D_2 receptors is necessary to produce the intracranial self-stimulation effect of cocaine in animals (Kita et al., 1999).

Regarding withdrawal, cocaine produces less severe symptoms than alcohol, sedatives or opioids (World Health Organization, 2004). However, after the effects of cocaine wear off, users report feelings of dysphoria, tiredness, strong cravings, irritability and depression (Volkow et al., 1997). The intense feelings of craving associated with cocaine withdrawal might be linked to hypoactivity within the prefrontal cortex, which is proportional to the levels of dopamine D_2 receptors in the striatum (Volkow and Fowler, 2000).

Amphetamine-Type Stimulants

Amphetamines include a large variety of stimulating drugs with similar behavioral and pharmacological effects. Frequently used substances of this category comprise delta-amphetamine, methamphetamine, methylphenidate, 3,4-methylenedioxymethamphetamine (commonly known as MDMA or ecstasy), ephedrine and cathinone.

In general, the behavioral effects of amphetamines are similar to cocaine and include increased alertness, arousal, motor and speech activity, suppression of appetite, energy, euphoria, increased self-confidence and concentration. Additionally, some substances like MDMA are reported to produce increased feelings of empathy, closeness and intimacy with other people (Shulgin and Shulgin, 1995). Moreover, overdoses of amphetamine are associated with severe side effects like irregular heartbeat, agitation, fever, sweating, confusion, paranoia, hallucinations, cerebral hemorrhage, seizures and coma (World Health Organization, 2004). In animal models, amphetamines show strong reinforcement properties (Pickens and Harris, 1968; Yokel and Wise, 1976).

In contrast to cocaine, the effects of most amphetamines are primarily mediated by stimulation of the dopamine release from nerve terminals via the dopamine transporter

(Fleckenstein et al., 2007). Furthermore, to a lesser extent than cocaine, amphetamines are also able to inhibit the reuptake of catecholamines. Moreover, amphetamines directly stimulate catecholamine receptors. Other stimulants, like MDMA and related drugs, primarily act upon serotonin receptors by binding to and blocking the serotonin transporter (Kalant, 2001). Withdrawal symptoms of amphetamine-type stimulants are in large part analogous to cocaine withdrawal (World Health Organization, 2004).

Cannabis

Cannabis sativa, which is the most prevalently used illicit substance, produces a group of chemicals known as cannabinoids. Of the 113 different cannabinoids isolated from cannabis, delta-9-tetrahydrocannabinol (THC) is the major compound responsible for its psychoactive properties (Aizpurua-Olaizola et al., 2016). Cannabis is usually inhaled by smoking or consumed orally. Cannabinoids are known to remain in the body for long periods and might even be found in urine samples for 2-3 days after smoking (World Health Organization, 2004).

Regarding its behavioral effects, cannabis is associated with feelings of relaxation and increased sensory awareness, appetite, antiemetic effects, analgesia and euphoria. Additionally, psychoactive effects include increased sense of self-confidence and subjectively heightened creativity (World Health Organization, 2004). Side effects of cannabis use include impaired memory, cognition and motor coordination as well as increased paranoia and hallucinations (Green et al., 2003).

The psychoactive effects of cannabinoids are mediated by their agonistic binding on the endocannabinoid system (Ashton, 2001). Specifically, pharmacological studies suggest that the intensity of the psychoactive effects of cannabinoids are correlated with their affinity towards CB-1 and CB-2 cannabinoid receptors (Kumar et al., 2001). The CB-1 cannabinoid receptor is highly expressed throughout the central nervous system, while the CB-2 receptor is mainly localized in the peripheral tissues of the immune system (Munro et al., 1993). Furthermore, THC increases dopamine activity in the mesolimbic pathway, normally within the NAcc shell (Fadda et al., 2006), and fires off dopamine neurons in the VTA (French, 1997) which is assumed to cause cannabis reinforcing properties in animal models. Despite its potential for abuse and dependence syndromes, there is little evidence of withdrawal reactions after the cessation of prolonged cannabis use (World Health Organization, 2004). This finding

is explained by the long half-life of natural cannabinoids like THC. However, recent studies suggest that synthetic cannabinoids in particular are able to produce severe withdrawal symptoms including anxiety, myalgias, dysphoria and anorexia (Nacca et al., 2013).

Hallucinogens

Hallucinogens are a chemically heterogeneous group of substances which share the common ability to induce distorted perceptions, mood and thought process alterations and hallucinations (World Health Organization, 2004). The hallucinogenic effects of these substances mostly occur at high doses. Hallucinations are most often reported as visual, however they might affect all senses as well as the perception of time, the world and the self. Furthermore, the psychoactive properties of hallucinogens vary greatly between individuals and intraindividually from one use to the next (Hofmann, 2010; Shulgin and Shulgin, 1997). Based on the structural similarity of the compounds, hallucinogens are divided into several subcategories (World Health Organization, 2004). These include:

(1) Indolealkylamines, which are structurally similar to serotonin and comprise amongst others lysergic acid diethylamide (LSD-25), d-lysergic acid amine (LSA), psilocybin and dimethyltryptamine (DMT). The pharmacodynamics of these substances are highly complex and a sufficient review would exceed the scope of this thesis (for an extensive review, see: Passie et al., 2008). In short, substances of the indolealkylamine family act as autoreceptor agonists in the raphe nucleus. Autoreceptors are defined as receptors for transmitters, which are released by the neuron (World Health Organization, 2004). The activation of an autoreceptor implies a negative feedback loop, which decreases the firing of the neuron. Furthermore, indolealkylamines act as agonists and partial agonists on a variety of serotonin receptors (Gregorio et al., 2016; Passie et al., 2008).

(2) Furthermore, phenylethylamine drugs like mescaline, methylenedioxyamphetamine (MDA), methylenedioxymethamphetamine (MDMA) and 2,5-Dimethoxy-4-methylamphetamine (DOM) bear a close structural relationship with amphetamines (Shulgin and Shulgin, 1995). However, regarding their hallucinogenic properties phenylethylamines seem to rely on pharmacological mechanisms of action similar to indolealkylamines, involving a complex mechanism of mixed agonism/partial-agonism of a variety of serotonin receptors (Passie et al., 2008; Swanson, 2018).

(3) Compounds of the atropinic family, including atropine, scopolamine and hyoscyamine, are found in many species of the nightshade plants (Rätsch, 2005). These substances predominantly act as antagonists of the muscarinic cholinergic receptors (World Health Organization, 2004).

(4) And dissociative hallucinogens like phencyclidine (PCP), ketamine and methoxetamine (MXE), which act as NMDA glutamate receptor antagonists (Morris and Wallach, 2014), as well as salvinorin A, a potent kappa opioid receptor agonist (Yan and Roth, 2004).

Furthermore, animal models suggest that all hallucinogens might be able to increase dopamine activity, but to a lesser degree compared to other categories of substances reviewed above (Seeman et al., 2009). Regarding their addictive effects, data from epidemiological studies indicate that isolated forms of hallucinogen addictions are relatively uncommon, while hallucinogen use is significantly associated with a variety of other mental disorders, including poly substance use disorder (Shalit et al., 2019). Moreover, there are no known cases of withdrawal related to any hallucinogenic substance (World Health Organization, 2004).

Volatile Solvents (Inhalants)

The term inhalants includes a highly diverse group of chemical substances, which are sniffed and produce psychoactive effects on the central nervous system (World Health Organization, 2004). This group of volatile solvents is comprised of such heterogeneous compounds as nitrous oxide, gasoline, nail-polish remover, paint stripper, glue or butane. Due to their ready availability, these substances are mainly used by children and adolescents, especially in socioeconomically underprivileged groups (Howard et al., 2011).

Behavioral effects of inhalants are rather similar to the effects of alcohol (World Health Organization, 2004). Shortly after inhalation, disorientation, excitation, euphoria and dizziness are observed. Furthermore, inhalant use is associated with depressed levels of consciousness, analgesia, hallucinations and delusions, accompanied by motor and speech incoordination, nystagmus and visual disturbances. In animal models, volatile solvents show significant reinforcing properties and share discriminative stimulus effects with ethanol, barbiturates and benzodiazepines (Bowen, 2006; Bowen et al., 1999).

Regarding the pharmacodynamics of inhalants relatively little is known, as they have received comparatively little attention in research (World Health Organization, 2004). Due to

their behavioral effects, it is assumed that inhalants induce biochemical changes in the GABAergic system, similar to ethanol, benzodiazepines and barbiturates (Lubman et al., 2008). In correspondence to this, studies conducted on animals indicate that the effects of solvents might be related to the activation of $GABA_A$, glycine and $5HT_3$ receptors and inhibition of NMDA receptors (Beckstead et al., 2001; Lubman et al., 2008). Furthermore, electrophysiological studies indicate that inhalants increase dopamine firing in the VTA and extracellular dopamine levels in the striatum (Riegel and French, 2002; Stengård et al., 1994). What is more, withdrawal after chronic exposure to inhalants is related to withdrawal effects of ethanol or sedatives/hypnotics and is associated with increased susceptibility to convulsions, hallucinations, runny eyes or nose, fast heartbeat, depressed mood, anxiety, vomiting and hallucinations (Perron et al., 2009).

Genetic Aspects of SUD

Numerous results of adoption studies indicate a stable relationship between SUD development and hereditary dispositions inherited from biological parents, which are independent of a shared environment (Hopfer et al., 2003; Cadoret et al., 1995; Cadoret et al., 1986). Furthermore, evidence from classical twin studies, comparing the similarity between monozygotic and dizygotic twins, indicates that genetic factors have a significant effect on the development of SUD (Kendler et al., 2003b; Hopfer et al., 2003). However, estimates for the heritability of substance use seem to be moderated by many factors, including sociocultural environment, age, gender and used psychoactive substances. Therefore, estimations exhibit a very wide range from 0-86% (Hopfer et al., 2003). With regard to the risk for the development of an addiction disorder, genetic factors are estimated to account for 30-60% of the variance (Kendler et al., 2003a; Tsuang et al., 1998).

Polymorphisms in several genes were found to be related to SUD. Genes related to the encoding of the endogenous opioid system have especially been of interest in scientific discourse. Subsequently, numerous genetic polymorphisms within the opioid system showed links to the development of SUDs (Reed et al., 2014). In this context, the opioid system modulates the transmission within other reward and mood related networks, like dopamine, GABA, glutamate and serotonin and has effects on the endogenous stress response system. Certain gene variants in the opioid system, which encode specific components of this system such as receptors, membrane transporter proteins or biosynthetic enzymes, seem to increase

the vulnerability for SUDs (Reed et al., 2014). Prominent examples for opioid-system related genes, involved in the development of SUDs, are the mu-opioid-receptor gene (OPRM1) and kappa-opioid-receptor gene (OPRK1), due to their important role in reward and reinforcement processes. Several studies were able to demonstrate links between specific polymorphisms in these genes and vulnerability to SUDs (Gelernter et al., 1999; Kreek et al., 2005a; Yuferov et al., 2004; Kreek et al., 2002; Kumar et al., 2012).

However, SUD associated variants of genes have been demonstrated in other neurotransmitter pathways as well, including genes in dopaminergic, noradrenergic, serotonergic, glutamatergic, cannabinoid and GABAergic networks (Reed et al., 2014; Kreek et al., 2005b). The complexity of the large number of genetic variants and their interactions, which contribute to the development of phenomena like addiction disorders, makes it difficult to derive definite etiologic determinates. Nevertheless, the influence of genetic dispositions on the pathogenesis of addictions is often hypothesized to be mediated through its influence on personality factors like risk taking, impulsivity, stress responsivity and attachment behavior (Krueger et al., 2002; Kreek et al., 2005b; Verdejo-García et al., 2008; Burkett and Young, 2012). Furthermore, the chronic abuse of psychoactive substances induces lasting transformations within the cellular genetic expression. Regarding chronic opiate abuse, this process is linked to an upregulation of intracellular cyclic adenosine monophosphate (cAMP), while chronic cocaine abuse leads to additional upregulations of adenylyl cyclase and protein kinase A in the NAcc (Nestler, 2016; Terwilliger et al., 1991). These changes induce the expression of specific genes, via the cAMP-Response-Elements-Binding-Protein (CREB), and the activation of certain transcript factors. In turn, this results in the adaptation of different receptors, predominantly within the mesolimbic system. This process contributes to the reduction of pleasurable effects, represented by cellular tolerance and - in absence of the substance - to the formation of withdrawal symptoms (Volkow et al., 2017).

Neuroanatomical Correlates of Addiction

Substance Use Disorder and the Mesolimbic Dopamine System

An early theory of a neuronal substrate for addiction disorders was developed by Wise and Bozarth (1987). They proposed the mesolimbic dopamine system (ML-DA) - often labeled as “brain reward system” - as a common denominator for addiction development since this network was activated by reinforcing objects related to psychomotor activation and

appetence behavior. The starting point of this predominantly dopamine-controlled network, which is a component of the medial forebrain bundle (MFB), is the VTA, located in the mesencephalon. From here neural paths are projected to the lateral hypothalamus and striatal areas like the NAcc. Additionally, the NAcc has a wide range of afferents, including links to the amygdala, hippocampus, nucleus caudate, prefrontal cortex (PFC), bulbus olfactorius and septum (Ikemoto, 2010). However, the ML-DA should not be seen as a strictly delimited system. It instead consists of many diffuse ramifications and feedback loops, including efferent links from NAcc to VTA or from NAcc to PFC (Schandry, 2007). The discovery of this network goes back to the study of Olds and Milner (1954; Olds, 1958) and their experiments with intracranial stimulation in rats. They observed that electric stimulation in MFB leads to intense reinforcement of operant behavior. In their experiments on intracranial self-stimulation, rats were able to trigger the electrodes themselves by pressing a lever. This had the effect of the animals pressing the lever with increasing frequency until complete exhaustion. Furthermore, they overcame painful obstacles (like heated or electrically charged bottom plates) to trigger the self-stimulation, neglected care of their offspring and preferred the self-stimulation over natural reinforcers like food and sex. These results have been continually replicated in other species (Carlezon Jr and Chartoff, 2007). Moreover, electric stimulation of this network shows similar effects in humans (Coenen et al., 2011; Schlaepfer et al., 2008; Heath, 1964). Many subsequent studies support the view of the ML-DA as a key structure in learning and addiction processes (Everitt and Robbins, 2016). Further studies on animals revealed that the presentation of conditioned stimuli like cocaine leads to increased dopamine release in the NAcc (Ito et al., 2000). Additionally, lesions, as well as the blocking of the NAcc through dopamine antagonists, make conditioning and the development of addictions impossible in animal models (Di Ciano et al., 2001). Other critical neural structures within the ML-DA for the development of SUDs are the central amygdala and the basolateral amygdala. Thereby it was shown that a disconnection between the basolateral amygdala or the central amygdala from the dorsolateral striatum leads to inhibited drug seeking behavior (Whitelaw et al., 1996; Murray et al., 2015).

Studies utilizing intracranial drug self-administration (ICSA), which involves self-application of small volumes of psychoactive substances into discrete brain regions in rats, further deepened insight into the circuitry involved in reward learning and consecutive

addiction development. In a review of ICSA literature, Ikemoto and Bonci (2014) identified a complex drug-reward circuit that included not only the VTA-ventral striatal dopamine system, but also the rostromedial tegmental nucleus, supramammillary nucleus and median and dorsal raphe nuclei. This network has extensive motivation and approach behavior related links to other brain regions, like the parabrachial nucleus, laterodorsal tegmental nucleus, locus coeruleus, posterior and lateral hypothalamic areas, preoptic areas, septal area, bed nucleus of stria terminalis (BNST), medial ventral pallidum and medial prefrontal cortex.

The consumption of psychoactive substances leads to sensitization, which is observable in an increased excitation of the psychomotor neurons within the ML-DA if drugs or drug cues are presented to the organism (Robinson and Berridge, 2000). It is hypothesized that these altered circuits do not convey a direct form of pleasure but rather mediate craving for the substance, which is dissociated from feelings of reward. Therefore, these authors propose a dichotomy between “wanting” and “linking”. This might be illustrated by the phenomenon that patients suffering from SUD often express reluctance towards their substance of abuse, despite suffering from an intense desire for it. Hence, addiction disorders are characterized by a neural adaption process, which results in less pleasure triggered by the consumption of substances, while at the same time craving for the substance increases. On a physiological level, this development is paralleled by a change in neural activation patterns in the striatum (Everitt and Robbins, 2016; Volkow et al., 2016). Shifts occur from activations predominantly in ventral striatal areas, which is related to rather consciously controlled substance intake, to a predominant activation of the dorsolateral striatum; this serves as a marker of lost control over substance intake. In this context, a study by Murray et al. (2015) was able to show that this change of the neural locus of control is driven by the basolateral amygdala and maintained in the long run by the central amygdala. This transition is paralleled by a shift from prefrontal control over substance use to an increased control through striatal areas (Everitt and Robbins, 2005). This drug induced neuroplasticity causes long lasting alterations of the brain, which at least partly explains why addictions are a chronic disease with a high risk of relapse even after successful physical withdraw.

Besides neural changes related to positive reinforcement, addiction development is further characterized by alterations related to negative reinforcement processes. As described above, the sustained abuse of dopamine releasing psychoactive substances causes a reduction

of dopamine D2 receptors and decreases dopamine and opioid transmission within the ventral striatum (Volkow et al., 2016). This results in reduced responsiveness for natural reinforcers. Furthermore, substance abuse leads to a chronically increased activation of the endogenous stress-system (Koob and Le Moal, 2005). However, as outlined above, the extent of withdrawal symptoms greatly depends on the consumed substance. For example, the chronic use of opioids leads to far-reaching changes in biochemical processes within the organism. Therefore, weaning an addict off of opioids induces flu-like symptoms with intense convulsions, physical pain and overall displeasure, while other psychotropic substances like cocaine and amphetamines predominantly generate psychological withdrawal symptoms, like craving and depressive symptoms (Hyman et al., 2006).

Substance Use Disorder and the Neocortex

While the association between addiction and the ML-DA system explains a great proportion of the deranged 'wanting' aspect of this disorder, it does not explain the impaired cognitive control over approach behavior typically found in SUD patients. In correspondence to this, recent neuroimaging meta-analyses emphasize the crucial role of the structural and functional abnormalities within neocortex areas in SUD patients, particularly within the PFC, anterior cingulate cortex (ACC) and insula (Ersche et al., 2013; Goldstein and Volkow, 2011). The PFC was found to be associated with decision making, behavioral inhibition, self–awareness, self-regulation and the cognitive processing of anticipation (Miller and Cohen, 2001; Levy and Glimcher, 2012). The ACC is part of the limbic system and mediates the regulation of emotional and cognitive processes as well as conflict detection and behavioral flexibility via its interactions with the PFC (Bush et al., 2000). The insula mediates the integration of interoceptive states into the consciousness and has bidirectional connections to the striatum and PFC (Menon and Uddin, 2010). Regarding structural changes in gray matter in SUD patients, Ersche et al. (2013) found decreased volumes in the insula, ventromedial prefrontal cortex (vmPFC), inferior frontal gyrus and pregenual anterior cingulate gyrus, while no increased volumes were observed. These findings are largely paralleled by functional neuroimaging studies investigating drug cue processing in SUD patients. A meta-analysis investigating alcohol cue reactivity in patients suffering from alcohol use disorder revealed greater activations in contrast to a control cue in the ventral striatum, ACC, vmPFC and posterior cingulate cortex (Schacht et al., 2013). Similarly, a review investigating functional

abnormalities in SUD patients in general observed hyperactivations within the PFC and ACC during drug cue presentation and hypoactivation of the PFC during exposure with emotional and cognitive challenges (Goldstein and Volkow, 2011). Furthermore, there is evidence that activity in the insula correlates with feelings of craving for drugs of abuse like nicotine, alcohol and heroin (Naqvi and Bechara, 2009), while lesions within the insula disrupt the urge for cigarette smoking (Naqvi et al., 2007). In summary, addiction might be seen as the product of an imbalance between different interacting neural systems, which is predominantly characterized by impaired top-down control of habitual behaviors mediated by the ML-DA, connected to dysfunctions within the PFC, ACC and insula (Noël et al., 2013). Moreover, this conclusion is further emphasized by recent research regarding functional connectivity in addiction disorders, which found widespread functional connectivity abnormalities in association with reward, emotional and cognitive processing in SUD patients (Sutherland et al., 2012). Despite sometimes conflicting results, cortico-cortical connections generally seem to be decreased in addiction, while corticolimibic connections commonly appear to be increased (Moeller et al., 2016). Furthermore, regarding regional cerebral blood flow, which is measured in studies using positron emission tomography, results indicate hyperactivation of the orbitofrontal cortex and ACC during episodes of craving, intoxication and bingeing, while these cortex areas are deactivated during withdrawal (Daglish et al., 2001; Goldstein and Volkow, 2002).

Substance Use Disorder and White Matter Integrity

In the last few years, neuroscientific research increasingly focused on microstructural abnormalities in SUD patients investigated with diffusion tensor imaging (DTI). Thereby fractional anisotropy (FA) is utilized as a measure of structural integrity. A review by Arnone et al. (2006) concluded that the integrity of the corpus callosum, which enables communication between cerebral hemispheres, might be particularly affected in SUDs, with most noticeable abnormalities in the genu and splenium region. However, more recent studies found widespread reductions in FA related to opiate addiction and polytoxicomania (Unterrainer et al., 2016; H. Unterrainer et al., 2017; Bora et al., 2012), additionally including the superior fasciculus longitudinalis, which connects the frontal, occipital, parietal and temporal lobes (Wang et al., 2016), and the superior corona radiata, which connects the cortex with the brain stem (Wakana et al., 2004). Moreover, Romero et al. (2010) did not find

differences within the corpus callosum between patients suffering from cocaine addiction and control but observed lower FA in the inferior frontal white matter at the anterior-posterior commissure plane and higher FA in the anterior cingulate white matter, which might indicate differences between various forms of addiction. Furthermore, the results imply that longer duration of substance abuse is associated with higher FA (Bora et al., 2012; Liu et al., 2008). However, it is still unclear if the impaired structural integrity of white fiber tracts and gray matter is solely caused by neurotoxic mechanisms induced by substance abuse, or if these abnormalities might indicate a premorbid vulnerability towards SUDs as well (Bora et al., 2012). Nevertheless, structural impairments within white matter fiber tracts might mediate the functional imbalance between cortical top-down and striatal bottom-up control observed in SUD patients.

Psychoanalytic Theories of Substance Use Disorder Development

Due to the wide spectrum of psychoanalytic theories on SUD development, it is useful to structure these approaches into the categories *drive theory*, *ego psychology* and *object relations theory* (see: Bilitza, 2008; Rost, 1987). In addition, this chapter will outline the addiction theory of structural psychoanalysis, which is related to the work of Jacque Lacan. These approaches are content wise connected but emphasize different etiological aspects. Authors of classical psychoanalysis or drive theory focus on the drive-economical relations between id, ego and super-ego and underline the importance of oral regression in addiction development. By contrast, etiological theories of ego psychology are predominantly concerned with impairments regarding ego-structural functions, which are compensated by the use of chemical substances. On the other hand, object relations theory centers around the pathogenic significance of failed internalizations of mature representations of the self and others, resulting in unbearable inner states. Finally, theories influenced by the Lacanian tradition of psychoanalysis highlight the role of jouissance and the clinical structure of the subject as central aspects of addiction development (Loose, 2002).

Drive Theory Approaches to Addiction Etiology

It is interesting to note that Freud, despite his work on the effects of cocaine (Freud, 1887/1996), did not develop a comprehensive theory regarding the development of SUDs. On the one hand, this fact might be explained by Freud´s serious nicotine addiction, which may

have led to a lack of inner distance towards this topic, making it difficult for him to investigate addiction in an objective manner (Subkowski, 2008). On the other, Freud´s initial excitement with cocaine caused him to recommend cocaine as a cure for his morphine addicted friend Fleischl-Marxow, which resulted in an additional cocaine addiction and contributed to Fleischl-Marxow´s early death in 1891 (Nitschke, 2008). This tragic experience might have further contributed to Freud´s resistance in developing a psychoanalytic theory of addiction etiology.

Masturbation as "Ursucht"

Freud´s notes on addiction are sparse and dispersed over several works. The earliest remarks regarding addiction can be found in his letters to Fließ, in which he argues that chronic substance use is a substitute for sexual impulses in general, and in a later remark that it replaces masturbation, which he identifies as "Ursucht" (Freud, 1986). In these early stages of psychoanalytic theory, addictive behaviors are therefore seen as a habit in the service of the pleasure principle bound to the unconscious, which is characterized by a tendency towards spontaneous wish fulfillment and tension reduction (Freud, 1905/2015). This desire is opposed by the reality principle, which refers to the demands of the external world. The later internalization of this principle is summarized in the term super-ego, while it is the function of the ego to negotiate between the dialectic tensions of drives and the external world (Freud, 1930/2013). In this context masturbation, as well as addictive behaviors, are understood as similar compromises between these two forces, since both are characterized by a withdrawal towards pleasurable phantasies of the internal world without the need of the other or biological purpose (Solms et al., 2015; Abraham, 1926).

Orality and Addiction

Later, in his *Three essays on the theory of sexuality* Freud (1905/1953; Freud, 1905/2015) describes the importance of oral fixation in addiction. The oral stage constitutes the initial stage of psychosexual development in which sexual pleasure is bound to stimulation of the oral cavity and lips. This phase develops in connection with early experiences of food intake (for example breastfeeding) and finds its expression in the blissful and sometimes autoerotic sucking of the infant. Abraham (1924) further developed this concept by proposing a second phase he termed oral sadism or oral cannibalism, which is characterized by biting and

reciprocal phantasies of devouring and destroying the object as well as getting devoured and destroyed by it. With reference to the first stage of oral libido organization, Freud (1905/1953, p.182) concludes: "It is not every child who sucks in this way. It may be assumed that those children do so in whom there is a constitutional intensification of the erotogenic significance of the labial region. If that significance persists, these same children when they are grown up will become epicures in kissing, will be inclined to perverse kissing, or, if males, will have a powerful motive for drinking and smoking." The idea that oral fixation and a consecutive disposition towards oral regression plays a significant role in the etiology of SUDs is referred to by a great proportion of later psychoanalytic addiction theorists, including Clark (1919), Abraham (1926), Rado (1926), Knight (1937), Fenichel (1945), Rosenfeld (1960), Limentani (1968), Khantzian (1978) and Wurmser (1978). These authors agree on the predominance of a regressive oral defense mode in response to conflicts, which emerges due to an interplay of unresolved traumatic childhood experiences and constitutional factors. The ego of addicts is seen as insufficiently developed and therefore unable to withstand the anxiety caused by stress states. Consequently, the relationship between addict and the psychoactive substance is interpreted as a representation of the fulfillment of primitive and ambivalent oral demands and phantasies (Subkowski, 2008).

Late Freudian Contributions to Addiction Theory

Later on, in reference to statements by artist Arnold Böcklin, who suffered from alcoholism, Freud (1912/2014; p.6) claims, "[i]f we listen to what our great alcoholics, such as Böcklin, say about their relation to wine, it sounds like the most perfect harmony, a model of a happy marriage. Why is the relation of the lover to his sexual object so very different?". Freud's view that psychotropic substances resemble an idealized substitute for sexual objects marks the first step towards a conceptualization of addiction etiology in connection with object relations. However, Freud's assessment of the object character of psychoactive substances differs significantly from perceptions of later object-psychologists like Glover (1932) and Rosenfeld (1960).

Furthermore, a considerable paradigm shift occurred with Freud's (1955a) controversial introduction of the death drive, which was originally proposed by Sabina Spielrein (1994). The term death drive describes a fundamental category of instincts which strives towards a complete dissolution of tensions and the transference of living organisms

into inorganic matter. This force is initially directed inwards, but are deflected outwards and manifest in the form of aggressive and destructive drives (Laplanche and Pontalis, 1988). The basic function of the death drive is summarized in the term "nirvana principle", which describes the assumed tendency of the psychic apparatus, or living organisms in general, to lower tensions to zero and or death. This principle opposes the life instincts ("eros") consisting of sexual drives and vital instincts. While eros is seen as the tendency towards unity and cohesion, the death drive destroys and dissolves connections. In Freud's first theoretical work since 1920, this fundamental inner psychic dualism replaced the central significance of the conflict between pleasure principle and reality. Another term closely linked to the death drive is "repetition compulsion", describing an unconscious force driving the individual to repeat reluctant experiences. However, Freud's introduction of this concept remains ambiguous and is associated with a number of theoretical difficulties (Lind, 1991). It was in part heavily criticized as an unjustifiable regression into metaphysics (Evans, 2006). Subsequently, a great proportion of psychoanalysts ultimately rejected the concept (see: Hartmann et al., 1947; Winnicott, D, W, 1960; Fenichel, 2014). Nevertheless, the death drive was taken seriously by influential analysts like Melanie Klein and Jacques Lacan, and as a result was further developed in the Kleinian and Lacanian school of psychoanalysis (Klein, 1946; Kernberg, 1985; Lacan, 2001; Evans, 2006). Consequently, in Kleinian object relations theory and Lacanian psychoanalysis the death drive plays an important role in addiction etiology (Glover, 1932; Rosenfeld, 1960; Loose, 2002). While Kleinian psychoanalysis emphasizes aggression and the destructive aspects of the death drive concept, Lacanian reception of this construct is more diverse and detached from Freud's original formulation, which is conceptually anchored in biology. While Lacan initially describes the death drive as a nostalgia for the lost harmony of the preoedipal fusion with the mother´s breast (Lacan, 1984), he later associates it with the tendency of the symbolic order to produce repetition (Lacan, 1988). Eventually, he sees the death drive as an aspect of every drive, as every drive involves repetition, the tendency of self-extinction and the attempt to transgress the pleasure principle into the realm of excess "jouissance" (Lacan, 1977). However, this results in pain and suffering as it involves an amount of pleasure the individual can´t endure.

Moreover, Freud's (1914) study "On narcissism: An introduction", which investigated the phenomena of self-love in relation to ego development from a libido-economical point of

view, marked a significant extension of the early psychoanalytic discourse on SUDs development. Despite not directly addressing the phenomena of addiction, Freud's concept of narcissism paved the way for the ego-psychological understanding of addiction development. He hypothesized a primal infantile narcissistic state in which the infant´s libidinous energy is predominantly attached to its own self. This is accompanied by feelings of greatness and omnipotence. However, as the subject matures and is exposed to demands of the external world, this grandiose self-image gradually and painfully vanishes and is replaced by more realistic representations of the self. Together with identification with idealized images of early caregivers, the state of infantile narcissism is seen as essential in the development of the ego-ideal, which for the subject serves as a reference point for later assessments of self-worth (Laplanche and Pontalis, 1988).

Finally, Freud (1930/2013) shifts the emphasis regarding addiction development from direct masturbatory satisfaction of the pleasure principle to the avoidance of unpleasure. This establishes the function of drugs as artificial defense mechanisms, which helps the individual to cope with external and internal stressors and establishes a psychological state comparable with mania, that reestablishes the phase of infantile narcissism. This thought is further developed by Simmel (1929; 1948), who sees addiction as an artificially evoked manic defense against melancholy, as alcohol attacks and ultimately disconnects the destructive super-ego of the addict.

Further Drive Theoretical Contributions to Addiction Development Theory

Abraham's (1926) essay on "the psychological relation between sexuality and alcoholism" (originally published in 1908) was the first psychoanalytic contribution exclusively focused on addiction. According to Abraham, alcoholism is not only linked to oral fixation but also constitutes an initial attempt to increase sexual performance. Thereby alcohol symbolizes male fertility and more specifically the semen of the father. However, in the later stages of addiction, the substance is used as a substitute for decreasing virility. In this context, alcoholism is linked to perversion. In response to increasing castration anxiety, the alcoholic beverage takes shape as a fetish, gradually replacing the genital sexual aim. Furthermore, he assumes that alcohol dissolves defense mechanisms like inhibition, repression and sublimation and therefore releases unconscious homosexuality and sadistic partial drives.

The essays of the Hungarian analyst Rado, which reiterate Freud´s (1905/1953; 1914) ideas on the link between orality, narcissism and SUDs, mark the peak of the drive-theoretical considerations regarding addiction development and ultimately its overcoming. His first essay (Rado, 1926) focused predominantly on the importance of oral fixation, which he linked to a concept termed "alimentary orgasm". This term refers to an orgasm which is initiated by food intake and digestion. However this approach gained little recognition and was rejected by a predominant part of later theorists (Rost, 1987). Despite this, his second essay (Rado, 1933) is regarded as seminal for later ego psychological conceptualizations of this disorder. His starting point is that drugs of abuse show two kinds of effects: An analgesic and sedative effect, which reduces pain and reluctance, as well as a stimulating and euphoria inducing effect, which generates pleasure. Regarding addiction development, the latter is seen as more dangerous, as it gradually starts to compete with the natural manner of sexual desire, especially if the subject´s possibilities of sexual satisfaction are restricted (Rado, 1926). Furthermore, he proposes that addicts are characterized by a predisposition towards a certain emotional response to frustrations, which he calls "tense depression" or "initial depression" (Rado, 1933; p.55). He defines this emotional dysfunctioning of SUD patients as the co-occurrence of both extraordinary painful tensions and decreased tolerance of pain. Drugs of abuse intervene in the insufficient affect regulation and serve as an artificial stimuli barrier against both outwards and inwards frustrations (Rado, 1926). Moreover, he refers to Freud´s (1914) theory of infantile narcissism by proclaiming that "[i]n the pharmacogenic elation the ego regains its original narcissistic stature" (Rado, 1933; p.57); a circumstance which appears even more compelling for the addict as it is achievable without effort and without the help of the other. However, in the following hangover, this blissful state is replaced by an exacerbated version of the initial depression, enhanced by feelings of additional guilt, a sharpened contrast between real-ego and ideal-ego, as well as an increased fear of reality. This, in turn, intensifies the craving for the next intoxication and a manic-depressive vicious cycle, composed of narcissistic elation and self-debasement, is set in motion. This process gradually shifts the ego organization from a realistic to a pharmacological regime. Due to the decreasing genital drives which succumb to pharmacological desire, feelings of castration anxiety are revived which, however, are displaced by fear regarding the vanishing effects of the psychoactive substance and increasing homosexual desires. Furthermore, a defusion of drives results in the release of

aggressive impulses, which - if turned against the self - result in increased feelings of guilt and a secondary need for punishment and masochistic desires (Rado, 1933).

Summary of Drive Theoretical Approaches to Addiction Development

In summary, early psychodynamic hypotheses regarding addiction development can be summarized as follows:

- Addiction is a replacement for masturbation and, therefore, is an expression of the pleasure principle, implying weak ego and super-ego structures of SUD patients.
- Drugs remove inhibition and repression, therefore sexual potency is initially enhanced.
- Addiction is a replacement for genital sexuality, characterized by oral fixation and a tendency towards perversion.
- Substances of abuse constitute an idealized replacement for external love objects.
- Addiction serves as an artificial manic defense against unpleasure and depression.

While the first three statements reflect classical drive theory of the early 20th century, the two last arguments echo an arising paradigmatic shift in psychoanalytic theory, which can be observed since the 1930s (Rost, 1987). This shift can be sketched as movement from a discourse dominated by Freud and drive theory, to a discourse increasingly involved with ideas of object relations theory and ego-psychology. Due to the persecution of psychoanalysis in Nazi Germany, this development initially took place in the British school of psychoanalysis. Later on, in the second half of the 20th century, the progression of psychoanalytic theory shifted its main focus to Anglo-America. Furthermore, a third string of psychoanalytic theory evolved in France. This paradigmatic shift is linked to the work of Jacques Lacan and the so called "linguistic turn" in psychoanalysis. The following chapters will give an overview of key concepts and contributions to addiction theory formulated in these schools.

Jouissance and Substance Use Disorder: The Lacanian Understanding of Addiction

Despite Lacan's call to "return to Freud", his writings might be the most opaque of all of Freud's successors and include a multitude of highly specific concepts. Therefore, it would go beyond the scope of this thesis to explain a sufficient number of them. However, a central concept of Lacan (2013), which is crucial for the understanding of the Lacanian addiction theory, might be the term "Symbolic Order", which is linked to the "Law/Name-of-the-Father"

(French translation: nom du père). As the child starts to enter the symbolic (or linguistic) order, it is still incomplete. Therefore, it fundamentally depends on the desire of its mother. Hence, the first object of desire for the child is to be the object of the primary caregiver's desire (Ruhs, 2010). According to Lacan (2013), a sensation of lack is the precondition for desire. Therefore, the child unconsciously identifies with the maternal lack, which is proposed as an imaginary phallus (Ruhs, 2010). However, this imaginary relationship is disturbed by the father, who is the bearer of the symbolic law (nom du père), which prohibits the identification of the child with the phallus. This process is called "symbolic castration" and includes the prohibition of incest (Lacan, 2013). As a reaction to this, the child identifies with the paternal figure instead, which marks its entrance in the order of language and constitutes the child as a separated subject.

While Lacan himself did not write much on addiction (Loose, 2011), in recent years scholars of Lacan contributed two major works on this subject (see: Baldwin et al., 2011; Loose, 2002). Following Freud's (1887/1996) writings on cocaine, Loose (2011) emphasizes the importance of the vulnerability within the subject in addiction development, in contrast to the pharmacological properties of the drug itself. Despite not denying the characteristic effects of specific psychoactive substances, he argues that the addict receives a subject-unique effect from his substance, which the non-addict does not experience. Furthermore, the concept of *jouissance* is given a central place in the Lacanian etiology of SUD (Loose, 2002, 2011). According to Lacan, *jouissance*, which can be translated as enjoyment of judicial rights, property and sexual orgasm, is linked to the subjects attempts to transgress the symbolic order tied to the pleasure principle (Evans, 2006). However, as already mentioned before, the transgression of the pleasure principal leads to pain and death (Lacan, 1988). Moreover, the prohibition of jouissance according to the pleasure principle is inherent to the symbolic order of language and includes the forgoing of attempts to serve as an imaginary phallus for the mother due to the castration complex or "Name-of-the-Father" (Evans, 2006). In correspondence to this, Loose (2011) argues that many addicts suspend the structural obstruction of jouissance via the administration of psychoactive substances, aiming at a jouissance which is "non-phallic", non-linguistic and independent of social attachments.

In correspondence to this, it is important to note that the Lacanian-framework proposes three different clinical structures which determine the function of the psychoactive substance

for the addicted subject. Thereby, Lacan (2013) differentiates between the (1) neurotic, (2) perverse and (3) psychotic clinical structure, which is distinguished by their predominant mode of defense against the castration complex or symbolic order. In correspondence to this, (1) a neurotic structure is linked to repression; (2) a perverse structure is linked to disavowal; and (3) a psychotic structure is linked to dismissal of the symbolic order (Evans, 2006; Ruhs, 2010). For neurotic and perverse subjects, these mechanisms result in an essential discontent with the pleasure principle, as what lies beyond the pleasure principle is "too much". However, the unavailability of that which is beyond generates a sense of "never enough" (Loose, 2002). In this context, addiction is understood as a technique to manage jouissance. For a structurally neurotic or perverse subject addiction is associated with the release of an extra jouissance, which would otherwise be obstructed by the symbolic order or "symbolic castration" (Loose, 2011). Thus, drugs play the role of an "object-cause-of-jouissance", helping the subject to bypass the desire of the Other as a precondition for enjoyment, as it is required by the symbolic order. In contrast, for a psychotic subject the chronic consumption of psychoactive substances aims at limiting the surplus jouissance, which he/she experiences as invading, threatening and often in the form of anxiety or pain (Loose, 2011). Therefore, within a psychotic structure drugs substitute the function usually executed by the symbolic order of language and the desire of the Other. Hence, the administration of psychoactive substances acts as a floodgate mechanism (Loose, 2002).

Ego Psychological Approaches towards Addiction

The psychoanalytic school of ego psychology prioritizes the etiological role of disturbances within the personality structure, consisting of id, ego and super-ego. In contrast to classical drive theory, the central focus of ego psychology is the ego and its functions. The theoretical origins of this psychoanalytic school can be traced back to Anna Freud's (1936) categorization of defense mechanisms. Ego psychology was then further developed in the writings of Heinz Hartmann (1939), Margaret Mahler (1952), Edith Jacobson (1964) and Roy Schafer (1981). A common agreement between the authors of ego-psychology is that symptoms are predominantly understood as the results of defects within personality structure, which arise due to disturbances (e. g. trauma, deprivation or innate defects) during the development of the ego (Marcus, 1999). In this context, personality structure is defined as the set of functions of the ego that ensure the maintenance of inner equilibrium and relationships

to others (Rudolf, 2002). Khantzian (1997) compares personality structure and affects to a container and its contents.

Regarding addiction, this "container" might be too porous, which then causes the addict to use drugs in order to self-medicate overwhelming, and therefore unbearable, affective states. This iterates Freud's (1930/2013) and Rado's (1933) remarks on addiction development. Similarly, Krystal and Raskin (1970), Heigl-Evers (1977) and Wurmser (1978) emphasize the etiological role of the addicts' inability to perceive and regulate affects. In this context, addicts use drugs as artificial defense mechanisms against overwhelming, unpleasurable and often undifferentiated affects. Thereby, the addicts' tendency towards depression and anxiety is often somatized, unverbalized and experienced as physical pain. Furthermore, Wurmser (1978) stresses the importance of narcissistic crises and intense feelings of depression, anxiety, rage, shame and loneliness in addiction development, which he links to traumatic childhood experiences and consequential conflicts between a deficiently functioning ego and an archaic-sadistic super-ego. The id and the ego then make an alliance against the super-ego and the external world. This is seen as an antithesis to neurotic disorders, which are characterized by an alliance between the ego, super-ego and the external world against the id. However, the averted super-ego aspects ultimately return within the dynamics of addiction e. g. the cruel super-ego comes back in the form of punishment from the external world and the averted ego-ideal returns in the overly high narcissistic demands of the addict.

Likewise, he systematized defense mechanisms, which he sees as characteristically for the addicted ego. These include splitting and denial of the internal and external reality, externalization of inner conflicts into the external world and identification with the aggressor. In addition, drug abuse is seen as the result of too rigid affect defenses as well (Krystal and Raskin, 1970; Khantzian, 1990). In this case, the addicted subject might take drugs in order to temporarily experience feelings of oneness with loved objects. This state of fusion would not be achievable in a sober state due to unrelenting defenses against aggression towards the loved objects.

Moreover, the authors of this school emphasize the importance of the concept of self-care in the etiology and treatment of SUD (Khantzian and Mack, 1983). Self-care, which is connected to reality testing and discernment, acts as a protective function against self-destructive tendencies and ensures avoidance of dangers. Similar to other ego-functions self-

care is hypothesized to develop in good-enough early mother-infant relationships, while the experience of childhood maltreatment disturbs its development. This is because feelings of pain and anxiety linked to early childhood trauma are often handled by the child with a neglect of its own feelings and self-worth. This results in self-destructive and dangerous behaviors regarding drug abuse, relationships and other threats (Dally, 2008; Khantzian, 2013).

In contemporary psychodynamic research, the influence of ego psychology is strongly resembled in the Operationalized Psychodynamic Diagnostics (OPD; Ristl and Tann, 2008), which aims to build a bridge between quantitative-empirical research and psychodynamic concepts. However, research regarding addiction utilizing the OPD is still sparse. Nevertheless, a recent study by Hiebler et al. (Submitted) was able to show that SUD patients exhibit deficits in a broad spectrum of ego functions in comparison to healthy controls.

In summary, authors of ego psychology emphasize the central importance of affects and affect-regulation in the development and treatment of SUD, and predominantly disregard the influence of drive and drive-conflicts. Regarding treatment of SUD, this is reflected in the recommendation of an empathetic and supportive therapist, who helps the patient in developing a more mature level of personality structure, fostering traits like self-care, affect perception and affect regulation (Khantzian, 1990; Dally, 2008).

Object Relations Theory of Addiction Etiology

Object relations theory is focused on early caregiver-child relationships and the early development of the child. The central importance of the early social environment contrasts the often rather monadic approach of ego psychology. Furthermore, while the classic oedipal paradigm of psychoanalysis emphasizes the development from dyadic (two persons) to triadic (three persons) relationships, object relations theory investigates the development from a primary symbiosis of child and caregiver to mature relationships and individuation. In correspondence to this, object relations theory hypothesizes the fixation points for a number of psychiatric disorders, like psychoses, bipolar disorder, borderline disorder, psychosomatic disorders and addictions in very early developmental phases (Rost, 1987). Major contributions to object relations theory were made by Melanie Klein and Ronald Fairbairn. While Klein built her theoretical work on Freud's late drive/structure model, Fairbairn and his followers - like Guntrip and Winnicott - shifted psychoanalysis to a relational/structure model, emphasizing the subjects' need for interpersonal relations rather than the desire for sexual

gratification (Greenberg, 1983). Fairbairn's work is closely linked to the so-called *Middle Group of British Analysts*. Furthermore, he strongly influenced John Bowlby and the development of attachment theory (Bretherton, 1992).

Regarding the early addiction theory of object-psychology, Melanie Klein's (1946) developmental concept proposing a shift from a primitive paranoid-schizoid position to a more mature depressive position is of central importance. The paranoid-schizoid position describes an early organization of defenses, anxieties and object relation structures, usually predominant in the first 4 months of the infant's life (Klein, 1946). Thereby, the inner universe of the child is dominated by split representations of the self and representations of others in the form of good or bad part-objects. Thus, part-objects are defined as a person who is perceived as single body parts (breast, penis, feces, etc.) and their symbolic equivalents (e.g. persecutory, soothing, benevolent) (Laplanche and Pontalis, 1988). Furthermore, this state of mind is characterized by projections of the death drive in the form of aggression and bad-part objects into the external world, leading to intense persecutory anxiety linked to an anxiety of fragmentation and annihilation. In this phase, the ego lacks the capacity for integration of ambivalent feelings of love and hate. However, with the experience of external good part-objects, which get gradually integrated into the infant's internal world, the integrative abilities of the ego develop stepwise (Hinshelwood, 1989).

The paranoid-schizoid position is then replaced by the more mature depressive position. However, this movement is not seen as strictly sequential but rather as non-linear and overlapping (Klein, 1946; Dodds, 2012). The depressive position, which arises usually at the age of four to six months, is defined by whole-object relationships, integrating the good/loved and bad/hated representations of the primary attachment figure, which is now perceived as a separate entity within the external world (Hinshelwood, 1989). This process is accompanied by intense feelings of guilt and sadness, called depressive anxiety in Kleinian terminology, as the formally projected aggressive impulses are recognized as one's own. Furthermore, the confluence of loved and hated part-object might form a dead, damaged or contaminated whole object, which impairs the infant's further development. Nevertheless, the achievement of the depressive position is regarded as a crucial component of mature relationships, since efforts to maximize loving aspects within the relationship towards the ambivalent whole-object are mobilized. This is in an attempt to repair the damaged object (Klein, 1935). The painful

process of integration of hate and love towards representations of oneself and others is presumed as a lifelong struggle. A preponderance of hate, e.g. due to early traumatic or abusive experiences, makes the wholeness of self and others difficult to sustain and fosters regression towards paranoid defenses, like splitting, projection and projective identification or manic defenses like control, contempt and triumph (Klein, 1935, 1946; Greenberg, 1983).

Glover's Kleinian Approach to Addiction Etiology

Early "object relations theory" considerations regarding addiction were initially developed by Glover (1932). In his essay "On the aetiology of drug addiction", Glover develops assumptions inspired by Kleinian theory. He sees drugs in the light of their part-object character, on the border between the internal and external world. Furthermore, he describes the etiological significance of phantasy and paranoid states. Moreover, the etiologic importance of primitive sadism, hate and aggression is emphasized and linked to early oedipal situations at the end of the first and beginning of the second year of life. In this phase, the infant diffusely perceives the existence of a third object, which is experienced as threatening part-object. He argues that addiction is characterized by fixation to a transitional Oedipus system, ensconced between an archaic Oedipus complex related to psychosis and paranoid as well as melancholic anxieties - as proposed by Klein (1997) - and the later neurotic phase of the Oedipus complex, described by Freud (1900/2013).

The central phantasy system of addiction disorders is characterized by Glover (1932; p.38) as: "[…] a condensation of two primary systems, one in which the child attacks (later restores) organs in the mother´s body, and one in which the mother attacks (later restores) organs in the child´s body." Thereby, the influence of aggressive drives in SUD development is proposed as less intense as in psychotic disorders and more intense than in neurotic disorders. In contrast, the role of libidinous drives is described as more intense as in psychosis disorders and less intense than in neurosis. Moreover, the intensity of destructive impulses is seen as decisive for the addict's choice of substance, with more aggression leading to the selection of more dangerous substances. Thus, in contrast to Abraham (1926), Glover proposes that drugs of abuse symbolize not only (libidinously charged) semen but also (sadistically charged) excrements. Consequently, the drug is alternatingly seen as good and bad part-object by the addict.

Furthermore, the affected individual internalized an ambivalently loved mother (part-) object, which at its core is hated and perceived as a hostile foreign body. Therefore, the addict tries to destroy this bad and dangerous inner object by means of the drug, while the good representations of the self and part-objects are projected onto the external world, in order to protect them against the individual's own sadism. This duplex effect of drugs is seen as crucial for the obsessive character of addiction disorders. In this context, drug addiction is functionally understood as a defense against regressive psychotic fragmentation linked to the paranoid-schizoid position. Moreover, paranoid/sadistic components are confined to the substance of abuse and applied as destructive self-medication against painful melancholic intrapsychic conflicts linked to the depressive position. Therefore, Glover proposes, that drug addictions essentially are a transitional state between psychosis and neurosis, but also represent a compromise between the projected aggression linked to paranoid states and introjected aggression linked to depressive states.

Rosenfeld's Contribution to Psychoanalytic Addiction Theory

Like Rado (1933), the Kleinian theorist Rosenfeld (1960) relates addictions to manic-depressive disorder, which he sees as similar yet not identical. He argues that the addict's ego is too weak to withstand depressive anxieties and, therefore, falls back to manic defenses. However, this has to be evoked by the use of psychoactive drugs, as the addict's ego lacks the resources for the production of mania on its own. He relates this process to infantile thumb-sucking, in which a baby uses its thumb in an act of hallucinatory wish fulfillment and imagines its thumb as an idealized breast to arouse a manic mood.

Furthermore, largely in accordance with Glover (1932), Rosenfeld argues that addicts exhibit a partial fixation to the paranoid-schizoid position and partially achieve the depressive position. He claims that with regards to his patients, regression of object relations and libido development was not always present - with the exception of acutely intoxicated states - while the defense mechanisms of their ego showed a regression towards very early developmental states. This involves a defensive manic formation centered around idealizing, identification with ideal objects and denial of persecutory fears and depressive anxiety. In addition to its defensive function, drug intake is understood as an identification with sadistic and destructive objects, which persecute the good representations of objects and the self in order to achieve omnipotent control of them. This enables the acting out of sadistic impulses without concerns,

feelings of guilt or control by the super-ego. This process is linked to the destructive aspects of mania and serves as a great obstacle in the treatment of the addict.

However, drug intake serves a depressive function as well, as the drug symbolizes a dead or damaged object which the patient feels obligated to incorporate and ultimately identify with, due to intense feelings of guilt. Moreover, Rosenfeld observed a typical splitting and projection of good and bad parts of the ego. As a result, good as well as bad parts are often projected onto external objects. On the one hand, this leads to attempts of the patient to control the people in which parts of the self have been projected to, but on the other hand this has the effect that the patient is overly dependent and sensitive to those same people. He sees this splitting mechanism as the central cause for the weakness of the addict's ego. Consequently, he proposes that the extent to which it is possible for the patient to integrate split ego aspects serves as a key marker of successful psychotherapeutic treatment.

Summary of the Early Object Relations Theory Approach

As exemplarily outlined with Glover and Rosenfeld, the Kleinian understanding of addiction seems to be more pessimistic than the concepts of ego-psychology. In the view of Kleinian object relation theory, the inner landscape of SUD patients is scattered and archaic. While ego psychology emphasizes the self-medication aspects of SUD, object relations theory highlights self-destructive impulses as the central driving force in the development of this disorder. Consequently, both Glover (1932) and Rosenfeld (1960) emphasize the dynamic of intense aggressive and sadistic conflicts in SUD development. In correspondence to this, they hypothesize a predominance of a rather primitive personality organization, fixated between the early paranoid-schizoid position and the later depressive position, and dominated by splitting and related mechanisms.

Drugs as Failed Transitional Objects

Another attempt at understanding the phenomena of addiction is made by Krystal and Raskin (1970) and Lürßen (1974), who see similarities between the use of drugs and Winnicott's (1986) concept of the transitional object. A transitional object is understood as a materialistic object, which has a significant value for an infant usually between 4 and 12 months of life, especially while falling asleep. These objects might be e.g. blankets or towels and the use of them is genetically situated between thumb sucking and playing with stuffed

animals. According to Winnicott (1986), this object plays an important role in the development of the infant's autonomy, as it adopts the soothing qualities of the caregiver and therefore can be applied if the caregiver is absent. This permits a gradual transition between the first oral relationships with the caregiver and the internalization of object relations.

Similarly, the drug addict - unable to build stable inner object representations - applies the drug as a soothing and seemingly ideal object. However, in contrast to Winnicott's concept, the drug does not stay on the border between the internal and external world but rather oscillates. The addict tries to incorporate this object in a bid to overcome his intense fear of abundance. However, this attempted introjection process necessarily fails since the drug ultimately transforms into a persecutory object inside of the addict's body. Therefore, the relationship between addict and drug expresses the persisting unintegrated ambivalence of the early infant-caregiver relationship, torn between love and hate as well as separation anxiety and need for autonomy (Rost, 1987).

The Integrative Approach of Otto Kernberg

Important impulses in the advancement of psychoanalytic theory originated from the work of Otto Kernberg. Strongly influenced by Melanie Klein, Edith Jacobson and Roland Fairbairn, he integrated findings of Kleinian object psychology, ego-psychology and the object relations theory of the Middle Group into a cohesive theoretical framework (Greenberg, 1983). Moreover, he emphasized the vital importance of (quantitative) empirical and neuroscientific research in the further development of psychoanalysis (Kernberg, 2015; Lenzenweger et al., 2001).

In line with Klein (1946) and Jacobson (1964), Kernberg (1988, 2015) argues that internalized object relations form the basic components of the organization of drives and the psychological structures of id, ego and super-ego. Thereby, an object relation is built of three components: (1) A self-representation, which indicates the image the self has of itself; (2) an object representation, which indicates the internalized image of the attachment figure; (3) an affect, connecting both self and object representation. According to Kernberg, these internalized object relations are conceptualized as influenced by early relationship experiences (Fonagy, 2003; Kernberg, 2015). Yet, in line with Kleinian psychoanalysis, Kernberg puts emphasize on the (phantasmatic) partial-object character of early relationship memories and

emphasizes the interaction between the infant's temperament and its environment (Greenberg, 1983; Kernberg, 1993, 2015).

The process of internalization of object relations runs parallel to Freud's (1905/2015) phases of psychosexual development and describes the development from the infant's initially undifferentiated ego-id towards the consolidation of the mature tripartite structure, as proposed by Mahler (1952) and Jacobson (1964). This takes place as consecutive layering sequences, mediated by the affective memory storage linked with the hippocampus (Kernberg, 2015). The process of internalization is further categorized into *introjection*, *identification* and *ego-identity*, describing progressively complex and mature forms of object relation internalization. This iterative procedure causes condensations within the mental apparatus and gradually shapes psychic structures and personality organization.

In correspondence to this, Kernberg's (1993; Kernberg and Caligor, 2005) model of personality organization differentiates between three levels of functioning: (a) Coherence of identity, meaning the stability of differentiated and integrated representations of oneself and others; (b) Maturity of defense mechanisms, describing the ability to cope with internal and external conflicts in a functional way; (c) Ability to test reality, meaning the capability to differentiate between external and internal stimuli. In this context, a constellation of severe identity diffusion, predominance of primitive defenses like splitting and related mechanisms as well as a relatively intact ability to test reality, is summarized in the so-called "borderline organization", which is closely related to Melanie Klein's concept of the paranoid-schizoid position (Kernberg, 2015), and conceptually related but not identical with borderline personality disorder (BPD) (Kernberg, 1985). In contrast, additionally decreased ability of reality testing, due to fused representations of the self and objects, is linked to a psychotic personality organization, while individuals with a neurotic personality organization show only marginal deficits in all three areas of functioning (Zimmermann et al., 2013). However, all three concepts are theoretically and empirically interlocked and display an overall continuum of personality functioning (Zimmermann et al., 2013). Furthermore, the concept of personality organization is applicable in empirical quantitative research and can be assessed by the Structured Interview of Personality Organization (STIPO; Clarkin et al., 2004) and by the self-rating measurements Inventory of Personality Organization (IPO; Lenzenweger et al., 2001) and Borderline Personality Inventory (BPI; Leichsenring, 1999). Research suggests that a low

level of personality organization is associated with increased aggressive dyscontrol and negative affect as well as decreased positive affect and dysphoria (Lenzenweger et al., 2001).

As for the psychoanalytic theory of affects, Kernberg (2006b, 2015) aims at integrating the dual drive concept of Freud and Klein with psychodynamic and neuroscientific affect theories as outlined by Fairbairn (1954), Jacobson (1964), Panksepp (1998) and Damasio et al. (2000). He argues that affects constitute biologically hard-wired motivational systems, bordering between physiological and psychological experience. Largely following Panksepp (1998), he distinguishes the affect systems of attachment, eroticism, fight-flight, play-bonding, separation-panic and seeking. These affective systems are organized into the supraordinate systems of libido and death drive, reflecting the basic distinction of positive and negative affective experience.

Regarding addiction and impulse neurosis (kleptomania, psychogenic obesity, etc.), Kernberg (1985) observes chronic repetitions of instinct driven behaviors, which are experienced as ego dystonic in most life situations, but very gratifying and ego syntonic during episodes of acting out. In correspondence to this, he emphasizes the etiological importance of splitting, which is in line with the addiction theory of Kleinian object psychology (Glover, 1932; Rosenfeld, 1960). Furthermore, for Kernberg (1985, 1993) splitting is the essential defense mechanism of the borderline personality organization. It refers to the active separation of internalizations with opposite - meaning libidinal or aggressive - affective quality. This process obstructs the integration or fusion of introjections and identifications with contrary characteristics, which for Kernberg serves as the main source of neutralization of aggression. Furthermore, he argues in line with Jacobson (1964, 1954), that the process of neutralization, which is linked to the prefrontal and anterior cingulate cortex (Kernberg, 2015; Roth and Dicke, 2006), provides crucial energy for ego growth. Moreover, a weak ego is predisposed to utilize splitting as splitting requires less energy than more mature forms of defense like repression, which results in a vicious circle of reciprocal reinforcement between an enfeebled ego and excessive use of splitting. This intrapsychic process is manifested in symptoms linked to low impulse control, which at the time of their expression are experienced as ego syntonic, including addictive behaviors or self-harming behavior.

Like repression, splitting is not an isolated mechanism but occurs simultaneously with other primitive defense mechanisms (Kernberg, 1985). These comprise: (1) Primitive

idealization, describing the tendency to perceive external objects as exclusively "good", for the purpose of protecting them from being spoiled or destroyed by the subject's own aggression. Furthermore, this is linked to an archaic fantasy formation serving the need for a powerful good object, which protects the self from the external world, perceived as predominantly persecuting.

(2) Projective identification, meaning the tendency to externalize the aggressive and exclusively "bad" self and object representations into external objects, while simultaneously sustaining empathy with the projected contents. Furthermore, this mechanism is characterized by efforts to control the object by unconscious manipulations, leading the object to experience what was projected onto him/her.

(3) Denial, which describes the phenomenon where a subject is aware that the current attitude (including feelings, perceptions and cognitions) towards himself or the external world are in opposition to the attitudes he/she had at other times, but this knowledge has no emotional significance and does not influence the current emotional state.

Finally, (4) omnipotence and devaluation, which is characterized by the unconscious need to control the idealized objects and to treat them as extensions of the self. In this context, the self is perceived as grandiose and especially privileged. If, however, the external object is no longer capable of providing the expected protection or gratification, it is dropped and defaced in an act of revenge, but also to prevent it from becoming a significant persecutory object. According to Kernberg, the process of devaluation significantly harms the development of the subjects internalized object relations and consequently the development of the mental apparatus and its ego functions.

Therefore, the excessive use of splitting and its related mechanisms in individuals with borderline personality organization is linked to substantial deficits in affect integration and regulation (Kernberg, 2015). Furthermore, the persistence of splitting obstructs the development of a "normal" or coherent identity marked by an integrated ("good" and "bad") sense of self and others. This fosters the syndrome of identity diffusion, which is characterized by dissociated representations of the self and others into multiple segments of idealized and persecutory representations (Kernberg, 2006a).

In correspondence to this, addiction is understood as an attempt to chemically seal gaps within a fragile personality structure, which are perceived as painful and chaotic affective

states. However, this creates a vicious circle, as the use of psychoactive substances further fosters the regression of ego functions and the fragmentation of its underlying object relations.

Recent results of quantitative-empirical research applying self-rating measures of personality organization support the assumed association between deficits in personality organization and addiction (Hiebler-Ragger et al., 2016; Unterrainer et al., 2016). Thereby, Hiebler-Ragger et al. (2016) compared healthy controls with inpatients diagnosed with SUD, applying the BPI (Leichsenring, 1999). Findings suggested that SUD patients showed medium to large differences in almost every personality structure dimension measured with the BPI.

These include increased "identity diffusion", "primitive defenses", "fear of fusion" and overall structural deficit. In contrast, the dimension "reality testing" revealed only small differences between healthy and inpatient participants. Similarly, the study by Unterrainer et al. (2016), which applied the IPO (Lenzenweger et al., 2001) to measure deficits in personality organization, revealed increased primitive defense mechanisms in SUD inpatients compared to healthy controls.

Summary of Psychoanalytic Addiction Concepts

The psychoanalytic literature on the subject of SUD encompasses over 100 years and several paradigmatic shifts regarding attempts at understanding this disorder. Early analytics tried to frame addiction in the light of drive, oral regression and perversion, while later theoreticians increasingly emphasized the importance of underlying object relations and ego structural deficits. However, most attempts at creating an etiological model of SUD are based on retrospective observations gained in qualitative case studies, which are prone to overgeneralizations of biographical findings and lack sufficient quantitative-empirical research validating the developed theories (Paula Ramos, 2004). Moreover, several large-scale quantitative longitudinal studies were unable to confirm central assumptions of "drive theoretical psychoanalytic addiction" theory, like increased orality in childhood and homosexual tendencies predicting alcoholism in adulthood (McCord and McCord, 1960; Robins et al., 1962; Vaillant, 1983). In addition, standard psychoanalytic treatment of SUD proved to be rather unsuccessful (Yorke, 1970), which brought about the necessity of adapted psychotherapeutic strategies.

Furthermore, for the most of the 20th century psychoanalysis neglected significant advances in neurobiology, leading to an increasing distance from natural science and academic

psychology (Kandel, 1999). However, this crisis of psychoanalytic theory fostered the development of the field of neuropsychoanalysis, which aimed at linking psychoanalysis with neuroscience and biological psychiatry.

Neuropsychoanalytic Perspectives on the Phenomena of Substance Use Disorder

At the beginning of his career, Freud (1955b) tried to build a psychology grounded in neurology, which he called "Project for a scientific psychology". However, he aborted his effort, as the scientific methods at the end of the 19th century were not sufficient for his intentions and instead developed the method of psychoanalysis (Schore, 2015; Solms and Turnbull, 2011). The attempt to embed psychoanalysis within a neuroscientific framework had a resurgence in the early nineteen-nineties. This endeavor aimed on the one hand to counteract the increasing scientific isolation and deadlock of psychoanalytic theory and on the other hand, to overcome the reductionist approach of biological psychiatry and neuroscience (Panksepp and Solms, 2012). The emerging approach is strongly influenced by the findings of Affective Neuroscience (AN), decisively developed by Jaak Panksepp (1998), which emphasize an evolutionary perspective and affective cross-species similarities.

This fusion of psychoanalysis and AN, labeled as neuropsychoanalysis, proposes a monistic relationship between mind and brain, which is expressed in the term *BrainMind* (Panksepp and Biven, 2012). The BrainMind

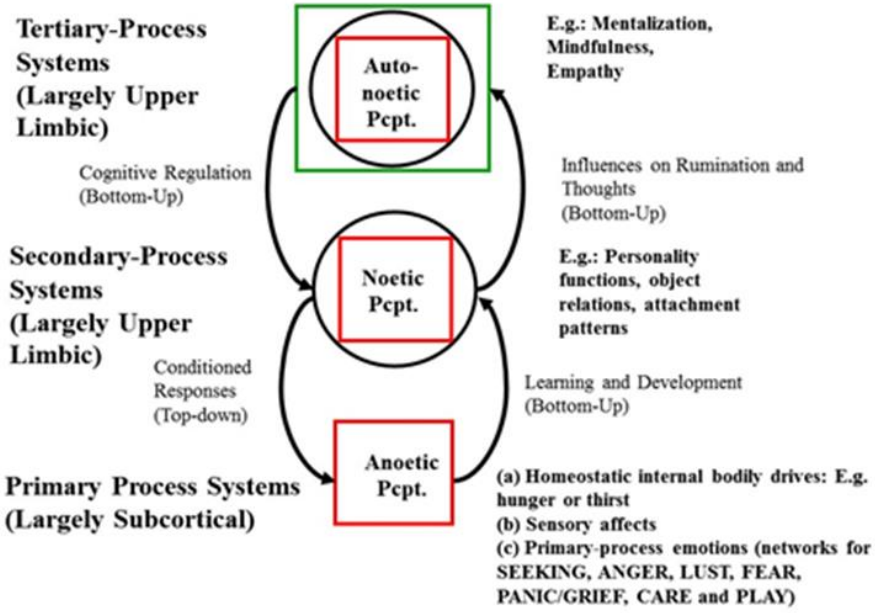


Figure 1. Schematic visualization of nested hierarchies of brain functions in which primary processes (red squares) influence secondary (black circle) and tertiary (green rectangle) processes, which in turn exert top-down control. The figure was drawn by J. Fuchshuber, based on theoretical concepts by Solms and Panksepp (2012) and Panksepp and Biven (2012). Notes. Pcpt. = Perception;

is conceptualized as an interdependent and multi-layered dynamic structure comprised of primary, secondary and tertiary processes (see Fig. 1) (Solms and Panksepp, 2012; Panksepp and Biven, 2012).

Concerning the dynamic between consciousness and unconsciousness, these layers are linked, with regard to Tulving (2002), to *anoetic* (non-language based forms of experience), *noetic* (knowledge and learning based forms of experience) and *autonoetic* (referring to the ability of self-awareness and to reflect the existence of oneself as an entity of time) levels of consciousness (Solms and Panksepp, 2012). Furthermore, these structures roughly correspond to MacLean's (1990) "triune brain" model, which proposes reptilian, paleomammalian (limbic system) and neomammalian (neocortex) layers in human brains, which are seen as sequentially developed in the course of evolution.

According to Solms and Panksepp (2012) primary processes are described as anoetic. As outlined in Fig. 1, they are comprised of largely subcortically (upper brainstem to the septal area) rooted networks including: (a) Homeostatic internal bodily drives like hunger or thirst; (b) Sensory affects like pleasurable taste or disgust; (c) Primary-process emotions, currently identified as networks for SEEKING, ANGER, LUST, FEAR, PANIC/GRIEF, CARE and PLAY. These primary processes serve as the primary motivational system of behavior.

Secondary processes correspond to noetic conscious operations, linked to cognition and exteroceptive representations, which are largely based in the basal ganglia and upper limbic structures and mediate memory and the ability to learn behavior via classical, instrumental and operant conditioning. Secondary processes include largely unconscious behavioral traits, like personality functions, object relations and attachment patterns.

Tertiary processes are described as autonoetic processes, linked to more abstract cognitive operations and reflective awareness. These processes are predominantly neocortically and language based and summarize a broad spectrum of complex memory, cognitive and executive functions like mentalization (meaning the ability to understand behaviors and mental states of oneself and others (Fonagy et al., 2011)), identity narratives, mindfulness and spirituality. In each case, the different layers are reciprocally linked and therefore influence each other via bottom-up processes and top-down regulatory control.

In particular, the assumption that primary process affects are anoetically conscious resembles a metapsychological specificity of the neuropsychoanalytic framework, as it puts the foundation of consciousness into the id, which is classically conceptualized as part of the unconscious (Freud, 1955a). In correspondence to this, Solms and Panksepp (2012) differentiate between cortical mechanisms, which generate representations of the external body, and subcortical mechanisms, which generate the internal body. The external body is understood on the one hand as the subjectively perceived body and on the other hand as the inner representations of the external world. In contrast, the internal body is no object of perception. The affective primary processes rather generate the unmediated experiencing foundation of consciousness, which builds a sentient scaffolding for the perception of objects of the internal and external word. This occurs based on serial pleasure-unpleasure differentiations, decisively generated within the periaqueductal gray (PAG) (Panksepp and Biven, 2012; Solms and Panksepp, 2012). From this perspective, the evolutionary aim of consciousness is the coding of vital approach and avoidance behavior.

As shown in Fig. 1, the mental apparatus of neuropsychoanalytic meta-psychology implies continuous feedback loops expressed between stratified layers of neuronal assemblages. As this model proposes a complex and dynamic system, they might be interpreted in terms of the epistemologically linked fields of chaos and complexity theory (Dodds, 2013; Scharff and Procci, 2002). Like other complex systems (e.g. weather, populations, etc.) mammalian brains tend to produce states of self-organization but are also susceptible to cascades of perturbations and disorder (Lorenz, 1991; Panksepp, 2004; Scharff and Procci, 2002). In correspondence to this, Panksepp (2004) suggests that primary emotions can be understood as strange attractor landscapes involving large assemblages of neurons, which on the one hand support the overall mental apparatus in creatively adapting to environmental changes, but on the other hand might energize the emergence of psychiatric disorders. As described by Lorenz (1991), complex systems are highly sensitive to their initial set of conditions. With regard to neuropsychoanalytic theory, this principle is expressed in the significance of early object relations. These constitute crucial “tuning variables”, determining the development of primary, secondary and tertiary processes (Scharff and Procci, 2002).

Primary emotions

Currently AN, and neuropsychoanalytic researchers distinguish seven primary emotion networks, which arise from the PAG and expand into the limbic forebrain (Panksepp and Biven, 2012). Four of those systems have evolutionary reptilian roots (Solms and Turnbull, 2002). These comprise SEEKING, which mediates appetitive foraging; FEAR, mediating freeze and flight behavior; LUST, mediating sexual and consummatory pleasure; and ANGER, mediating aggressive attack behaviors.

Moreover, three primary emotion networks specifically manifest in evolutionarily higher species like mammalians and certain birds. These networks consist of PANIC/GRIEF or SADNESS, which mediates separation distress; CARE, mediating nurturing behavior; and PLAY, mediating rough and tumble playing behavior (Panksepp and Biven, 2012; Panksepp, 1998; Solms and Turnbull, 2002).

In the following, the neurological and behavioral correlates of these primary affect circuits will be described in more detail.

SEEKING

The SEEKING system refers to the neural structure, whose arousal is linked to the generation of unspecific exploratory, approach and foraging behavior, as well as anticipation and maintenance of goal directed behavior (Alcaro and Panksepp, 2011; Wright and Panksepp, 2012). Moreover, within the subject, this system evokes positive, euphoric feelings and is linked to reinforcement learning or coupling of urges with objects in the external and internal world (Alcaro and Panksepp, 2011; Panksepp, 1998; Panksepp and Biven, 2012). If, however, this system is damaged then a generalized stupor results (Panksepp, 1998; Panksepp and Biven, 2012).

Furthermore, according to Panksepp (1998) the SEEKING system consists of four parts, namely: (1) Regulatory imbalances, serving as trigger for the activation of the SEEKING network; (2) Consummation, referring to the satisfaction of the detected somatic need; (3) External stimulus, meaning the desired object expected to satisfy the need; (4) An intense state of expectancy or anticipation, which refers to psychic and motoric energization linked to the activation of the SEEKING system.

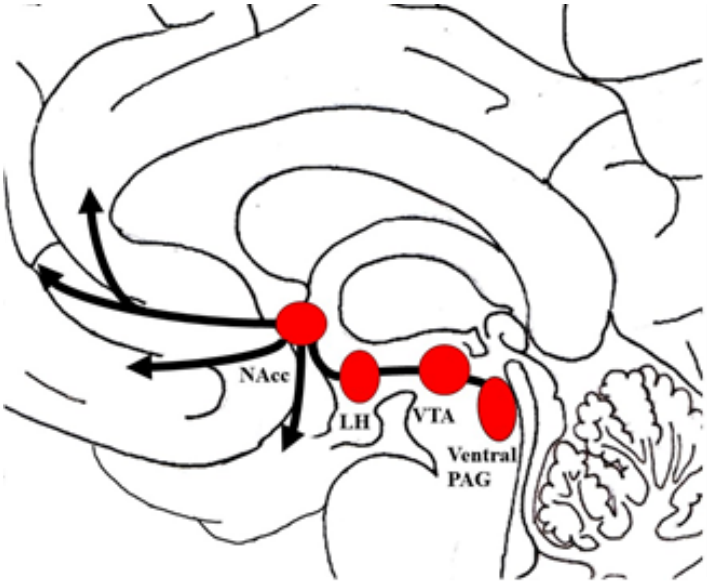


Figure 2. Schematic visualization of the SEEKING system ; The figure was drawn by J. Fuchshuber, based on theoretical concepts by Panksepp (2011).
Notes. LH = Lateral hypothalamus, NAcc = Nucleus accumbens, PAG = Periaqueductal gray, VTA = Ventral tegmental area.

Neuroanatomically, the SEEKING system largely corresponds to the medial forebrain bundle (MFB) (see Fig. 2), and includes a complex network between the dorsal PAG, VTA, lateral hypothalamus, NAcc (which projects towards the amygdala), frontal cortex areas and the ACC (Panksepp, 2011; Solms and Turnbull, 2002). Neurochemically, the SEEKING system is modulated largely by dopamine projected by the VTA, but also by descending GABA and glutamate systems and other ascending catecholamine systems (like norepinephrine and serotonin) as well as neuropeptides projected from source neurons within the lateral hypothalamus (Johnson, 2008; Wright and Panksepp, 2012).

This network has been referred to in behaviorist terminology as the “brain-reward-network”. However, AN-researchers argue that this is a misconception, as this system does not generate pleasure per se, but is associated with an unspecific desire to seek for rewarding stimuli (Panksepp and Biven, 2012). In contrast, the neurological substrate of reward/pleasure is linked in neuropsychoanalytic terms to the LUST system, which is interconnected to the SEEKING system (Solms and Turnbull, 2002; Wright and Panksepp, 2012). This dichotomy between SEEKING and LUST largely corresponds to Robinson and Berridge’s (2000) differentiation between “wanting” and “liking”. In correspondence to this, the process of

learning is understood as a coupling between psychomotor SEEKING impulses ("wanting") and the experience of pleasure mediated by the LUST system ("liking"). Furthermore, the dualism of a seeking/wanting and pleasure/liking system shows strong similarities to Freud's (1955a) definition of drive and satisfaction as well as Lacan's (1977) conceptualization of the contrast between jouissance and pleasure (Bazan and Detandt, 2013, 2017).

Regarding connections between Freud's drive theory and Panksepp's (1998) model of SEEKING, Shevrin (2003) notes the following parallels: (1) Regulatory imbalances correspond to Freud's somatic source of the drive (e.g. hunger, thirst and sex). (2) Consummation is paralleled by Freud's aim of the drive. (3) The external stimulus in Panksepp's model corresponds to the object of libidinous cathexis expected to provide consummatory satisfaction. (4) The intense state of expectancy or anticipation linked to the activation of the SEEKING network, which is observable by increased exploratory behavior in animals (Panksepp, 1998), is in accordance with Freud's description of motor pressure arising from the libido.

Notably, recent neuroscientific research observed that the activity of MFB/SEEKING is essential in the generation of dreams (Solms, 2000, 2014). In contrast to assumptions made by Hobson (2000) - who claimed that dreaming is generated solely in rapid eye movement (REM) sleep - lesion studies revealed that damage to brain areas involving REM sleep does not lead to the cessation of dreaming, amplifying previous research reporting the existence of non-REM dreams (Domhoff, 2005; McNamara et al., 2010). By contrast a large number of case studies revealed the obliteration of dreams by focal lesions affecting parts of the MFB/SEEKING system (Solms, 2000). Given the appetitive function of the SEEKING network, this observation is consistent with Freud's (1900/2001) claims that dreams serve as hallucinatory wish fulfillment derived from libidinal urges.

Concerning parallels with Lacan's concept of jouissance, defined as the rewarding experience deriving from the body/motor tension of the activated drive, Bazan and Detandt (2013) highlight the phenomenon of autoshaping, which is neurologically linked to the activation of the MFB/SEEKING system (Di Ciano et al., 2001). In correspondence to this, autoshaping describes that once a response to a conditioned stimulus has been established in an animal, it will eventually treat the conditioned stimulus as reward, even if no actual reward is imminent, as the animal's response becomes rewarding for itself (Shevrin, 2003). For

example, a pigeon which is conditioned to expect food after the appearance of a light will start to peck at the light. This behavior will continue even if the administration of the food is suspended. This paradox persistence of motor action invested for itself, despite the lack of pleasurable stimuli, shares striking similarities to Lacan's (1977) description of repetition compulsion, which he links to the structural tendency of jouissance to transgress the limits prescribed by the pleasure principle. However, beyond the pleasure principle the acting subject will ultimately experience suffering and death (Evans, 2006). This is underlined by studies investigating the effects of intracranial self-stimulation in the MFB of mammalians (Olds and Milner, 1954), as these experiments ultimately resulted in complete and often fatal exhaustion of the investigated animals, due to the compulsive repetition of the self-stimulating behavior (Bazan and Detandt, 2013).

Moreover, the connection between the psychoanalytic drive concept and activation of the MFB is highlighted in the results of an experimental treatment with deep brain stimulation in patients suffering from depression resistant to standard treatment (Coenen et al., 2009; Coenen et al., 2011; Schlaepfer et al., 2008). Thereby, electrodes are implanted in the MFB. In some patients, stimulation of this area induces symptoms of mania like increased ideomotor pressure, euphoria, a decreased need for sleep, an inflated sense of self, increased risk-taking behavior and hypersexuality (Coenen et al., 2009). Despite the subjective knowledge that these behaviors are "wrong", these patients report the feeling of being possessed and driven by some internal force. However, after the cessation of the MFB-stimulation, these behaviors stop almost instantly.

LUST

The LUST system, which is linked to pleasure, sexual urges and gratification, is reciprocally connected to the SEEKING network. Its activation diminishes SEEKING driven appetence behavior and triggers behaviors and feelings of satisfaction (Solms and Turnbull, 2011). Regarding its neuroarchitecture, the LUST network is not yet fully understood in humans and its structural connectivity is inconsistent across different authors. Inferred from animal models it consists of a complex group of structures, descending from the hypothalamus to the posterior parts of the midbrain (see Fig. 3) (Solms and Turnbull, 2002). Most authors agree that the LUST system is composed of the BNST, the central tegmental field, the preoptic area and the ventromedial hypothalamus, the NAcc shell, septum area and the ventral PAG

(Solms and Turnbull, 2002; Panksepp and Biven, 2012; Holstege and Huynh, 2011; Berridge and Kringelbach, 2015; Hashikawa et al., 2016). Neurochemically, the LUST system is largely controlled by endorphins acting on mu-, delta- and kappa-opioid receptors in the NAcc shell, and hormones like vasopressin, testosterone and oxytocin (Panksepp and Biven, 2012; Solms and Turnbull, 2011; Berridge and Kringelbach, 2015).

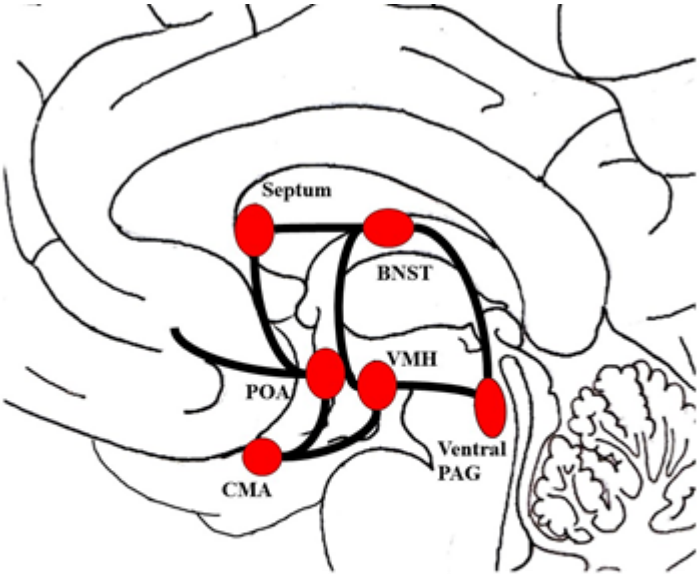


Figure 3. Schematic visualization of the LUST system; The figure was drawn by J. Fuchshuber, based on theoretical concepts by Panksepp (2011) and Solms and Turnbull (2002).
Notes. BNST = Bed nucleus of the stria terminalis, CMA = Cortico-medial amygdala, POA = Preoptic area, PAG = Periaqueductal gray, VMH = Ventromedial hypothalamus.

Moreover, recent studies in humans investigating the neural effects of orgasms with PET scans (Georgiadis et al., 2006; Holstege et al., 2003; Holstege and Huynh, 2011) observed increased blood flow within the upper brainstem and cerebellum. What is more, men showed increased activation in the insula, while women exhibited increased activation in the somatomotor and somatosensory cortex. Moreover, deactivation in the left temporal lobe and ventral prefrontal cortex was observed.

ANGER

While predatory aggression ("cold aggression") is linked to the SEEKING network and neocortical areas, the AN-framework proposes a specific ANGER or RAGE system as a subcortical substrate mediating defensive rage behavior and feelings of anger or rage ("hot aggression") (Panksepp and Zellner, 2004; Panksepp and Biven, 2012; Siegel and Victoroff, 2009).

Inferred from electric brain stimulation in animals, the neural architecture of the ANGER system consists of a complex neural network including the medial amygdala, the BNST, the medial and perifornical hypothalamus and dorsolateral parts of the PAG (see Fig. 4) (Panksepp and Zellner, 2004; Panksepp, 2011). Moreover, the ANGER system shows several overlaps with the LUST network, including the BNST, posterolateral cortical amygdala, the main olfactory bulb and the medial and posterolateral amygdala (Hashikawa et

al., 2016). Furthermore, the ANGER system is predominantly excited by glutamate, acetylcholine, substance P, dopamine and norepinephrine, while mu- and delta-opioids, GABA and serotonin show predominantly inhibiting effects (Panksepp and Zellner, 2004; Siegel et al., 1999; Siegel and Victoroff, 2009). Furthermore, the activation of the ANGER system is linked to sympathetic arousal marked by increases in blood pressure and heart rate (Siegel and Victoroff, 2009).

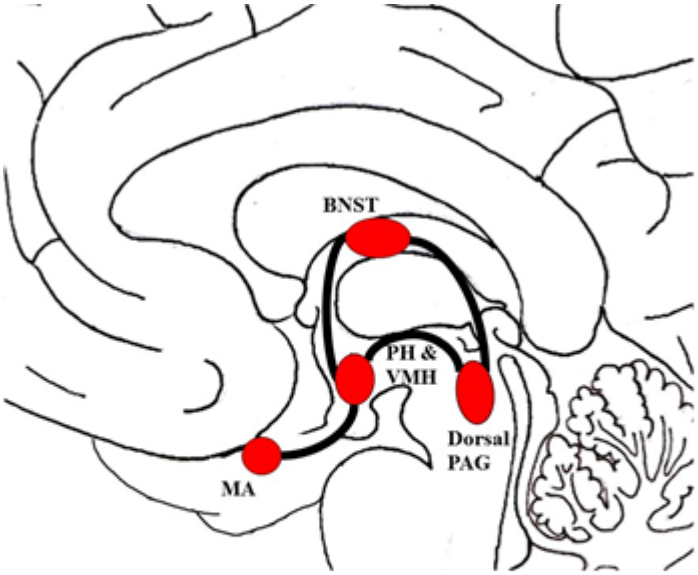


Figure 4. Schematic visualization of the ANGER system; The figure was drawn by J. Fuchshuber, based on theoretical concepts by Panksepp (2011) and Solms and Turnbull (2002).
Notes. BNST = Bed nucleus of the stria terminalis, MA = Medial amygdala, PH = Perifornical hypothalamus, PAG = Periaqueductal gray, VMH = Ventromedial hypothalamus.

On a behavioral level, the ANGER network elicits aggressive behaviors in response to frustrations, restraints to the organisms freedom of action or threatening stimuli (Panksepp, 2011; Siegel and Victoroff, 2009). Increased ANGER activity triggers a stereotypical motor program linked to fighting reactions, observable in the baring of one's teeth, aggressive sounds like growling, typically stable body postures, the exhibition of claws or fists and impulsive outbursts of aggressive actions (Solms and Turnbull, 2002; Siegel and Victoroff, 2009). In contrast to the SEEKING system, the ANGER system is usually only activated on specific occasions. However a chronic, low level activation of ANGER is referred to as irritability, which is linked to the frustration of goal directed behaviors (Solms and Turnbull, 2002).

FEAR

The FEAR system refers to the neural substrate mediating the behavioral response and affective perception of fear and anxiety (Panksepp and Biven, 2012; Panksepp, 1998). The activation of this network generates motoric responses linked to flight or freeze reactions and is emotionally perceived as anxiety-fear. Furthermore, AN-researchers differentiate this emotional state from panic-fear, which is linked to the PANIC/GRIEF system described below. As outlined in Fig. 5. the FEAR circuit consists of links from the central and lateral

amygdala to the medial hypothalamus and ends in the dorsal PAG (Panksepp, 2011). Animals and humans stimulated in these areas, especially the dorsal PAG, show intense anxiety reactions (LeDoux, 1992; Nashold Jr et al., 1969; Panksepp, 2011; Watt, 2000).

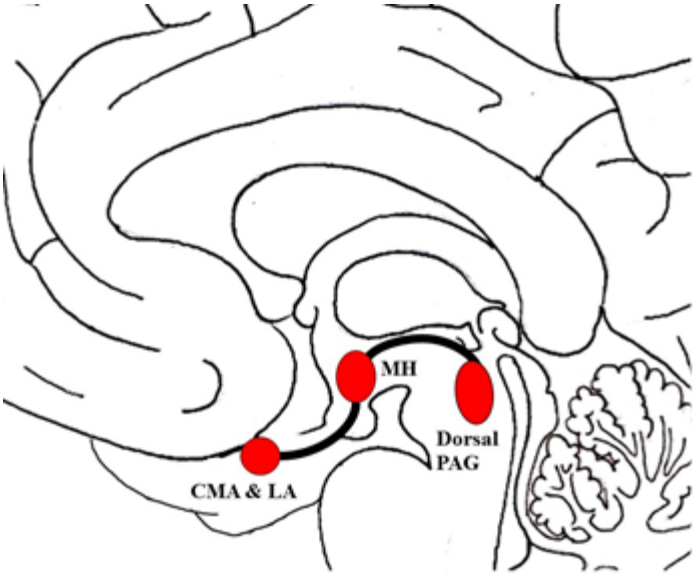


Figure 5. Schematic visualization of the FEAR system; The figure was drawn by J. Fuchshuber, based on theoretical concepts by Panksepp (2011) and Solms and Turnbull (2002).
Notes. CMA = Corticomedial amygdala, LA = Lateral amygdala, MH = Medial hypothalamus, PAG = Periaqueductal gray.

The key neuromodulators controlling this system are glutamate, corticotropin releasing factor, adrenocorticotrophic hormone and cholecystokinin, which excite FEAR, as well as GABA and neuropeptide Y, which inhibit the FEAR system (Panksepp and Biven, 2012). Physiologically, the activated FEAR system generates similar effects as the ANGER system, related to increased sympathetic arousal like increased heart rate, fast and flat breathing, diminished blood flow in the digestive system and increased circulation in the muscular system (Solms and Turnbull, 2002). The link between ANGER and FEAR is further emphasized by observations of patients suffering from Klüver-Bucy syndrome, which is a rare condition resulting from bilateral lesions of the amygdala (Adolphs et al., 2001; LeDoux, 1992). These patients are unable to experience or express both fear and anger/rage. Moreover, they are characterized by hypersexuality and hyperorality (Solms and Turnbull, 2002). In summary, this highlights the central importance of the amygdala for both fear and anger, as well as the inhibiting function of these networks regarding the activation of LUST.

PANIC/GRIEF

The PANIC/GRIEF or separation distress network is not only associated with panic-anxiety but also with feelings of sadness, loss and loneliness (Solms and Turnbull, 2002; Panksepp, 2011). In infant animals, the activation of this structure, either by isolation of the infant from its caretaker or direct brain stimulation, triggers a specific set of behavioral patterns, signaling the need for care (Nelson and Panksepp, 1998). This includes specific

separation calls and initially increased SEEKING activity, characterizing the "protest" or agitated panic phase of separation distress (Bowlby, 1969; Panksepp and Biven, 2012). However, sustained overactivity of the PANIC/GRIEF system decreases SEEKING driven behavior and therefore leads to behaviors associated with the "despair" phase of separation distress (Bowlby, 1969; Panksepp and Biven, 2012). From an evolutionary perspective, the initial panic phase of the infant might aim at increasing the chances of a reunion with the lost caregiver, while the subsequent withdrawal behavior might decrease the probability to get caught by a predator (Freed and Mann, 2007; Solms and Turnbull, 2002). In correspondence to this, the activation of the separation distress network is associated with subjective feelings of panic, grief and pain associated with object loss, while its deactivation mediates feelings of warmth, comfort and secure attachment (Panksepp, 2011; Watt and Panksepp, 2009).

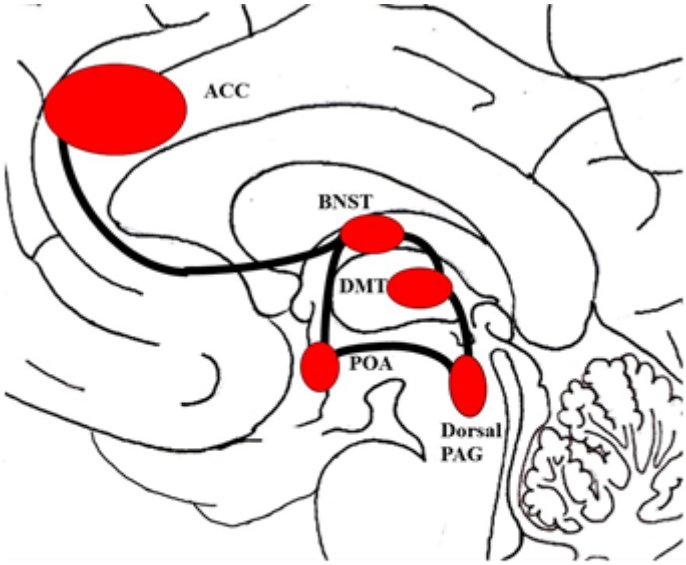


Figure 6. Schematic visualization of the PANIC/GRIEF system; The figure was drawn by J. Fuchshuber, based on theoretical concepts by Panksepp (2011) and Solms and Turnbull (2002).
Notes. ACC = Anterior cingulate cortex, BNST = Bed nucleus of the stria terminalis, DMT = Dorsomedial Thalamus, POA = Preoptic area, PAG = Periaqueductal gray.

In mammalians, the PANIC/GRIEF system includes connections between the ACC, the BNST, the preoptic area and the dorsomedial thalamus which descend to the PAG (see Fig. 6) (Panksepp, 2011; Panksepp and Biven, 2012). This system is predominantly controlled by endogenous mu-, delta- and kappa-opioid-receptors. In correspondence to this, endogenous mu and delta opioid receptor ligands (like enkephalins and endorphins) deactivate the PANIC/GRIEF system, while kappa-opioid ligands (like dynorphins) increase PANIC/GRIEF activity (Panksepp and Biven, 2012; Watt and Panksepp, 2009). Moreover, this system is deactivated by the hormones oxytocin and prolactin and activated by CRF and the neurotransmitter glutamate (Panksepp, 2011). Furthermore, the neural and affective mechanisms of the PANIC/GRIEF system suggest that the mammalian attachment system might function based on negative reinforcement processes linking separation with painful

feelings. Thus, young animals and infants learn to stay close to their caregivers in a very efficient manner (Panksepp and Biven, 2012; Solms and Turnbull, 2002).

CARE

The maternal nurturance or CARE system promotes parental care and attachment behavior in mammals and birds (Numan and Insel, 2006; Riters, 2011; Panksepp, 2011). Neurobiologically, the CARE system is closely related to PANIC/GRIEF (Panksepp, 2011). Therefore, CARE might be seen as a substructure of PANIC/GRIEF (Solms and Turnbull, 2002). In correspondence to this, the CARE system includes connections between the ACC, BNST, preoptic area and VTA descending into the PAG (see Fig. 7). Furthermore, its activity is increased by oxytocin, prolactin, dopamine and endogenous mu- and delta-opioid ligands.

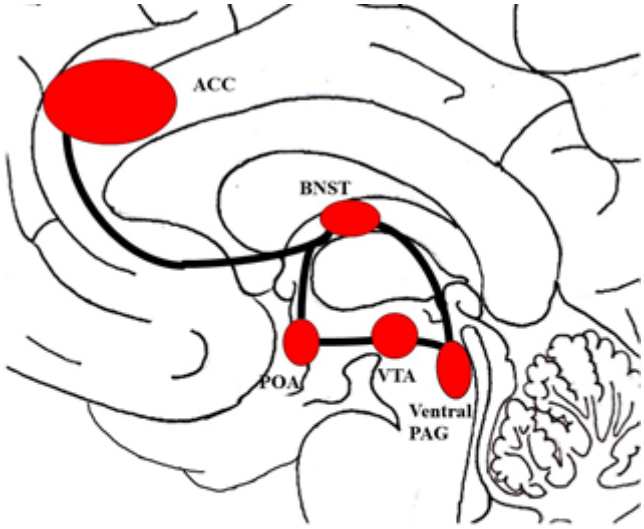


Figure 7. Schematic visualization of the CARE system; The figure was drawn by J. Fuchshuber, based on theoretical concepts by Panksepp (2011).
Notes. ACC = Anterior cingulate cortex, BNST = Bed nucleus of the stria terminalis, POA = Preoptic area, PAG = Periaqueductal gray, VTA = Ventral tegmental area.

PLAY

Panksepp (1998; Panksepp and Biven, 2012) proposed the PLAY or joy network as the evolutionarily most recent primary emotion network. He observed that play behavior in young rats is accompanied by specific 50 kHz chirps, which he also observed if rats were tickled by humans (Panksepp, 2011). Moreover, these ultrasonic sounds - which Panksepp associates with joyful laughter - were also expressed if

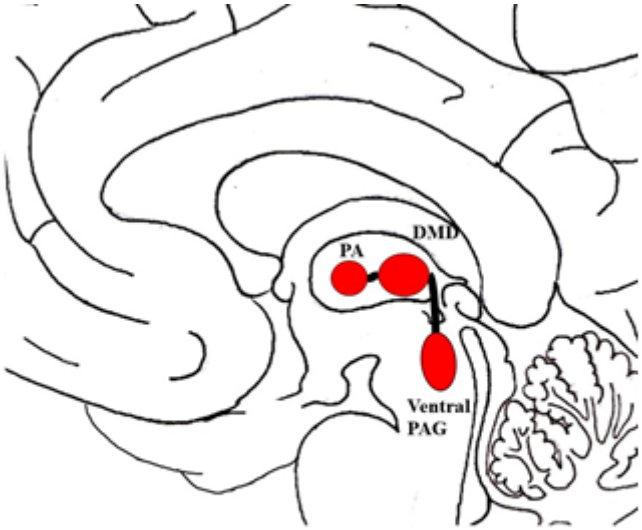


Figure 8. Schematic visualization of the PLAY system; The figure was drawn by J. Fuchshuber, based on theoretical concepts by Panksepp (2011).
Notes. DMD = Dorso-medial diencephalon, PA = Parafascicular area, PAG = Periaqueductal gray.

certain brain areas were electrically stimulated (Panksepp, 2011). In addition, rats extensively self-stimulate this network, suggesting that PLAY might be energized by the SEEKING network (Burgdorf et al., 2007).

Neuroanatomically, the PLAY system includes the dorso-medial diencephalon and the parafascicular area and descends into the PAG (see Fig. 8) (Panksepp, 2011). Moreover, this system is largely controlled by endogenous opioids, cannabinoids, acetylcholine and glutamate (Panksepp and Biven, 2012). Furthermore, Panksepp (2011, 1998) proposes that the PLAY system follows homeostatic principals, as rats deprived of the ability to play excessively catch up on their lost play time if they regain the ability to do so. Finally, he suggests that PLAY serves an important function in the development of social behavior, communication and empathy (Panksepp and Lahvis, 2011).

The Role of Primary Emotions in Addiction Development

As shown in the summary Table 1, all seven primary emotion networks are postulated to have relationships with a variety of psychiatric disorders (Panksepp, 2004). Regarding the etiology of SUD, AN addiction theory predominantly focuses on the significance of SEEKING and PANIC/GRIEF (Alcaro and Panksepp, 2011; Panksepp, 2004; Solms et al., 2015; Zellner et al., 2011).

The SEEKING System and Addiction

Largely in consensus with Berridge (2009; Robinson and Berridge, 2000), AN theorists propose that addiction is characterized by pathological changes within the SEEKING/wanting system. In the course of developing SUD, SEEKING is increasingly and ultimately predominantly activated in association with substance related appetitive memories, substance consumption and the desire to alleviate negative affective states (Alcaro and Panksepp, 2011; Koob and Le Moal, 2005; Zellner et al., 2011). Furthermore, it is emphasized that several lines of evidence support the hypothesis, that individuals predisposed to addiction might be vulnerable to the development of this disorder due to specific psychological and neural predispositions, like hyperexcitability of the brain stress system or depressiveness. In turn, this might promote the reorganization of SEEKING towards drugs or other addictive behaviors like gambling (Alcaro and Panksepp, 2011). In correspondence to this, animals predisposed to addiction showed traits associated with the concept of “novelty

Table 1. *Summary of behavioral, neuroanatomical, neurochemical and clinical aspects of primary emotion systems in the mammalian brain proposed by Panksepp (2004, 2011).*

Primary Emotion System	**Associated Emotions**	**Key Brain Areas**	**Key Neuromodulators**	**Proposed Associated Psychiatric Disorder**
SEEKING	Interest, Euphoria, Craving, Motivation	NAcc, VTA, Mesolimbic and mesocortical outputs, Lateral hypothalamus, PAG	Dopamine (+), Glutamate (+), Opioids (+), Neurotensin (+), Orexin (+), several other neuropeptides	Obsessive-compulsive disorder, Schizophrenia, Substance use disorder, Mania
LUST	Erotic feelings, Jealousy, Pleasure	Septum, Cortico-medial amygdala, BNST, Preoptic hypothalamus, Ventromedial Hypothalamus, PAG	Steroids (+), Vasopressin, Oxytocin, LH-RH, CCK, Opioids	Paraphilic disorder, Hypersexual disorder
ANGER	Anger, Rage, Irritability, Hatred	Medial amygdala, BNST, Medial and perifornical hypothalamus, PAG	Substance P (+), Acetylcholine (+), Glutamate (+)	Personality disorders
FEAR	Simple anxiety	Central and lateral amygdala, medial hypothalamus, Dorsal PAG	Glutamate (+), DBI, CRF, CCK, alpha-MSH, NPY	Generalized anxiety disorders, Phobias, Post-traumatic stress disorder
PANIC/GRIEF	Separation distress, Panic, Mourning, Sadness, Grief	Anterior cingulate cortex, BNST, Preoptic area, Dorsomedial thalamus, PAG	Opioids (+/-), Oxytocin (-), Prolactin (-), CRF (+), Glutamate (+)	Panic disorder, Depression, Agoraphobia, Social phobia, Autism
CARE	Nurturance, Love, Attraction	Anterior cingulate cortex, BNST, Preoptic area, VTA, PAG	Oxytocin (+), Prolactin (+), Dopamine (+), Opioids (+)	Dependent personality disorder, Autism, Attachment disorders
PLAY	Joy, Happy playfulness	Dorso-medial diencephalon, Parafascicular area, PAG	Opioids (+/-), Glutamate (+), Acetylcholine (+), Cannabinoids	Mania, Attention deficit hyperactivity disorder

Notes. alpha-MSH = alpha-melanocyte stimulating hormone, BNST = Bed nucleus of the stria terminalis, CCK = Cholecystokinin, CRF = Corticotropin releasing factor, DBI = Diazepam binding inhibitor, LH-RH = Human luteinizing hormone-releasing hormone, NAcc = Nucleus accumbens, NPY = neuropeptide Y, VTA = Ventral tegmental area, PAG = Periaqueductal gray; Adapted from Panksepp (2004, 2011).

seekers" or "sensation seekers" (Ersche et al., 2010; Everitt et al., 2008; Zuckerman, 1971), like increased locomotion and explorative behavior in novel environments as well as a higher preference for novel environments (Alcaro and Panksepp, 2011; Piazza et al., 1989). Furthermore, animal models indicate that vulnerability to addiction is linked to increased approach behavior towards cues previously associated with rewards, in contrast to approach behavior towards the reward itself (Flagel et al., 2009; Flagel et al., 2010). This enhanced conditioning power of environmental stimuli is described by the "incentive salience hypothesis" by Berridge and Robinson (1998). In this model, it is proposed that dopamine activity predicts the reward gained from a specific object, which is called "incentive". In turn, this motivates the organism to approach this object, which is summarized in the term "salience". Regarding addiction, the drug induced increased dopamine release might lead to an overly strong incentive of the drug and associated environmental cues, which promotes their excessive salience (Berridge and Robinson, 1998; Berridge, 2009; Volkow et al., 2009).

In this context, the hyperexcitability of the dopamine driven SEEKING network of individuals predisposed to addiction might further increase the secondary reward value (incentive salience) of drugs, promoting the emergence of compulsive drug taking habits. What is more, the hyperexcitability of SEEKING in animals vulnerable to addiction has been linked to an increased firing rate of dopamine neurons in the midbrain in basal conditions (Marinelli and White, 2000). However, this is contrasted by findings indicating that vulnerable animals show decreased resting-state dopamine release and uptake in the NAcc (Chefer et al., 2003). In conclusion, the increased firing rate of dopamine neurons in addiction vulnerable animals might be associated with decreased dopamine transmission in resting-state condition characterizing addiction vulnerability (Alcaro and Panksepp, 2011). This is further underlined by findings indicating low basal dopamine levels and dopamine D2 receptor availability in humans predisposed to addiction and with a history of addiction (Nader et al., 2006; Volkow et al., 2007; Volkow et al., 2017). In line with this, AN-researchers argue that a predisposition towards addiction is linked to a general hypoactivity of the SEEKING/ML-DA network (Alcaro and Panksepp, 2011; Solms et al., 2015; Zellner et al., 2011). In turn, this is linked to a diminished capacity to seek rewards in the external world. This fosters a gradual development in which the individual learns that only excessive surges of dopamine D2 driven excitation, as triggered by addictive drugs, allows for the achievement of pleasurable objects

in the external world (Solms et al., 2015). Therefore, AN-theory proposes that the object of addiction is not the addictive substance per se, but rather the *possibility* of actual biological, social or sexual rewards, facilitated by the effect of the substance (Alcaro and Panksepp, 2011; Solms et al., 2015; Zellner et al., 2011). In correspondence to this, the SEEKING network would play an important etiological role especially regarding SUDs involving stimulating drugs, like cocaine and amphetamines (Solms et al., 2015; Zellner et al., 2011). This is further emphasized by recent results indicating that striatal dopamine receptor availability is diminished in individuals suffering from stimulant and alcohol addiction, but not in patients suffering from opiate or cannabis addiction (Nutt et al., 2015).

Another line of evidence linking SEEKING and SUD is based on research on so called "drug dreams" in addicted subjects (Johnson, 2001). With regard to Solm's (2000, 2014) neuropsychoanalytic dream theory - identifying the SEEKING system as essential for the generation of dreams - several studies observed that SUD patients frequently report dreams related to their craving of the drug they are addicted to (Christo and Franey, 1996; Colace, 2004; Colace et al., 2010; Johnson, 2000; Yee et al., 2004). Usually, these dreams contain episodes in which subjects seek for drugs, use them or attempt to use them. Furthermore, these dreams were observed to be associated with increased drug-craving (Choi, 1973; Christo and Franey, 1996; Colace, 2004; Fiss, 1980). In correspondence to this, drug dreams are understood as hallucinatory wish fulfillment of drug cravings mediated by an upregulated ML-DA/SEEKING system (Colace et al., 2010).

PLEASURE/LUST, PANIC/GRIEF and Addiction

Furthermore, according to AN-theory the most crucial emotion circuits regarding the development of SUD are the PLEASURE/LUST and PANIC/GRIEF networks (Solms et al., 2015; Zellner et al., 2011). In correspondence to this, dopamine surges of the artificially excited SEEKING system might not be the primary object of addiction, but rather the feeling of reward itself, mediated in large part by the predominantly opioid controlled PLEASURE/LUST and PANIC/GRIEF systems. Moreover, it is proposed that there might be a clinically useful differentiation between SUDs primarily involving substances which stimulate the SEEKING system ("upper") and SUDs primarily involving substances which stimulate the PLEASURE/LUST and PANIC/GRIEF system ("downer"), with the latter being the clinically more severe disorder (Solms et al., 2015; Zellner et al., 2011).

This perspective resonates with Mentzos's (2017) differentiation between regressive and pseudoregressive forms of addictions. Thereby, the pseudoregressive form of addiction is based on the pathological use of "uppers" like cocaine and amphetamines, which help the addict to achieve an inflated sense of a grandiose self; this helps compensate for underlying deficits in his/her self-regulation. In contrast, regressive forms of addiction involve the chronic use of "downers" like opioids. In this, the addict tries to achieve an undifferentiated and contended "nirvana-state", making the addict inaccessible to unpleasurable stimuli.

What is more, the neuroarchitecture of attachment in mammalians, primarily mediated by the PANIC/GRIEF system, and SUD share striking similarities, which are mirrored by a significant overlap in the behavioral aspects of both social dependence and addiction (Burkett and Young, 2012; Flores, 2004; Insel, 2003; Panksepp, 1998; Zellner et al., 2011). Common neurochemical sites of action and change regarding attachment and addiction development include dopamine D1 and D2 receptors, mu-, delta- and kappa-opioid receptors and CRF (Burkett and Young, 2012). Behavioral similarities between attachment/loss and addiction/withdrawal include: Social bonding – drug dependence; drug tolerance – estrangement; and drug withdrawal – separation distress (Panksepp, 1998; Solms et al., 2015; Zellner et al., 2011). Furthermore, especially the behavioral aspects of opioid withdrawal show strong resemblances to separation distress, comprising psychological and somatic pain, crying, loss of appetite, depression, sleeplessness and aggressiveness (Panksepp, 1998; Solms et al., 2015; Zellner et al., 2011). In this context, addiction might be understood as a dysfunctional attempt to compensate for overwhelming feelings of isolation, loss and sadness mediated by an overactive PANIC/GRIEF system. Thereby, abuse of mu- and delta-opioid receptors agonists might especially act as a replacement for secure love objects, substituting the warmth and comfort usually experienced in close relationships.

In this context, AN-researchers reinterpret Freud's (1905/1953) claims regarding the link between masturbation and addiction. They argue that, similar to masturbation, addiction is a form of "empty pleasure", characterized by direct and objectless stimulation of the PLEASURE/LUST network, which does involve the desire for secure love-objects, but this desire is ultimately frustrated (Solms et al., 2015; Zellner et al., 2011). The proposed link between PANIC/GRIEF and addiction is supported by a recent psychometric study by

Unterrainer et al. (2017), which found increased SADNESS dispositions in addicts diagnosed with polytoxicomania compared to a healthy control group.

Summary of the Affective Neuroscience Addiction Theory

In summary, the AN-framework proposes three main routes linking primary emotions to the etiology of SUDs (Zellner et al., 2011). (1) Addiction development is driven by the ML-DA/SEEKING network. Furthermore, it is proposed that substance abuse is a compensative strategy against the dysphoria linked to a hypoactive SEEKING system, which might be especially important regarding addictions involving stimulants. (2) A feedback loop between the primary processes SEEKING and PLEASURE/LUST allows for learning to occur and thus is necessary for the emergence of SUDs. (3) The PANIC/GRIEF system plays the most significant role in the development of SUDs. Thereby, addiction is understood as a deranged form of social attachment, as the purpose of the feedback loop between SEEKING and PLEASURE/LUST is the reduction of PANIC/GRIEF.

Furthermore, until now the role of other primary emotion systems in the emergence of addiction cycles has been largely neglected in AN-theory and research. However, Unterrainer (2017) was able to show increased SADNESS, FEAR and ANGER in patients suffering from polytoxicomania compared to healthy controls. Moreover, very little is known about the role of PLAY and CARE in addiction etiology. With regard to the neurochemistry of PLAY, which relies on the endogenous cannabinoid system (Panksepp and Biven, 2012), it might be plausible to assume that PLAY is involved in cannabis addiction, however this assumption lacks empirical support (H. Unterrainer et al., 2017). Similarly, so far there is no data suggesting the significance of CARE in SUD development in humans (H. Unterrainer et al., 2017). Nevertheless, animal research showed that lactating dams exhibited reduced brain activity in the ML-DA, compared to virgin females, if the animals were exposed to cocaine (Ferris et al., 2005). Therefore, it is still unclear if addiction might be a self-medication strategy against negative affects in general, as proposed by authors of ego-psychology (e.g. Khantzian, 1997), rather than a more specific coping mechanism against increased PANIC/GRIEF and decreased SEEKING as proposed in AN-theory.

Despair as a Common Denominator of Depression and Addiction

In correspondence to the proposed relation between SUDs, decreased SEEKING and increased PANIC/GRIEF, the AN-framework sheds new light on the link between depression and addiction, already emphasized by Rado (1926; 1933). AN-theory conceptualizes depression as an evolutionarily conserved mechanism in which the overactive PANIC/GRIEF system shuts down the acute panic or protest phase of separation distress and triggers a state of *despair* which is characterized by sustained overactive GRIEF and discontinuation of the SEEKING system, experienced as intense dysphoria (Watt and Panksepp, 2009). This mechanism might be promoted by increased dynorphin activity, diminishing dopamine transmission within the ML-DA (Nestler and Carlezon, 2006; Panksepp, 2010). Similarly, addiction development is driven by the opponent affective process triggered by the dysphoria of diminished SEEKING resources, either because of sustained artificial over-stimulation through drug consumption, a premorbid disposition towards SEEKING hypoactivity, or chronic hyperactivity of the PANIC/GRIEF network (Zellner et al., 2011). Therefore, despair (increased PANIC/GRIEF and decreased SEEKING) is proposed as the common affective core of both disorders. However, individuals suffering from addiction would chronically self-medicate this painful emotional state through the use of psychoactive substances. The plausibility of this assumption is emphasized by current progress in the neurobiological research underlining the important role of opioid and dopamine systems in the etiology and treatment of both depression and addiction (Treadway and Zald, 2011; Riva-Posse et al., 2017; Volkow et al., 2016) and the firmly established correlation between both disorders (Grant et al., 2015; Grant et al., 2016). Furthermore, there has been a long tradition linking both addiction and depression to loss, mourning and insecure attachment (Bowlby, 1969; Freud, 1966, 1905/1953; Glover, 1932).

Trauma, Attachment and Addiction

In psychodynamic theory, the experience of childhood trauma has been assumed to play a crucial role in the etiology of psychiatric disorders since its beginnings at the end of the Nineteenth century (Charcot, 1879; Freud, 1906). In a psychoanalytic context, trauma is defined as an event so intense and overwhelming that it is impossible for the subject to integrate this experience within a symbolic structure (Laplanche and Pontalis, 1988). Empirically, childhood trauma is often assessed by the retrospective amount of emotional,

physical and sexual abuse, as well as emotional and physical neglect and deprivation, a subject has suffered (Bernstein et al., 1994; Bernstein et al., 1997).

Meanwhile, contemporary research has gathered a considerable amount of evidence linking traumatic environments in childhood to a wide range of adult psychopathology (van Nierop et al., 2015). In correspondence to this, a recent review by Teicher and Samson (2016) suggested that childhood trauma is substantially associated with structural changes in a number of brain regions, linked with processing and modulation of emotions. Specifically, this includes the anterior cingulate, dorsal lateral prefrontal and orbitofrontal cortex, the corpus callosum and the hippocampus. Furthermore, childhood trauma is associated with increased amygdala response to emotional cues and conflict processing as well as reduced striatal response to anticipated rewards. In this context, converging results indicate that the association between childhood trauma and adult psychopathology might be mediated by disturbances in the neurobiological development linked to cognitive control and emotion regulation (Heim and Nemeroff, 2001; Pechtel and Pizzagalli, 2011; Tottenham et al., 2010).

In correspondence to this, the development of secure attachment - which in line with AN-theory might be seen as a secondary order process (Panksepp and Biven, 2012) - has been linked to the development of emotional functioning (Schore and Schore, 2008). Bowlby (1969) observed that infants who were not able to establish a secure attachment to their caregiver were at higher risk for the emergence of developmental disorders, severe depression and delinquent behavior. Thereby, attachment theory assumes that the development of affect regulation is based on the early nonverbal communication between infant and primary caregiver (Schore, 2002; Fonagy, 2010). Ideally, primary caregivers perceive the nonverbal affective expressions of the infant and co-regulate these through symbolic mirroring and by providing physical as well as verbal comfort. This process supports the infant in tolerating its intense and primarily non-verbal affects. The repetition of this process leads to a gradual internalization of positive inner working models of the self and others. The positive inner working models serve as an internalized secure base which supports the individual in regulating emotions in a relatively autonomous and functional way, and enables him/her to explore the external world on his/her own (Fonagy, 2003). Furthermore, secure attachment helps the individual form stable and functional relationships, allowing the individual to regulate emotions with the help of others (Flores, 2004). In contrast, internalized traumatic

early experiences promote the development of corresponding negative inner working models and insecure attachment patterns that obstruct the functional regulation of emotions and the formation of stable relationships (Belsky, 2002; Fonagy, 2010; Fonagy et al., 2011; Schore, 2001).

Following Ainsworth and Bell (1970), insecure attachment styles are subdivided into anxious-ambivalent, anxious-avoidant and disorganized attachment patterns in infants, which corresponds to Bartholomew's and Horowitz's (1991) differentiation into anxious-preoccupied, dismissive-avoidant and fearful-avoidant attachment patterns in adults. Longitudinal studies were able to show that the attachment styles shown in early infancy form relatively stable traits, which are traceable to adulthood (Fraley, 2002; Waters et al., 2000). In correspondence to this, the anxious-preoccupied attachment style refers to people with a negative working model of oneself but a positive view of others, associated with an increased separation anxiety and preoccupation with relationships (Bartholomew and Horowitz, 1991; van Buren and Cooley, 2002). The dismissive-avoidant attachment style describes a pattern consisting of a positive inner working model of oneself and a negative working model of others, resulting in the avoidance of intimate relationships and a strong desire for independence. A fear-avoidant attachment pattern is characterized by negative inner working models of the self and others, resulting in a high level of distrust coupled with a simultaneous belief that one is unworthy of love.

Due to the relationship between insecure attachment and affective dysregulation, insecure attachment has been repeatedly linked to the development of addiction disorders (Schindler and Bröning, 2015; Unterrainer et al., 2017). Largely in line with psychoanalytic object relations theory and ego-psychology, substance abuse is seen as chemical affect regulation strategy, substituting a secure attachment figure and acting as an artificial "secure base" for the consumer (Flores, 2004; Schindler, 2014). Initially, this has a stabilizing effect on the self and its affect regulation capabilities. However, ultimately substance abuse further weakens attachment abilities and affect regulation, which triggers the vicious addiction circle of increased substance abuse, gradually leading to a complete loss of control. The assumed association between SUD and insecure attachment is well supported by a multitude of empirical studies applying psychometric attachment measures (Schindler et al., 2005; Schindler and Bröning, 2015; Unterrainer et al., 2017). Results linking addiction to specific

patterns of insecure attachment are less conclusive, but a tendency primarily linking dismissive-avoidant and fearful-avoidant attachment patterns to addiction can be observed (Schindler and Bröning, 2015). Moreover, so far research regarding the association between specific attachment styles and different groups of substance addictions has been sparse. The existing literature indicates links between heroin abuse and fearful-avoidant and between cannabis abuse and avoidant-dismissive patterns, while evidence concerning other classes of substance abuse is more heterogeneous (Schindler et al., 2009; Schindler and Bröning, 2015).

Summary of the Neuroscientifically Informed Psychodynamic Approach Towards Addiction Etiology

All psychodynamic theories share a common etiological structure explaining the emergence of SUD and other psychiatric disorders, although all approaches emphasize different aspects (Bilitza, 2008). Therefore, all psychodynamic approaches can be summarized in the following formula: (1) An interaction between biography and hereditary dispositions determine (2) the individual's level of integration regarding his/her personality structure, which comprises the relationship between primary (including drives and affects), secondary and tertiary processes (including ego and super-ego structures). These development deficits are reflected on a neurobiological level and promote (3) a failing adaption to reality and its demands. In turn, this leads to (4) the manifestation of psychiatric disorders, which (5) in the case of maladaptation by the use of psychoactive substances leads to the development of addictive behaviors and ultimately to the manifestation of SUD (Bilitza, 2008; Rudolf, 2002).

As outlined above, the historical development of the psychoanalytic discourse on the phenomena of addiction might be described as a movement, starting from an emphasis of sexual and aggressive drives - sometimes crossing the border to moral judgement and stigmatization - to a broader and more empathetic understanding of addiction as a dysfunctional coping strategy, aimed at managing intolerable pain and suffering (Verma and Vijayakrishnan, 2018). This theoretical development is paralleled by a refinement of psychodynamic treatment strategies for subjects affected by SUD. Instead of the traditional psychoanalytic method, which is largely based on the interpretation of latent conflicts by an abstinent analyst (Laplanche and Pontalis, 1988), contemporary psychoanalysis stresses a more supportive, understanding and active role of the psychotherapist (Johnson, 2018; Khantzian, 1990; Leichsenring and Rabung, 2014). In correspondence to this, the

psychodynamic therapist attempts to be perceived by the patient as a "sufficiently good" object, which might be gradually internalized. In turn, this is aimed at fostering increased interpersonal, affect regulation and mentalization capabilities on the part of the patient (Heigl and Heigl-Evers, 1991; Savov and Atanassov, 2012).

Chapter II: Original Research

Research Aims

Based on the empirical research and theoretical models outlined above, seven studies were implemented. As quantitative-empirical research investigating the validity of the neuroscientifically informed psychodynamic addiction theory is still rather scarce, their aim was to further investigate this framework in regards to addiction development and treatment. Specifically, the following subjects were explored:

1. The role of neurobiology and attachment in addiction etiology and treatment

Four studies addressed the role of neurological and behavioral correlates in SUD pathogenesis and treatment in adults, with a special focus on adult attachment. These studies aimed at increasing the understanding of the high treatment drop-out rates of SUD inpatients (Brorson et al., 2013), and tried to increase the understanding of the underlying neurological and attachment related characteristics of this disorder. This basic research is directed at paving the way for improved treatment options for SUD.

2. The relationship between childhood trauma, personality, primary emotions and adulthood psychopathology

Three studies investigated the influence of childhood trauma on different facets of personality and primary emotion systems, as proposed by Panksepp (1998). Gained insights might help to explain how childhood trauma unfolds its pathogenic effect in adulthood and might ultimately assist the development of more effective affect regulation oriented treatment strategies. Furthermore, these studies tried to deepen the understanding of the influence of personality regarding affect integration and emotional functioning. As addiction is often

conceptualized as a dysfunctional affect regulation strategy (Khantzian, 2013), it is crucial to explore the underlying mechanisms of affect regulation in order to develop improved treatment strategies.

The following chapter will give a short overview of the research conducted in the course of this thesis. Because these studies have already been published or are submitted for publication, the following will briefly summarize their most important research aims, applied methods, results, methodological considerations and discussion. Then, in the last chapter, the integrated conclusions from these studies will be outlined along with an overall outlook on future research and therapeutic implications.

1. The Role of Neurobiology and Attachment in Addiction Etiology and Treatment

Background

Based on previous studies investigating links between attachment and SUD (Hiebler-Ragger et al., 2016; Unterrainer et al., 2016), we further examined behavioral and neurobiological correlates of attachment in inpatients treated for this disorder. The first study (H. Unterrainer et al., 2017), focused on differences between primary emotions, adult attachment and fiber tract integrity in SUD patients in contrast to healthy controls. The second study (Fuchshuber et al., 2018b) investigated the role of adult attachment in treatment adherence of SUD patients within a therapeutic community. The third study (Tatzer et al., Submitted) explored the role of oxytocin in SUD. Lastly, the fourth study (Unterrainer et al., 2019) predominantly focused on neurological alterations affecting patients diagnosed with poly substance use disorder (PUD).

In line with previous research (Unterrainer et al., 2016), it was expected that SUD patients would show decreased attachment security, diminished positive primary emotions, decreased existential well-being and impaired integrity of their neural fiber tracts - specifically in the superior corona radiata (SCR) and the superior longitudinal fasciculus (SLF) - reductions in gray matter (GM) volume and reductions in cortical thickness (CT). For this aim, study one (H. Unterrainer et al., 2017) compared patients treated for poly-drug use disorder with participants who either did not use illegal drugs or used them recreationally. In addition, exploratory correlations were conducted, which tried to relate psychodynamic measures with

neurobiological parameters. Moreover, study four (Unterrainer et al., 2019) compared an accumulative sample of PUD patients with healthy controls, to investigate neurological changes in SUD in more detail.

Furthermore, there is little research regarding the association between treatment adherence and adult attachment. However, the existing literature proposed a negative effect of comorbidity, age, cognitive defects and insecure attachment on treatment outcome and compliance (Bennett et al., 2011; Brorson et al., 2013; Ciechanowski et al., 2001; Fowler et al., 2013). Therefore, we expected to find a similar pattern in our study, which focused on treatment adherence within the first six months in a therapeutic community.

Finally, based on research which indicated decreased levels of oxytocin in SUD patients (McGregor and Bowen, 2012; Tops et al., 2014), we aimed at exploring differences in the influence of an attachment related stimulus on oxytocin levels in SUD patients currently undergoing maintenance treatment, in contrast to healthy control participants. In line with existing literature, we assumed that patients should exhibit decreased baseline oxytocin levels and decreased oxytocin reactivity.

Study 1.1.

The results of this study were published in the following article:

Unterrainer H. F., Hiebler-Ragger M., Koschutnig K., **Fuchshuber J.**, Tscheschner S., Url M., Wagner-Skacel J., Reininghaus E. Z., Papousek I., Weiss E., Fink A. Addiction as an attachment disorder: White matter impairment is linked to increased negative affective states in poly-drug use. *Frontiers in human neuroscience*. 2017; 11.

Methods

The total sample consisted of 59 right-handed men between the age of 18 and 35. This was comprised of patients treated for poly substance use disorder (PUD; n = 19) and two non-clinical control groups. The control groups included students who were non-smokers and did not use illegal drugs (NUC; n = 20) and students who reported a habit of nicotine abuse and used illegal drugs recreationally (RUC; n = 20). The ethics committee of the University of Graz gave approval for this study. Imaging data was acquired via a 3T Siemens Skyra (Siemens Medical Systems, Erlangen, Germany), which uses a 32-channel head coil. Overall acquisition time for the scans was 7 minutes. Behavioral measures included:

The *Adult Attachment Scale* (AAS; Collins and Read, 1990; German version: Schmidt et al., 2004), which assesses the subject's anxiety about being rejected or unloved ("Anxiety"); comfort with closeness ("Close") and comfort with depending on others ("Depend"). The German version consists of 15 items (5 items per scale), which are rated on a 5-point Likert scale ranging from 1 ("strongly disagree") to 5 ("strongly agree").

The *Multidimensional Inventory for Religious/Spiritual Well-Being (*MI-RSB; Unterrainer et al., 2010), which consists of 48 items, measuring the subscales Hope Immanent, Forgiveness and Experience of Sense and Meaning, as facets of Existential Well-Being (EWB) and Hope Transcendent, General Religiosity and Connectedness, as facets of Religious Well-Being (RWB). The items are rated on a 6-point Likert scale ranging from 1 ("strongly disagree") to 6 ("strongly agree").

The *Brief Affective Neuroscience Personality Scales* (BANPS; Barrett et al., 2013), which is the short version of the Affective Neuroscience Personality Scales (ANPS; Davis et al., 2003a) and assesses dispositions towards SEEKING, SADNESS, FEAR, ANGER, CARE and PLAY in accordance with Panksepp's (1998) model of primary emotions circuits. The questionnaire includes 33 items, rated on a 4-point Likert scale (1 "strongly disagree" to 4 "strongly agree").

The *Wonderlic Personnel Test* (WPT; Wonderlic, 1999), which assesses cognitive abilities associated with fluid intelligence. The WPT consists of 50 items measuring the ability to organize disordered sentences, build analogies, number series, make word and sentence comparisons and geometrical figures.

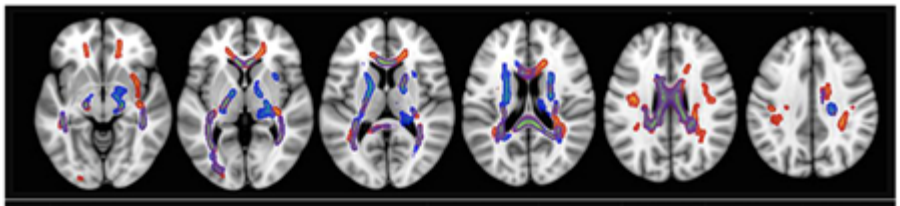
Results

Participants in the PUD group reported significantly increased levels of Anxiety compared to both control groups ($eta^2 = .21$; $p < 0.01$). Furthermore, PUD showed higher dispositions towards negative primary emotions, including ANGER ($eta^2 = .14$; $p < .05$), FEAR ($eta^2 = .15$; $p < 0.05$) and SADNESS ($eta^2 = .14$; $p < 0.05$), compared to NUC.

Regarding neurological parameters, PUD exhibited several clusters with diminished fractional anisotropy (FA) in WM tracts in both hemispheres, including the corpus callosum, superior corona radiata (SCR), superior longitudinal fasciculus (SLF), internal capsule, posterior thalamic radiation, sagittal stratum and tapetum (see Fig. 9). Furthermore, A regions

of interest (ROI) analysis was conducted, which included SLF and SCR, to further explore group differences.

PUD patients showed diminished FA in the right and left SLF (eta² = .15 and .22; both $p < 0.05$) and in the right and left SCR (eta² = .14 and .26; both $p < 0.05$) compared to both control groups. Furthermore, correlations in the PUD group between ROIs, including the right and left SCR and SLF and behavioral measures, revealed significant large (Cohen, 1992) correlations between the right SCR and Dependence ($r = .58$; $p < 0.01$), as well as between the right SCR and FEAR ($r = -.46$; $p < 0.05$).



No.	Region	Voxel	1-*p*	X (mm)	Y (mm)	Z (mm)
		PUD < NUC				
1	Corpus callosum Cerebral peduncle L Internal capsule R/L Corona radiata R/L Posterior thalamic radiation R/L Sagittal stratum R/L External capsule R Cingulum L Superior longitudinal fasciculus R/L Tapetum R/L	9885	1	1	-40	12
2	Internal capsule R	113	0.992	22	-1	16
		PUD < RUC				
1	Corpus callosum Cerebral peduncle L Internal capsule R/L Corona radiata R/L Posterior thalamic radiation R/L Sagittal stratum R/L External capsule L Cingulum L Superior fronto-occipital fasciculus L Tapetum R/L	7411	0.999	1	-38	17
2	Middle cerebellar peduncle Pontine crossing tract Corticospinal tract R/L Medial lemniscus R/L Cerebellar peduncle R/L Cerebral peduncle R/L Internal capsule R Corona radiata R External capsule R Fornix (cres) / Stria terminalis (can not be resolved with current resolution) R Superior fronto-occipital fasciculus (could be a part of anterior internal capsule) R	3893	0.998	21	0	14

Figure 9. Clusters with decreased FA in PUD compared to NUC and RUC. Only Clusters with a size more than 100 voxel are presented. FA, Fractional Anisotropy; NUC, Non-using controls; RUC, Recreational using controls; PUD, Poly-drug use disordered patients; PUD < NUC, Decreased FA in PUD in comparison to NUC (red-yellow); PUD < RUC, Decreased FA in PUD in comparison to RUC (blue-green); No., Number; Region, Included regions according to JHU ICBM-DTI-81 White-Matter Labels; R, Right; L, Left; Voxel; Number of voxel per cluster; 1-p, Statistical peak-value for each cluster; X–Y–Z (mm) = Peak-coordinates for each cluster. Significantly different clusters have been thickened with the FMRIB Software Library option "tbss_fill."; Adapted from Unterrainer et al. (2017).

Methodological Considerations

Due to the small sample size (n =19) resulting in a lack of statistical power, the results of the correlation analysis can be considered as highly explorative. Therefore, they need to be

replicated in future studies. Moreover, due to the lack of statistical power, more precise evaluations including controlling for sociodemographic parameters and total brain volume was not possible. Furthermore, substance use of the control group was not assessed with a validated measure. Hence, our results which indicated no differences between these groups should be interpreted with caution.

Study 1.2.

The results of this study were published in the following article:

Fuchshuber J., Hiebler-Ragger M., Ragger K., Rinner A., Kapfhammer H. P., Unterrainer H. F. Increased attachment security is related to early therapy drop-out in substance use disorders. BMC research notes. 2018; 11..

Methods

The investigated sample included 122 inpatients (34 female) treated for Alcohol Use Disorder (AUD; n = 66) and Poly Drug Use Disorder (PUD; n = 57) in a therapeutic community. At the beginning of their treatment, all of the participants filled out the *Attachment Style Questionnaire* (ASQ; Feeney et al., 1994; German version: Hexel, 2004), which includes 40 items, rated on a 6-point Likert scale. The ASQ assesses five dimensions of adult attachment: “Discomfort with Closeness”, “Confidence in Self and Others”, “Relationships as Secondary”, “Need for Approval” and “Preoccupations with Relationships”. Six weeks after entry, the remaining participants (n = 47) completed the ASQ for a second time.

The ethics committee of the Medical University of Graz granted approval for this study.

Results

An agglomerative cluster analysis, which included all ASQ scales and the total sample, suggested a two-cluster solution. Cluster I included patients characterized by an increased secure attachment pattern. These participants reported increased “Confidence in Self and Others” ($eta^2 = .63$; $p < 0.001$) and decreased scores in every other ASQ scale ($eta^2 = .10 – 11$; all $p < 0.001$), with the exception of “Preoccupation with Relationships” (p = n.s.). In contrast, patients assigned to Cluster II reported an increased insecure attachment pattern, characterized by lower “Confidence in Self and Others” and increased scores in every other scale of the

ASQ with the exception of "Preoccupation with Relationships". In a next step, χ^2-analysis revealed that participants in Cluster II were more likely to remain in treatment than participants in Cluster I ($\chi^2_{(1)} = 10.44$, $p < 0.001$). As shown in Table 2, a hierarchical regression analysis was conducted, to investigate the predictive value of the attachment Cluster with regards to treatment adherence: In step 1, sex was entered as a control variable (B = 0.95, Nagelkerke $R^2 = .05$, $p < 0.05$). In the second step, psychiatric comorbidity was introduced into the model (B = -1.05, Nagelkerke $R^2 = .12$, $p < 0.01$). Finally, step attachment security was entered (B = -1.10, Nagelkerke $R^2 = .18$, $p < 0.01$). Hence, attachment security increased the explained variance of treatment adherence by approximately 6%.

Table 2. *Predictors of treatment adherence after six weeks (Hierarchical Logistic Regression Modelling; n = 122).*

	Variable	B	Model χ^2	p-Value	Nagelkerke R^2
Step 1			4.69	.03	0.05
	Sex	0.95		.04	
Step 2			11.16	.01	0.12
	Sex	0.63		.19	
	Comorbidity	-1.05		.01	
Step 3			17.65	.01	0.18
	Sex	0.79		.12	
	Comorbidity	-0.70		.12	
	Attachment security	-1.10		.01	

Note. Sex: Female = 0; Male = 1; Comorbidity: No Comorbidity = 0; Comorbid Disorder = 1; Attachment security: Cluster II (insecure attachment pattern) = 0; Cluster I (more secure attachment pattern) = 1; Adapted from Fuchshuber et al. (2018b).

Methodological Considerations

Limitations of this study include the relatively small sample size as well as the use of self-report measures, which might have led to distorted results, due to deficient self-reflection abilities in our sample. Moreover, the study only investigated the first six weeks of treatment. Therefore, future research should aim at investigating longer treatment periods and might benefit from the application of semi-standardized interviews to strengthen the validity of these results.

Study 1.3.

The results of this study will be published in the following article:

Tatzer J., Hiebler-Ragger M., **Fuchshuber J.,** Trinkl F., Kimmerle A., Buchheim A., Schrom S., Rinner A., Leber B., Pieber T., Weiss E., Kapfhammer H.P. & Unterrainer H.F. Decreased attachment-related oxytocin reactivity in poly-drug users undergoing maintenance therapy compared to healthy controls (Submitted)

Methods

This study investigated a total sample of 49 men, including 24 patients treated in a therapeutic community for poly-drug use disorder (PUD) at the time of the study, and 25 healthy control participants (HC). In order to investigate changes in oxytocin after the presentation of an attachment related stimulus, participants were asked to complete the Adult Attachment Projective Picture System (AAP; George and West, 2001). Oxytocin levels were measured before and after the presentation of the AAP. Furthermore, this study applied:

The *Alcohol, Smoking and Substance Involvement Screening Test* (ASSIST; Humeniuk et al., 2008), is a standardized interview that is used to assess psychoactive substance use and related problems. This questionnaire measures lifetime use and substance related symptoms of 10 substance groups including tobacco, alcohol, cannabis, cocaine, amphetamines, inhalants, sedatives, hallucinogens, opioids and "other drugs." Questions 2-5 are rated on a 7-point Likert scale ranging from 0 ("never") to 6 ("daily or almost daily"). These scales assess the "Frequency of drug use," "Craving to use the drug," "Problems" (health, social, legal or financial) because of drug use and "Failed expectations." Moreover, questions 6, 7 and 8 are rated on a 4-point scale (0 = "no, never"; 3 = "yes, but not in the past 3 months"; 6 = "yes, in the past 3 months") and cover "Expressed concerns by relatives or friends," "Failed attempts to cut down drug use" and "Drug injection." For this study a total score (global continuum of substance risk) and total scores for the specific substance classes were calculated.

The German version of the *Adult Attachment Scale* (AAS; Collins and Read, 1990; German version: Schmidt et al., 2004) (described in detail above).

The *Brief Symptom Inventory* (BSI-18; Derogatis, 2001; German version: Spitzer et al., 2011). The BSI-18, is comprised of 18 items which measure the amount of symptom burden in the last seven days with regards to depression, anxiety and somatization. Items are rated on a

5-point Likert scale ranging from 0 “absolutely not” to 4 “very strong”. The total score “Global Severity Index” can be generated by adding the scores of every item.

The German version of the *Affective Neuroscience Personality Scales* (ANPS; Davis et al., 2003a; Germen version by: Reuter et al., 2017). The ANPS is a self-report measure which assesses behavioral traits associated with Panksepp’s (1998) concept of primary emotion circuits. It consists of 110 items rated on a 4-point Likert scale ranging from 1 (“strongly disagree”) to 4 (“strongly agree”). The scales of the ANPS include “SEEKING”, “SADNESS”, “FEAR”, “ANGER”, “CARE” and “PLAY” as well as an additional scale for spirituality.

The *Operationalized Psychodynamic Diagnostics Structure Questionnaire* (OPD-SQS; Ehrenthal et al., 2015). The OPD-SQS is a self-report measurement, which assesses deficits in personality structure as proposed in the Operationalized Psychodynamic Diagnostic (OPD Task Force, 2008). This measure is comprised of 12 items which are rated on a 5-point Likert scale ranging from 0 (“strongly disagree”) to 4 (“strongly agree”) and includes the subscales: (a) *Self*, which measures deficits in identity cohesion, self-reflection, affect differentiation and affect tolerance, (b) *Relationship*, assessing deficits with regards to internalization, self-object differentiation and realistic object perception and (c) *Contact*, assessing deficits in regulation of self-esteem, anticipation and affect communication. The total score indicates deficits in overall personality structure.

Oxytocin was measured via blood samples which were taken from antecubital veins into 3 ml vacutainer blood vacuettes (Greiner Bio-One International GmbH, Austria) containing Aprotinin (500 KIU/ml of blood) (Sigma-Aldrich, Germany). Levels of oxytocin were assessed at the Center for Medical Research at the Medical University Graz by authorized personnel via the Oxytocin ELISA kit (ADI-900-153A, Enzo Life Sciences, USA), a colorimetric competitive enzyme immunoassay kit.

The study was approved by the ethics committee of the Karl-Franzens University of Graz.

Results

Table 3. *Group differences (ANOVA) in behavioral and biological measures.*

		PUD (n = 24)		HC (n = 24)				
Measures	α	M	SD	M	SD	$F_{(2, 45)}$	η^2	p
BSI-18								
	0.690	2.17	2.73	2.13	2.35	0.00	0.00	0.955
Somatisation								
Depression	0.852	6.25	5.57	2.71	2.33	8.27*	0.15	0.006
Anxiety	0.816	4.54	5.01	3.46	2.41	0.91	0.02	0.344
GSI	0.869	12.96	11.14	8.71	5.39	2.83	0.06	0.099
Oxytocin								
Pre		60.64	24.87	44.74	15.68	7.02*	0.13	0.011
Post		60.38	17.25	60.46	38.73	0.00	0.00	0.992
Reactivity		10.92	13.51	28.04	31.80	5.90*	0.11	0.019
AAS								
	0.731	16.13	4.89	18.42	3.31	3.61	0.07	0.064
Dependence								
Closeness	0.786	11.63	3.93	13.92	4.03	3.97	0.08	0.052
Anxiety	0.678	12.29	3.91	12.29	3.75	0.00	0.00	1.000
OPD-SQS								
Total Score	0.752	22.25	7.74	19.21	7.27	1.97	0.04	0.167
ANPS								
SEEKING	0.782	30.42	5.12	28.25	5.09	2.16	0.05	0.149
CARE	0.616	30.21	5.56	30.58	4.09	0.07	0.00	0.791
PLAY	0.788	29.17	6.99	27.71	5.03	0.69	0.02	0.411
FEAR	0.825	34.25	6.52	34.71	5.26	0.07	0.00	0.790
ANGER	0.740	31.96	5.43	35.67	5.09	5.97	0.12	0.018
SADNESS	0.749	35.38	6.25	37.00	5.41	0.93	0.02	0.341

Notes. *p < 0.05; PUD = Poly-drug use disordered patients, HC = Healthy controls, Pre = Baseline OT-levels, Post = OT-levels after confrontation with attachment related cue, BSI = Brief Symptom Inventory, GSI = Global Severity Index, AAS = Adult Attachment Scales, OPD-SQS = Operationalized Psychodynamic Diagnostics Structure Questionnaire, ANPS = Affective Neuroscience Personality Scales; Adapted from Tatzer et al. (Submitted).

As shown in Table 3, results indicate that PUD, despite, showing higher baseline oxytocin levels (eta² = .14; p < 0.01), exhibited less oxytocin reactivity than HC after confrontation with an attachment related stimulus (eta² = .10; p < 0.05). Furthermore, PUD reported diminished structural ability for relationship (eta² = .18; p < 0.01) and less ANGER (eta² = .09; p < 0.05).

Regarding correlations between neurophysiological and behavioral measures in both groups, results indicated that oxytocin baseline levels was correlated with the AAS scales Closeness (r = -0.33, p < 0.05) and Anxiety about being unloved (r = -0.30, p < 0.05). Moreover, oxytocin reactivity was significantly correlated with Lifetime substance use (*r* = -0.36, p < 0.05), Global continuum of substance risk (*r* = -0.37, *p* < 0.05), Dependence (*r* = -.32, p < 0.05), Abuse (*r* = -.34, p < 0.05) and diminished SEEKING (r = -.31, p < 0.05;).

Furthermore, correlations which investigated both groups separately showed a similar pattern. However, due to a smaller sample size in PUD only the correlation between oxytocin reactivity and anxiety about being unloved ($r = -.55$, $p < 0.05$) remained significant. Moreover, in HC oxytocin reactivity was correlated with Depression ($r = .41$, $p < 0.05$).

Methodological Considerations

Besides a rather small sample size, the interpretation of the results of this study are limited by the use of self-assessment questionnaires and the exclusion of female participants. Furthermore, oxytocin baseline levels might have been influenced by differences in pre-study conditions. For example, PUD participants did not abstain from nicotine and caffeine prior to blood sampling. Moreover, the very close social environment of the therapeutic community might have contributed to higher baseline oxytocin levels found in the clinical group (Insel, 2010). Finally, future research should also include abstinent patients in order to investigate the influence of maintenance treatment on oxytocin.

Study 1.4.

The results of this study will be published in the following article:

Unterrainer H. F., Hiebler-Ragger M., Koschutnig K., **Fuchshuber J.**, Ragger K., Perchtold, C., Papousek I., Weiss E., Fink A. Brain Structure Alterations in Poly-drug Use: Reduced Cortical Thickness and White Matter Impairments in Regions Associated with Affective, Cognitive and Motor Functions. *Frontiers in Psychiatry.* 2019; 10.

Methods

The investigated sample comprised 153 right handed men, aged between 18 and 41 years. The overall sample consisted of two subgroups, including one clinical group (PUD; n = 78; M = 28.71; *SD* = 5.15) diagnosed for PUD (F19.2), and one non-clinical control group (CG; n = 75; M = 25.28; *SD* = 3.37) comprised of university students. This study integrated data from three previous studies (Hiebler-Ragger et al., Submitted; Unterrainer et al., 2016; H. Unterrainer et al., 2017). At the time of data acquisition the PUD patients were undergoing inpatient SUD treatment within a therapeutic community for a mean time of 25 weeks (SD = 18.46). Participants' consent was obtained according to the Declaration of Helsinki. The study was approved by the ethics committee of the Karl-Franzens University Graz. Imaging data was acquired via a 3T Siemens Skyra (Siemens Medical Systems, Erlangen, Germany), which

uses a 32-channel head coil. In the course of this study, the following behavioral measures were analyzed:

The *Wonderlic Personnel Test* (WPT; Wonderlic, 1999) (described in more detail above).

The *Brief Symptom Inventory* (BSI-18; Derogatis, 2001; German version: Spitzer et al., 2011) (described in more detail above).

The following magnet resonance imaging (MRI) data processing techniques were applied:

Diffusion and tract quantification: Data pre-processing was performed using the software package MRtrix (Tournier et al., 2012) and FSL (Smith et al., 2004). Whole-brain tractography data were imported into the AFQ software package (Yeatman et al., 2012) running on MATLAB, which identifies 20 major fiber tracts, including the right and left thalamic radiations, forceps major and minor of corpus callosum, right and left inferior fronto-occipital, inferior longitudinal, arcuate and uncinate fasciculi, corticospinal tract and cingulum. The mean FA in each node was calculated and group differences were analyzed for each node within each pathway. The family wise error corrected alpha value for pointwise comparison was computed for each tract to correct for multiple comparisons. As a result, p-values below a threshold of <.0025 (.05/20 tracts) were considered significant.

Voxel-based morphometry: Structural scans were analyzed using the Computational Anatomy Toolbox (CAT12; r 1274) implemented in SPM12, running under Matlab 2017 to asses voxel-wise comparisons of grey matter volume (GMV) differences.

Cortical thickness: The CAT12 toolbox was again used to extract cortical thickness. This fully automated method uses tissue segmentation as already done in the VBM Analysis and uses a projection-based algorithm to compute CT (Dahnke et al., 2013). Age and TIV (only for VBM) were included in the statistical model as regressors of no interest. Results were considered statistically significant with $p < .05$ corrected for family-wise error.

Table 4. *Group differences (ANOVAs) in demographics and behavioral measures.*

		CG (*n*=75)		PUD (*n*=78)			
Measure	*α*	*M*	*SD*	*M*	*SD*	$F_{(1,34)}$	η^2
Age	-	25.28	3.37	28.71	5.15	23.48**	.14
Education (years)	-	13.92	2.82	11.51	2.58	30.39**	.17
Treatment (weeks)	-	-	-	24.88	18.46	-	-
WPT	-	28.95	6.02	17.51	7.16	113.89**	.43
BSI							
GSI	.88	10.32	7.66	15.47	11.01	11.22**	.07
Anxiety	.73	4.67	3.56	5.85	3.92	3.79	.02
Depression	.78	3.45	3.67	6.08	4.67	15.79**	.10
Somatization	.72	2.22	2.77	3.55	3.94	5.79*	.04

Notes. * p<.05, ** p<.01, CG = Control group, PUD = Polydrug users, BSI = Brief Symptom Inventory, GSI = Global Severity Index, WPT = Wonderlic Personnel Test; Adapted from Unterrainer et al. (2019).

Results

Behavioral and descriptive results

As shown in Table 4, PUD patients were older than CG participants ($p <. 001$; $\eta^2 = .14$), and reported significantly fewer years of education ($p < .001$; $\eta^2 = .17$). Furthermore, PUD reported a higher amount of Depressiveness ($p < 0.01$; $\eta^2 = .10$), Somatization ($p < 0.05$; $\eta^2 = .04$) and a higher score for the total Global Severity Index in the BSI-18 ($p < 0.01$; $\eta^2 = .07$). Moreover, the analysis revealed higher cognitive abilities in the control group ($p < 0.01$; $\eta^2 = .43$)

Differences in white matter, gray matter, and cortical thickness between PUD and controls

White matter fiber tracts

PUD patients exhibited significant reductions in fractional anisotropy (FA) compared to controls across the entire left and the majority of nodes of the right corticospinal tract. Moreover, significant FA reductions in posterior portions of the bilateral inferior longitudinal fasciculi and in smaller portions of the left thalamic radiation, the right inferior fronto-occipital fasciculus and the right arcuate fasciculus were observed (see Fig. 10).

Grey matter volume

No significant differences in GMV were observed.

As shown in Fig. 11, compared to controls PUD showed significant reductions of CT in the left insular and the left lateral orbitofrontal cortex. Moreover, there were significant CT bilateral reductions in the orbitofrontal cortex. Furthermore, areas with reduced CT included the right and left inferior frontal gyri (pars opercularis) and the right and left precentral gyri. What is more, analyses revealed CT reductions in a cluster involving the left postcentral gyrus and small portions of the supramarginal gyrus in addition to a cluster in the right inferior temporal lobe.

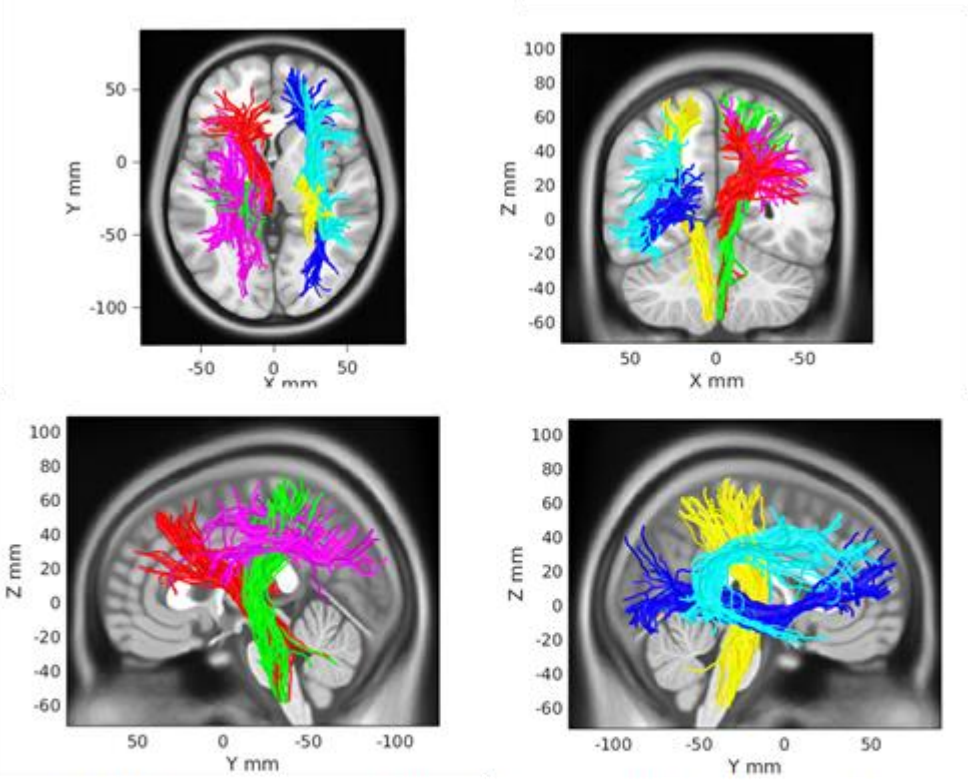


Figure 10. 3D-visualization (first row: axial, coronal view; second row: sagittal view) of the relevant fiber tracts. Left thalamic radiation = red; Left corticospinal tract = green; Right corticospinal tract = yellow; Right inferior fronto-occipital fasciculus IFOF = blue; Left SLF = violet; Right arcuate fasciculus = cyan; Adapted from Unterrainer et al. (2019).

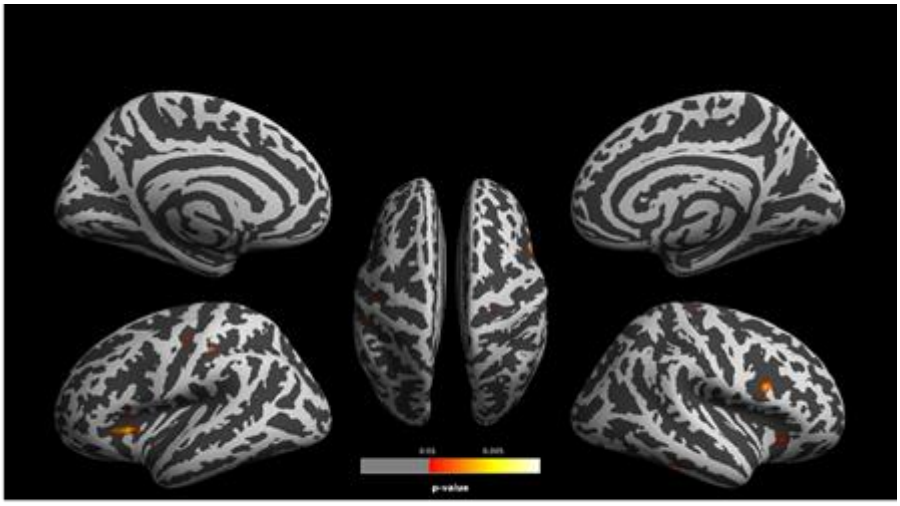


Figure 11. Brain regions with significant (red-yellow) group differences in cortical thickness between polydrug dependents and controls; Adapted from Unterrainer et al. (2019).

Methodological Considerations

As this study integrated the sample of Unterrainer et al. (2017) within its analysis, both studies must not be seen as independent evidence of neurological differences characteristic of PUD. Furthermore, due to the cross-sectional design of this study, our results do not allow for causal interpretation.

Discussion

In summary, the results of three studies reviewed above (Fuchshuber et al., 2018b; Tatzer et al., Submitted; H. Unterrainer et al., 2017), highlight the importance of attachment in the etiology and treatment of SUDs (Burkett and Young, 2012; Flores, 2004; Schindler and Bröning, 2015). Furthermore, our findings indicate that this is not only reflected on a behavioral but also on a neurophysiological level (Tatzer et al., Submitted; H. Unterrainer et al., 2017). Moreover, study four (Unterrainer et al., 2019) was able to underline the severe association between SUDs and impairments regarding neurological structures previously associated with affective and behavioral control (Ersche et al., 2013; Jacobus et al., 2013; Daniels et al., 2013).

In correspondence to this, our findings largely confirm previous research indicating substantial impairments of WM fiber tracts and CT in PUD patients (Arnone et al., 2006; Ersche et al., 2013). However, we did not observe significant differences in GMV, which is in clear contrast to previous findings (Ersche et al., 2012; Tanabe et al., 2009). This surprising result might be related to the relatively young age of PUD participants (Unterrainer et al., 2019). Comparable studies that did find GMV deficits in heroin dependents like Qiu et al. (2013), investigated considerably older participants (M = 35 years, SD = 4.2). Therefore, it might be possible that GMV impairments in SUD take more time to manifest in individuals than structural deficits in WM and CT. However, the interpretation of this finding should be regarded as preliminary and speculative. Hence, future research should aim at further investigating the age dependent effect of GMV deterioration in SUD patients.

Furthermore, possibly due to the relatively small sample sizes in our studies, some of our findings regarding the relationship between attachment and SUD seem relatively inconsistent. While Unterrainer et al. (2017) found increased “Anxiety of being Unloved or Rejected” in SUD patients, Tatzer et al. (submitted) was not able to replicate this finding but found increased structural deficiencies regarding relationships in the clinical group. However, with regard to the small sample sizes and the direction of the statistically insignificant tendencies found in this sample, the findings of both studies might be interpreted as an overall pattern indicating deficits in attachment security as a characteristic of addiction disorders. In correspondence to this, poly drug use disorder might be linked to rather general insecure

attachment attitudes, in contrast to a more specific attachment style, which is in line with recent reviews concerned with this topic (Schindler and Bröning, 2015; Schindler, 2014).

With regard to the role of attachment in SUD treatment adherence, our study revealed rather surprising results indicating that self-reported secure attachment attitude is related to early therapy drop-out. Due to the application of self-report measures in this study, these findings might be explained by diminished self-reflection abilities in the investigated SUD patients (Savov and Atanassov, 2012). The plausibility of this assumption is further underlined if it is taken into consideration that both treatment drop-out and higher attachment security was significantly linked to increased comorbidity. Hence it seems likely that our findings might reflect idealized self and object representations (Fuchshuber et al., 2018b). In turn, this might be linked to results indicating increased borderline personality organization in SUD patients (Hiebler-Ragger et al., 2016). This assumption might also provide an explanation for the decreased "Confidence in Self and Others" after six weeks of treatments within the therapeutic community, as the high amount of group cohesion and the associated confrontation with reality might have led to increasingly more realistic images of self and others (Fuchshuber et al., 2018b). However, the confronting approach of therapeutic communities might also foster intense cognitive dissonance in subjects with unrealistic self and object representations and thus promote early therapy drop-out. Therefore, these results highlight the importance and complexity of considering adult attachment in an inpatient addiction treatment setting.

Furthermore, study one (H. Unterrainer et al., 2017) and three (Tatzer et al., Submitted) explored possible links between attachment, primary emotions and neurophysiology. The findings indicate links between increased negative affectivity, increased insecure attachment and impaired structural integrity of white matter fiber tracts in the right SCR. This might be interpreted as an indication of a common neurological ground for both attachment and affect regulation, which is involved in SUD etiology (Schore, 2015). With regards to associations between self-reported attachment attitude, primary emotions and oxytocin, results are less clear. Our results indicate that only SEEKING is negatively correlated with oxytocin reactivity, while both "Comfort with Closeness" and "Anxiety of being Rejected or Unloved" showed negative relationships with baseline oxytocin. Considering the blunted oxytocin reactivity found in SUD patients, the relationship between

SEEKING and oxytocin reactivity might be interpreted in line with AN-theory (Zellner et al., 2011), which frames many SUDs as a compensative strategy against a hypoactive SEEKING system. However, neither Unterrainer et al. (2017), nor Tatzer et al. (submitted) were able to show any significant role for self-reported SEEKING in SUDs. These findings might be linked to the fact that PUD participants were undergoing treatment in a therapeutic community setting. The stimulating environment associated with this form of treatment might have increased SEEKING activity in the inpatients group (De Leon, 2000). Future research should aim at investigating larger samples, including participants not undergoing a current treatment, to explore this relationship in more detail.

Similarly, the relationship between adult attachment "Comfort with Closeness" and "Anxiety of being Rejected or Unloved" with baseline oxytocin might need further research to strengthen the validity of our results. A possible explanation for these seemingly contradictory results might be linked to the effects of maintenance treatment, as recent research suggests reduced self-reported attachment anxiety and comfort with closeness as a result of methadone administration (Torres et al., 2019). Nevertheless, these findings contribute to the mapping of the endocrinological and neurological substrate of adult attachment and SUD, which might open up new pharmacological treatment options (McGregor and Bowen, 2012; Strathearn et al., 2009).

2. The Relationship Between Childhood Trauma, Personality, Primary Emotions and Adulthood Psychopathology

Background

In correspondence to previous research linking addiction to deficits in personality organization and primary emotional functioning (Hiebler-Ragger et al., 2016; Unterrainer et al., 2016; H. Unterrainer et al., 2017), we aimed at deepening the understanding of this relationship by investigating the impact of childhood trauma and applying path analytical and structural equation modelling techniques in extensive samples. For this purpose, the first study (Fuchshuber et al., 2018a), which tested assumptions proposed by Zellner et al. (2011) and Solms et al. (2015), focused on investigating the role of childhood trauma, despair and personality organization in the development of SUD and depressive symptoms. For this aim, structural equation modelling technique was applied. By using path analysis, the second study

(Fuchshuber et al., 2019a), which was based on an extended sample of Fuchshuber et al. (2018a), examined the role of childhood trauma, adult attachment and personality organization on overall primary emotion functioning in more detail. Finally, study three (Fuchshuber et al., 2019b) conducted a secondary analysis of the sample described in study two (Fuchshuber et al., 2019a), but focused on the relationship between gender, primary emotions and symptoms of SUD and mood pathology.

Based on research outlined above (Solms et al., 2015; Zellner et al., 2011), we aimed at exploring the common neuropsychodynamic structure of SUD and depressive symptoms. Both disorders, which are two of the most frequently observed psychiatric disorders (Kessler et al., 2005) are known to be considerably correlated (Grant et al., 2015; Grant et al., 2016). As extensively described in the first chapter of this thesis, AN-theory proposes a common primary affective core for both disorders, which is characterized by dysregulations within the SEEKING and SADNESS or PANIC/GRIEF system (Solms et al., 2015; Zellner et al., 2011). In correspondence to this, patients suffering from SUD and patients suffering from depression were expected to report increased SADNESS scores and decreased SEEKING scores. Therefore, the investigated model included the latent variable "despair", which was composed of low SEEKING and high SADNESS. Furthermore, based on previous research (Kernberg, 1993; Hiebler-Ragger et al., 2016; Unterrainer et al., 2016), we expected significant associations between both disorders and impairments in personality organization. Moreover, with regard to a long line of research linking childhood trauma to impaired personality structure, increased negative affect and adult psychopathology (Charcot, 1879; Freud, 1906; Fonagy, 2010; Heim and Nemeroff, 2001; van Nierop et al., 2015; Janet, 1889), we assumed a mediating role for despair and personality organization in the relationship between childhood trauma, SUD and depressive symptoms.

Building upon insights gained in the previous research (Bowlby, 1969; Fuchshuber et al., 2018a; Schore, 2015; H. Unterrainer et al., 2017), the second study (Fuchshuber et al., 2019a) focused on mapping the relationship between childhood trauma, adult attachment, personality organization and primary emotion functioning in more detail. In correspondence to this, we expected the influence of childhood trauma on emotional functioning to be mediated by adult attachment and personality organization, as recent psychodynamic literature assumes

these concepts to be influenced by early childhood relationships and, in turn, associated with affect regulation in adults (Kernberg, 2015; Schore, 2015).

In a second step, we further explored assumptions proposed by Kernberg (1985, 1993). Kernberg assumes a predominance of primitive defense mechanisms, including splitting denial, projection and dissociation - which result from abusive childhood relationships - as core mechanisms of emotional instability or borderline personality organization. Therefore, we tested if primitive defense mechanisms might act as a mediator between childhood trauma and adult attachment, as a predominance of this dysfunctional coping strategy might prevent traumatized individuals from forming stable relationships. In turn, this might contribute to the development of an insecure attachment pattern linked to affect dysregulation.

Furthermore, predominantly based on animal models, AN-theory proposes dysregulations in subcortical affective systems as an important factor in the etiology of a variety of psychiatric disorders (Panksepp, 2004; Panksepp and Biven, 2012). However, studies testing these hypotheses in human subjects have been sparse. To further investigate these claims within a quantitative-empirical framework, study three (Fuchshuber et al., 2019b) examined the relationship between psychopathological symptoms (SUD, depression, anxiety disorder and somatization) and different dimensions of primary emotions (SEEKING, FEAR, ANGER, SADNESS, PLAY and CARE). Furthermore, by applying multi-group path analysis, this study tested the possible moderator effects of gender and psychiatric lifetime diagnosis.

Study 2.1.

The results of this study were published in the following article:

Fuchshuber J., Hiebler-Ragger M., Kresse A., Kapfhammer H. P., Unterrainer H. F. Depressive symptoms and addictive behaviors in young adults after childhood trauma: the mediating role of personality organization and despair. Frontiers in Psychiatry. 2018;9.

Methods

This study investigated a sample of young adults aged between 18 and 39 years (M = 26 years; SD = 5.51), which included 500 (63.2% female) German-speaking participants. The recruitment took place via advertising on social networks like Facebook, public forums and public announcement at the Karl-Franzens University of Graz and Medical University of Graz. The study was approved by the ethics committee of the Medical University of Graz. Data

acquisition took place via the online-platform LimeSurvey. Participants were included based on the age criteria for young adults as outlined by Erikson (1993), if they graduated high school, stated no recent psychotic episode and filled out all questionnaires. 37.4% of the investigated participants reported a lifetime diagnosis with a psychiatric disorder. A majority of these participants declared a diagnosis with depression (n = 129; 69%) and 9% reported a diagnosed form of SUD.

As proposed by Kline (2015), the goodness of fit for the structural equation model was assessed by the following fit-indices: (a) The comparative fit index (*CFI*) > 0.90; (b) Tucker-Lewis index (*TLI*) relative fit index > 0.90; (c) the square root error of approximation (*RMSEA*) < 0.08 and the upper bound of its 90% confidence interval < 1. For the comparison of competing models, the Akaike information criterion (AIC) was used, with smaller values indicating statistical superiority. In accordance with Cheung and Lau (2008), indirect effects were estimated by a bootstrap analysis with a bias-corrected confidence interval of 95% and 1000 bootstrap samples. AMOS 18.0 was used to estimate the paths and fit indices of the measurement model and structural equation model.

In the course of this study, participants filled out the following questionnaires, which were analyzed accordingly:

The German version of the *Affective Neuroscience Personality Scales* (ANPS; Davis et al., 2003b; German version by Reuter and Hennig (2014; see Montag et al., 2017 for a more recent version)) (described in more detail above).

The *16-Item Inventory of Personality Organization* (IPO-16; Zimmermann et al., 2013). The IPO-16 is a self-assessment questionnaire which measures deficits in personality organization as outlined by Kernberg (1993). The questionnaire includes the three subscales (a) “Identity Diffusion”, assessing deficits in the ability to integrate representations of oneself and others; (b) dominance of the “Primitive Defense”, including splitting, denial, projection and dissociation and (c) “Reality Testing”, which assesses deficits to differentiate between internal and external stimuli. Items are rated based on a 5-point Likert scale ranging from 1 (“never”) to 5 (“always”).

The *Childhood Trauma Questionnaire* (CTQ; Bernstein et al., 1997; German version by Wingenfeld et al., 2010), which is a self-report questionnaire that assesses the amount of traumatizing childhood experiences. The CTQ consists of 28 items and includes the subscales

“Emotional Abuse”, “Physical Abuse”, “Sexual Abuse” and “Emotional Neglect”. Due to poor reliability in previous studies (Kilpatrick et al., 2000), the subscale “Physical Neglect” was not analyzed in this study.

Depressive symptoms were assessed by the “Depression” subscale of the *Brief Symptom Inventory* (BSI-18; Derogatis, 2001; German version: Spitzer et al., 2011) (described in more detail above). The Depression subscale measures the amount of depressive symptom burden based on six items, which assess suicidal thoughts, hopelessness, feelings of worthlessness, melancholy, loneliness and apathy.

The *Alcohol, Smoking and Substance Involvement Screening Test* (ASSIST; Humeniuk et al., 2008) (described in more detail above). For the purpose of this study, the ASSIST was adapted as a self-report measure. Furthermore, due to the severe non-normality of all investigated subscales, logarithmic transformations were performed (Kline, 2015). The investigated scales included total scores on substance related “Frequency,” “Craving,” “Problems,” “Failed expectations,” “Concerns,” and “Failed attempts to cut down use”.

Results

Measurement Model

In order to test our hypotheses, a measurement model was constructed, which included the latent variables “Addictive Behaviors”, “Depressive Symptoms”, “Childhood Trauma”, “Despair” and “Structural Deficit” and the single indicator “sex”. The latent variable Addictive Behavior was comprised of: Frequency ($\beta = 0.78$), Craving ($\beta = 0.83$), Problems ($\beta = 0.72$), Failed Expectations ($\beta = 0.60$), Concerns ($\beta = 0.76$) and Failed Attempts (to cut down use) ($\beta = 0.75$). The latent variable Depressive Symptoms included: Suicidal Thoughts ($\beta = 0.69$), Hopelessness ($\beta = 0.87$), (Feeling of) Worthlessness ($\beta = 0.87$), Melancholy ($\beta = 0.77$), Loneliness ($\beta = 0.81$) and Apathy ($\beta = 0.70$). Moreover, Childhood Trauma was comprised of: Emotional Abuse ($\beta = 0.94$), Physical Abuse ($\beta = 0.66$), Sexual Abuse ($\beta = 0.47$) and Emotional Neglect ($\beta = 0.77$). Structural Deficit included: Identity Diffusion ($\beta = 0.68$), Primitive Defense ($\beta = 0.86$) and Reality Testing ($\beta = 0.63$). Finally, Despair consisted of the following indicators: SADNESS ($\beta = 0.81$) and SEEKING ($\beta = -0.37$). Every assigned indicator loaded significantly onto its latent variable ($p < 0.001$). Further analysis revealed a good model fit for the specified measurement model: RMSEA = 0.06 (90% CI: 0.06, 0.07); TLI = 0.92; CFI = 0.93; AIC = 728.180.

Correlations among latent variables revealed significant correlations between every investigated factor ($p < 0.001$), which were in line with previous assumptions (see Table 5). Furthermore, female sex was negatively correlated with Addictive Behaviors ($r = -0.25$; $p < 0.001$) and marginally correlated with Despair ($r = 0.16$; $p < 0.01$).

Table 5. *Correlations among latent variables and sex for the measurement model*.

Variable	1	2	3	4	5	6
1. Addictive Behaviors	-					
2. Depressive Symptoms	.39**	-				
3. Despair	.33**	.90**	-			
4. Structural Deficit	.56**	.64**	.71**	-		
5. Childhood Trauma	.29**	.52**	.51**	.46**	-	
6. Sex	-.25**	.02	.16*	.01	.12	-

Note. $n = 500$; * $p < .01$; ** $p < .001$; Sex: female = 1; male = 0; Adapted from Fuchshuber et al (2018).

Structural Equation Modelling

The initial standardized solution for the structural equation modelling (see Fig. 12) exhibited a good model fit: RMSEA = 0.06 (90% CI: 0.06, 0.07); TLI = 0.92; CFI = 0.93; AIC = 737.575. In this model, Addictive Behaviors is significantly associated with

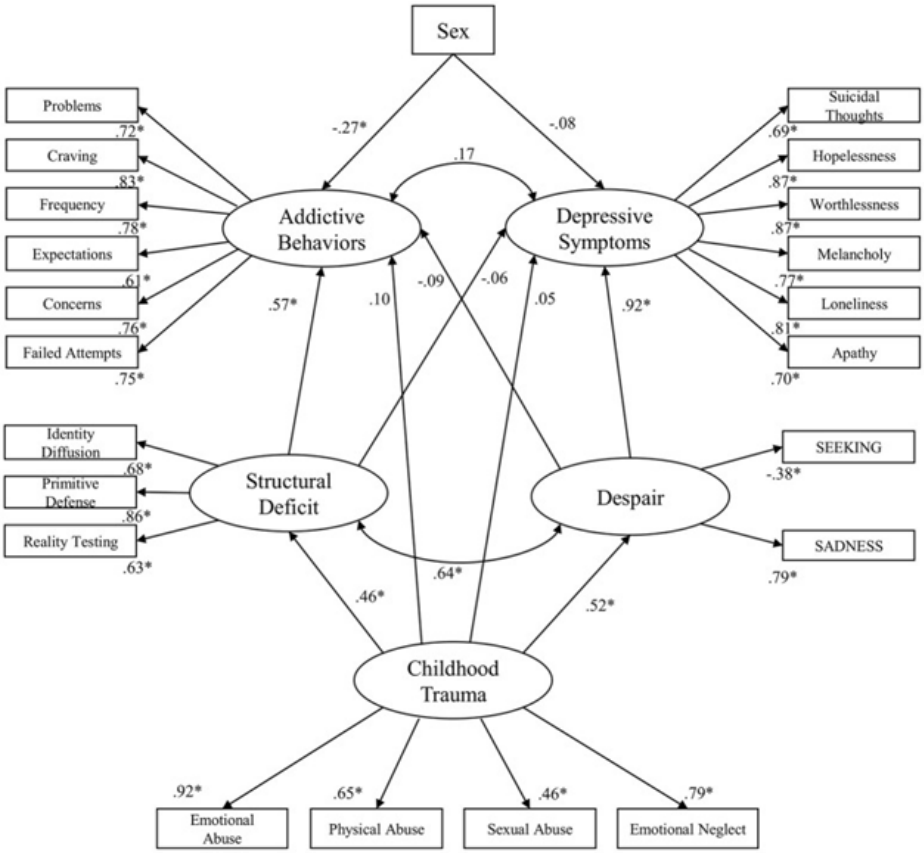


Figure 12. Initial standardized solution for the structural equation model; *p < 0.001; Sex: Female = 1; Male = 0.; Adapted from Fuchshuber et al. (2018).

Structural Deficit (β = 0.57; p < 0.001) and sex (β = -0.27; p < 0.001), while Despair significantly predicted Depressive Symptoms (β = 0.92; p < 0.001). Furthermore, Childhood Trauma did not show significant direct effects on both psychiatric variables but was associated with Structural Deficit (β = 0.46; p < 0.001) and Despair (β = 0.52; p < 0.001). Bootstrap analysis showed significant indirect effects of Childhood Trauma on Addictive Behaviors via Structural Deficit (β = 0.22; p < 0.01) and on Depressive Behaviors via Depressive Symptoms (β = 0.44; p < 0.01).

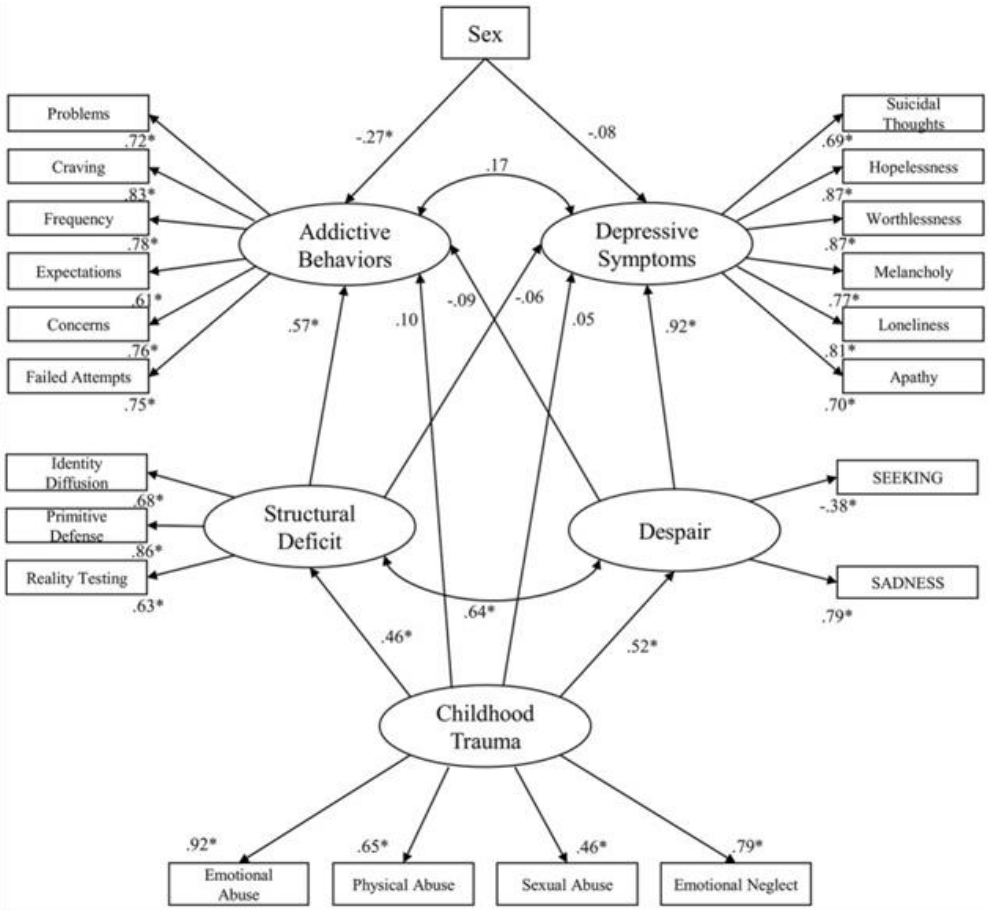


Figure 13. Final standardized solution for the structural equation model; *p < 0.001; Sex: Female = 1; Male = 0; Adapted from Fuchshuber et al. (2018).

The final model (see Fig. 13) was constructed by the use of a pruning strategy that removed non-significant paths from the initial model. The final model showed good fit: RMSEA = 0.06 (90% CI: 0.06, 0.07); TLI = 0.92; CFI = 0.93; AIC = 734.855. Compared to the initial model, the final model revealed a smaller AIC with approximately Δ3 (737.575 compared to 734.855), indicating a higher parsimony and therefore better fit for the empirical data.

Methodological Considerations

As Despair and Depressive Symptoms showed a remarkably high correlation (r = 0.90), we tested an alternative model which included an overarching latent variable termed

"Depression" that was comprised of both Despair and Depressive Symptoms. However, a comparison between AIC scores revealed that the alternative model showed a higher AIC with approximately Δ12 (740.041 compared to 728.180), indicating statistical superiority of the initial model. Furthermore, in order to test hypotheses proposed by Zellner et al. (2011) and Solms et al. (2015) this study only included Despair (low SEEKING, high SADNESS) in its investigated model and did not explore the clinical relevance of other primary emotions. In line with previous research indicating additional associations between SUD and ANGER and FEAR (H. Unterrainer et al., 2017) and between depressive symptoms and FEAR (Montag et al., 2017), future research should apply a more explorative strategy to investigate the role of primary emotions in both disorders by including all ANPS subscales. Finally, the analyzed community sample included a relatively high proportion (37.4%) of participants who reported a psychiatric lifetime diagnosis. In line with the assumption of a continuum between mental health and mental disorder (Montag et al., 2017), participants were not analyzed separately. However, in this study psychiatric symptom burden was assessed by self-report measures, which are vulnerable to distorted self-reflection. Furthermore, a question asked the participants to report if they have ever been diagnosed with a psychiatric disorder by a licensed psychiatrist and a follow up question assessed the specific diagnosis, which limits the descriptive value of our data regarding psychiatric diagnoses. Therefore, future research should aim at assessing psychiatric diagnoses in more detail by applying standardized interviews. Finally, due to the cross-sectional design of this study the results of the structural equation models are associative in nature and do not allow for causal interpretation.

Study 2.2.

The results of this study will be published in the following article:

Fuchshuber J., Hiebler-Ragger M., Kresse A., Kapfhammer H.P. & Unterrainer H.F. The influence of attachment styles and personality organization on emotional functioning after childhood trauma. *Frontiers in Psychiatry.* 2019; 10.

Methods

For this study, a community sample of 616 adults (61.9% female) was investigated. The mean age of participants was M = 30 (SD = 9.53) and ranged between 18 and 69 years. 39.4% of the participants reported a psychiatric lifetime diagnosis. A majority (60%) of these

participants were diagnosed with depression. The sample was recruited via public announcements. Data gathering was carried out with the online survey platform LimeSurvey. The ethics committee of the Medical University of Graz granted approval for this study.

In line with Kline (2015), the following fit indices were considered as markers for an acceptable model fit: (1) The comparative fit index (CFI) > 0.90; (2) Tucker-Lewis index (TLI) relative fit index > 0.90; (3) the square root error of approximation (RMSEA) < 0.08 and the upper bound of its 90% confidence interval < 1. The Bayesian information criterion (*BIC*) was used to compare competing models, thereby a smaller value indicates a more parsimonious model and therefore a better fit. In line with Cheung and Lau (2008), indirect effects were assessed by a bootstrap analysis with a bias-corrected confidence interval of 95% and 1000 bootstrap samples. AMOS 18.0 was used to estimate paths and fit indices of the path analytic models.

In this study, all participants filled out the following questionnaires:

The *Adult Attachment Scale* (AAS; Collins and Read, 1990; German version: Schmidt et al., 2004) (described in detail above).

The *16-Item Inventory of Personality Organization* (IPO-16; German version by Zimmermann et al., 2013) (described in detail above).

The German version of the *Affective Neuroscience Personality Scales* (ANPS; Davis et al., 2003b; German version by Reuter and Hennig (2014; see Montag et al., 2017 for a more recent version)) (described in detail above).

The *Childhood Trauma Questionnaire* (CTQ; Bernstein et al., 1997; German version by Wingenfeld et al., 2010) (described in detail above).

Results

Descriptive Results

As shown in Table 6, with the exception of CARE group comparisons between healthy participants and participants who reported a lifetime diagnosis of a psychiatric disorder revealed small to moderate differences in every examined variable ($p < 0.001$; $\eta^2 = 0.03$ - 0.15). Thereby, participants reporting a psychiatric lifetime diagnosis reported decreased attachment security, decreased personality organization, more experiences of childhood trauma, decreased positive primary emotions and increased negative primary emotions.

Table 6. *Descriptive statistics and differences between participants with psychiatric diagnosis (N = 243) and without (N = 373).*

		Healthy		Diagnosis				
Measure	α	*M*	*SD*	*M*	*SD*	$F_{(1, 614)}$	p	η^2
AAS								
Depend	0.85	15.87	4.57	11.90	4.95	103.89	.000	.15
Close	0.87	13.18	4.82	10.30	5.17	49.83	.000	.08
Anxiety	0.81	11.07	4.52	13.68	5.12	44.38	.000	.07
IPO								
Structural Deficit	0.88	33.25	10.72	39.68	11.49	49.91	.000	.08
Primitive Defense	0.80	10.52	4.33	13.41	5.08	57.10	.000	.09
CTQ								
Childhood Trauma	0.93	32.64	12.84	42.44	16.65	67.52	.000	.10
ANPS								
SEEK	0.75	2.89	0.38	2.70	0.42	33.62	.000	.05
FEAR	0.89	2.64	0.52	3.06	0.51	96.66	.000	.14
ANGER	0.85	2.53	0.48	2.71	0.53	17.89	.000	.03
SADNESS	0.78	2.52	0.48	2.87	0.43	99.73	.000	.14
CARE	0.76	2.90	0.45	2.85	0.47	1.53	.216	.00
PLAY	0.83	2.89	0.45	2.60	0.48	57.70	.000	.09

Notes. AAS = Adult Attachment Scales; IPO = Inventory of Personality Organization; CTQ = Childhood Trauma Questionnaire; ANPS = Affective Neuroscience Personality Scales; Adapted from Fuchshuber et al. (2019a).

Furthermore, Childhood Trauma showed positive correlations to Structural Deficit, Primitive Defense, Anxiety, ANGER, FEAR and SADNESS (all $p < 0.001$) and negative correlations to Depend, Close, SEEKING, CARE and PLAY (all $p < 0.001$). Moreover, Structural Deficit and Primitive Defense was correlated with Depend and Close and Anxiety (all $p < 0.001$) and correlated with every facet of primary emotion disposition, with the

exception of CARE (p = n.s.). Additionally, all attachment scales were correlated with every primary emotion disposition (all $p < 0.001$) (see Table 7).

Table 7. *Descriptive statistics, sex differences and correlations among examined variables.*

Variable	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Childhood Trauma	-												
2. Structural Deficit	.37*	-											
3. Primitive Defense	.37*	.87*	-										
4. Close	-.44*	-.48*	-.50*	-									
5. Depend	-.55*	-.50*	-.52*	.60*	-								
6. Anxiety	.35*	.67*	.54*	-.37*	-.53*	-							
7. SEEK	-.24*	-.17*	-.15*	.28*	.34*	-.20*	-						
8. FEAR	.25*	.46*	.36*	-.32*	-.44*	.55*	-.33*	-					
9. ANGER	.20*	.34*	.41*	-.20*	-.32*	.28*	-.09	.34*	-				
10. SADNESS	.36*	.51*	.45*	-.36*	-.54*	.65*	-.32*	.73*	.37	-			
11. CARE	-.14*	.08	-.13*	.28*	.25*	.07	.28*	.09	-.06	.06	-		
12. PLAY	-.34*	-.23*	-.23*	.53*	.53*	-.25*	.56*	-.39*	-.11	-.41*	.41*	-	
13. Sex	.09	-.01	-.03	.04	.00	.06	.03	.14*	.06	.15*	.34*	.03	-
M or *n*	36.50	35.79	11.66	12.04	14.30	12.10	2.81	2.81	2.60	2.66	2.88	2.78	381
SD or %	15.22	11.47	4.85	5.15	5.10	4.93	0.40	0.55	0.51	0.45	0.43	0.48	61.9

Notes. $n = 616$; * $p < .001$; Sex was coded as: 0 = male; 1 = female; Adapted from Fuchshuber et al. (2019a).

Path analysis

An initial model, which was controlled for age and sex (see Fig. x), yielded a model that fit the data well: RMSEA = 0.00 (90% CI: 0.00, 0.05); TLI = 1.00; CFI = 1.00; BIC = 535.63. The second model was established by removing non-significant paths from the model. This included: (1) Paths from Close to FEAR, SADNESS and ANGER; (2) paths from Anxiety to ANGER, SEEK and PLAY; and (3) Paths from Structural Deficit to SADNESS, FEAR, CARE and SEEK (see Fig. 14).

The trimmed model exhibited an improved model fit: RMSEA = 0.03 (90% CI: 0.01, 0.05); TLI = 0.99; CFI = 1.00; BIC = 490.35, suggesting a reduction in BIC score with Δ 45 compared to the initial model. The trimmed model suggested the following associations: Childhood Trauma was significantly associated with Depend ($\beta = -0.56$; $p < 0.001$), Close ($\beta =$

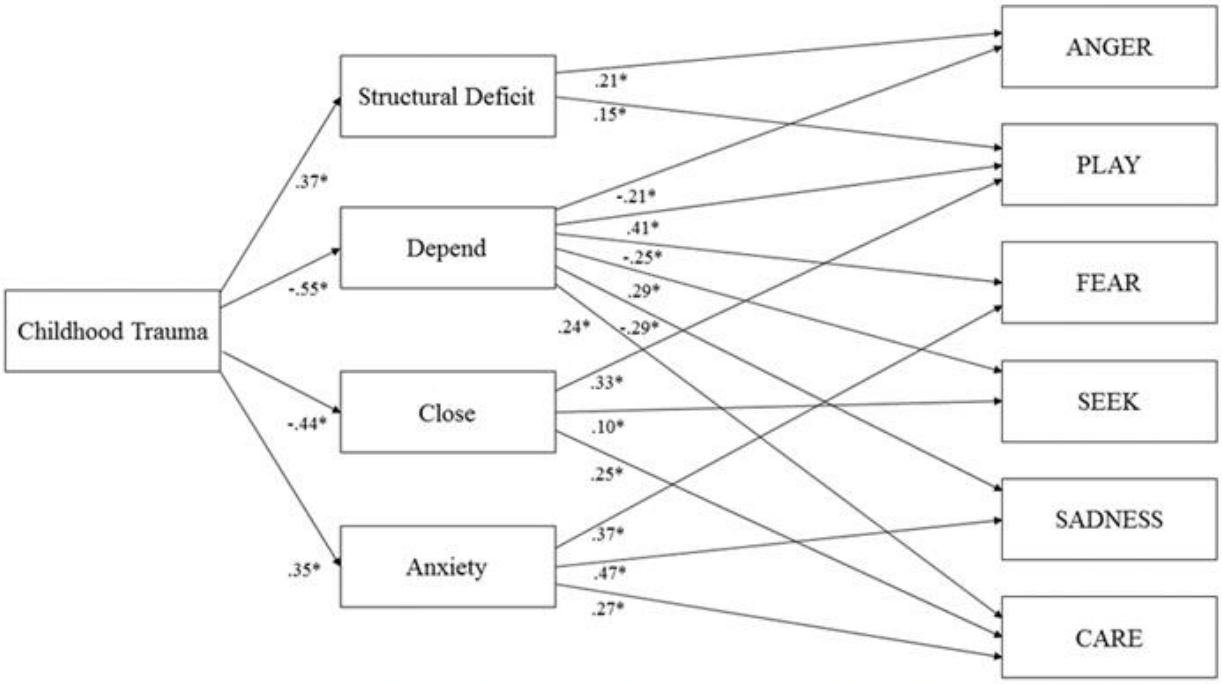


Figure 14. Final model of Childhood Trauma, Structural Deficit, adult attachment and primary emotions controlled for Age and Sex; *p < 0.001; Adapted from Fuchshuber et al. (2019a).

-0.44; p < 0.001); Anxiety (β = 0.36; p < 0.001) and Structural Deficit (β = 0.39; p < 0.001). Structural Deficit was associated with ANGER (β = 0.21; p < 0.001) and PLAY (β = 0.12; p < 0.001). Depend was associated with SADNESS (β = -0.29; p < 0.001); ANGER (β = -0.21; p < 0.001) and SEEK (β = 0.29; p < 0.001); FEAR (β = -0.25; p < 0.001); PLAY (β = 0.41; p < 0.001) and CARE (β = 0.24; p < 0.001), while Close was associated with SEEK (β = 0.10; p < 0.02); PLAY (β = 0.33; p < 0.001); and CARE (β = 0.25; p < 0.001). Anxiety was associated with FEAR (β = 0.37; p < 0.001); SADNESS (β = 0.47; p < 0.001) and CARE (β = 0.27; p < 0.001). Finally, Structural Deficit was significantly correlated with every attachment scale (p < 0.001) and every attachment scale was correlated with each other (p < 0.001). In sum, the trimmed model was able to explain 14% of the variance of ANGER; 35% of FEAR; 48% of SADNESS; 13% of SEEK; 38% of PLAY and 28% of CARE.

With regard to the indirect effects of Childhood Trauma, bootstrap analysis revealed associations with SEEK (β = -0.18; p < 0.01) mediated by Close and Depend; with ANGER, mediated by Structural Deficit and Depend (β = 0.20; p < 0.01); with CARE (β = -0.15; p < 0.01), mediated via Anxiety, Depend and Close; with FEAR (β = 0.29; p < 0.01), mediated by Structural Deficit, Depend and Anxiety; with PLAY (β = -0.31; p < 0.01), mediated by

Structural Deficit, Depend and Close; and SADNESS ($\beta = 0.31$; $p < 0.01$), mediated by Depend and Anxiety.

Finally, a second model was tested. The model proposed a mediational role of Primitive Defense in the relationship between Childhood Trauma and attachment security. Indices for this model suggested an excellent fit: RMSEA = 0.00 (90% CI: 0.00, 0.05); TLI = 1.00; CFI = 1.00; BIC = 535.63. On a local level, results suggested significant associations between Primitive Defense with Close ($\beta = -0.40$; $p < 0.01$), Dependence ($\beta = -0.36$; $p < 0.01$) and Anxiety ($\beta = 0.45$; $p < 0.01$). Furthermore, Childhood Trauma had direct effects on Primitive Defense and attachment scales ($\beta = -0.42$ - 0.19; all $p < 0.001$) and small indirect effects on adult attachment ($\beta = -0.14$ - 0.17; all $p < 0.01$), suggesting a partial mediation role of Primitive defense in the relationship between attachment and Childhood Trauma. In sum, Childhood Trauma and Primitive Defense explained 33% of the variance of Close; 42% of Dependence and 31% of Anxiety. Finally, estimated paths suggested a direct effect of Primitive Defense on ANGER ($\beta = 0.33$; $p < 0.001$) and indirect effects on PLAY ($\beta = -0.32$; $p < 0.01$); FEAR ($\beta = 0.29$; $p < 0.01$); SEEK ($\beta = -0.18$; $p < 0.01$) and SADNESS ($\beta = 0.33$; $p < 0.01$), mediated via adult attachment attitudes.

Methodological Considerations

The results presented in this study relied on an extended sample already investigated in Fuchshuber et al. (2018a), therefore the possibility of alpha inflation should be considered in the interpretation of our findings (Everitt, 2006). To counteract this problem an adjusted alpha level of $\alpha = 0.01$ was applied in these studies. Furthermore, the finding of a marginal positive association between Structural Deficit and PLAY might hint towards a suppression effect in our model (MacKinnon et al., 2000), which might be caused by the substantial interrelation between personality organization and adult attachment. The plausibility of this assumption is further emphasized by our finding a small negative correlation between Structural Deficit and PLAY (see Table 7). Finally, in contrast to Fuchshuber et al. (2018a), the present study applied path analysis, which is a special case of structural equation modeling (Kline, 2015). While this technique has the advantage of increased flexibility in model construction, path analysis assumes that its observed variables are measured without error, which is rarely achieved in psychological research. Therefore, this circumstance should be considered as a limiting factor in the interpretation of our results.

Study 2.3.

Fuchshuber J., Hiebler-Ragger M., Kresse A., Kapfhammer H.P., Unterrainer H.F. Do primary emotions predict psychopathological symptoms? A multi-group path analysis. *Frontiers in Psychiatry*. 2019; 10.

Methods

This study reanalyzed the sample (N = 616; 61.9% female) investigated in Fuchshuber et al. (2019a), which was described in more detail above. Data from the following questionnaires was evaluated in the course of this study:

The German version of the *Affective Neuroscience Personality Scales* (ANPS; Davis et al., 2003b; German version by Reuter and Hennig (2014; see Montag et al., 2017 for a more recent version)) (described in detail above).

The *Brief Symptom Inventory* (BSI-18; Derogatis, 2001; German version: Spitzer et al., 2011) (described in more detail above).

The *Alcohol, Smoking and Substance Involvement Screening Test* (ASSIST; Humeniuk et al., 2008) (described in more detail above).

Fit indices considered as markers for an acceptable model were evaluated in line with Kline (2015) (described in more detail above). The alpha level was set to $\alpha = 0.01$.

The study was approved by the ethics committee of the Medical University of Graz.

Results

Correlative Results

As shown in Table 8, all negative primary emotion dispositions (SADNESS, FEAR and ANGER) showed significant positive correlations with every assessed psychiatric variable (Global Continuum of Substance Risk, Depressive Symptoms, Anxiety Symptoms and Somatization) (all $p < 0.001$). Furthermore, CARE did not show significant correlations with any clinical marker (all p = n.s.). Moreover, PLAY and SEEKING, which showed substantial intercorrelations ($r = .56$; $p < 0.001$), were negatively correlated with Depressive Symptoms, Anxiety Symptoms and Somatization ($p < 0.001$); however, both were not correlated with Global Continuum of Substance Risk (p = n.s.). Finally, while male sex was positively correlated with Global Continuum of Substance Risk ($r = .20$; $p < 0.001$), sex had no significant relationship to other investigated psychiatric symptoms (p = n.s.).

Table 8. *Descriptive statistics, sex differences and correlations among examined variables.*

Variable	1	2	3	4	6	7	8	9	10	11	12
1. Global Continuum of Substance Risk	-										
2. Depressive Symptoms	.44*	-									
3. Anxiety Symptoms	.40*	.69*	-								
4. Somatization	.38*	.52*	.67*	-							
6. SEEK	-.12	-.37*	-.19*	-.15*	-						
7. FEAR	.19*	.59*	.53*	.33*	-.33*	-					
8. ANGER	.19*	.25*	.27*	.24*	-.09	.34*	-				
9. SADNESS	.26*	.69*	.53*	.35*	-.32*	.73*	.37	-			
10. CARE	-.08	-.08	.01	.01	.28*	.09	-.06	.06	-		
11. PLAY	-.10	-.45*	-.29*	-.22*	.56*	-.39*	-.11	-.41*	.41*	-	
12. Sex	-.20*	-.01	.08	.00	.03	.14*	.06	.15*	.34*	.03	-
M or N	39.89	13.49	11.91	10.39	2.81	2.81	2.60	2.66	2.88	2.78	381
SD or %	35.22	6.72	4.91	4.30	0.40	0.55	0.51	0.45	0.43	0.48	61.9

Note. $n = 616$; * $p < .001$; Sex was coded as: 0 = male; 1 = female; Adapted from Fuchshuber et al. (2019b).

Path analysis

The initially proposed model, which included paths between all primary emotions and all psychiatric symptoms and was controlled for sex and age, showed a poor fit due to insufficient RMSEA values: RMSEA = 0.07 (90% CI: 0.03, 0.12); TLI = 0.92; CFI = 1.00; AIC = 186.60. Therefore, a second model was tested that excluded CARE, as this dimension of primary emotion did not show significant correlations within the clinical variables. The second model showed a poor fit as well: RMSEA = 0.09 (90% CI: 0.04, 0.14); TLI = 0.90; CFI = 1.00; AIC = 160.95. In a third step, the second model was trimmed by deleting all non-significant paths between variables (see Fig. 15). This included: (a) Paths between ANGER, Depressive Symptoms and Anxiety Symptoms; (b) Paths between SEEKING, Global Continuum of Substance Risk, Anxiety Symptoms and Somatization; (c) Paths between FEAR, Global Continuum of Substance Risk and Somatization; (d) Paths between PLAY and Global Continuum of Substance Risk.

The third model showed an acceptable fit: RMSEA = 0.05 (90% CI: 0.03, 0.08); TLI = 0.97; CFI = 0.99 AIC = 159.74. The trimmed model suggested the following associations: Global Continuum of Substance Risk was associated with male sex (β = -.25), SADNESS (β = .25) and ANGER (β = .10). Depressive Symptoms were associated with increased SADNESS (β = .53) and FEAR (β = .10), and decreased dispositions to SEEKING (β = -.10) and PLAY (β = -.15). Anxiety Symptoms were related to increased SADNESS (β = .33), FEAR (β = .21) and decreased PLAY (β = -.10). Somatization was linked to increased SADNESS (β = .26) and ANGER (β = .09) and decreased PLAY (β = -.12) (all p < .01). In summary, the final model was able to explain 14% of the variance of Global Continuum of Substance Use Risk, 52% of Depressive Symptoms, 32% of Anxiety symptoms and 14% of Somatization.

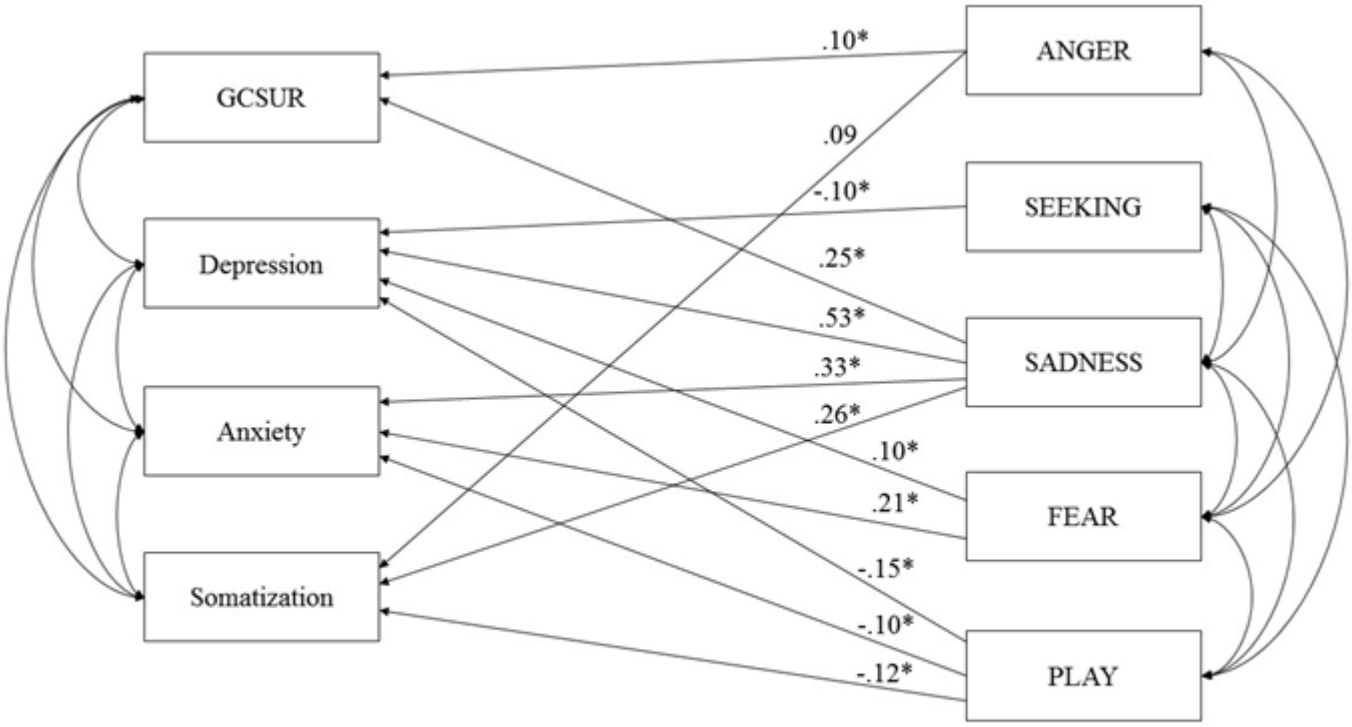


Figure 15. Final model of primary emotions and psychiatric symptoms controlled for Age and Sex; *p < 0.001; curved arrows indicate significant correlations (p < 0.001); Adapted from Fuchshuber et al. (2019b).

Furthermore, to examine possible moderation effects of psychiatric lifetime diagnosis and gender, additional multi-group analysis was conducted. The comparison between groups (female vs. male; "healthy" vs. participants reporting a lifetime psychiatric diagnosis) revealed no significant difference between paths (all p = n.s.).

Methodological Considerations

The present study reanalyzed the sample investigated in (Fuchshuber et al., 2019a). Therefore, the results of our analysis should not be interpreted independently from both Fuchshuber et al. (2018a) and Fuchshuber et al. (2019a). Furthermore, as there is no validated measure for the assessment of LUST currently available, it is impossible to estimate the clinical relevance of this primary emotion system. Despite having a key role in AN- and neuropsychoanalytic theory, LUST was not included in the ANPS, as its authors claimed that people would not be open enough to report about their sexuality (Davis et al., 2003a). However, this assumption seems questionable, especially with regards to the variety of self-report measures of sexuality already existing. Hence, future research should aim at developing a self-report measure for LUST, to fully map the AN-framework and its role in psychiatric etiology.

Discussion

The research presented in this chapter investigated the complex relations between childhood trauma, (neuro-)psychodynamic personality traits and adult psychopathology. Largely in line with previous research (Carr et al., 2013; Schimmenti and Caretti, 2016; Granieri et al., 2018) and theoretical assumptions in psychoanalytic literature (Fonagy, 2003, 2010; Freud, 1906; Jacobson, 1964; Kernberg, 1988, 2015), our findings underline the harmful effects of early traumatic relationships on the development of personality organization, adult attachment and emotional functioning. This result resonates with evidence gathered by Schimmenti and Caretti (2016) and Granieri et al. (2018) indicating that the effects of childhood trauma on adult psychopathology are partially mediated by dissociation, which is conceptualized as a primitive defense mechanism related to splitting (Kernberg, 1993; Klein, 1946). In correspondence to this, our results expand this understanding by suggesting that deficits in emotional functioning and personality organization fully mediate the effect of childhood trauma in the emergence of SUD and depression in adults. Furthermore, results of the studies presented above (Fuchshuber et al., 2018a; Fuchshuber et al., 2019a; Fuchshuber et al., 2019b), echo previous research, which suggested significant associations between personality organization, attachment, primary emotions and addiction (Hiebler-Ragger et al., 2016; Schindler and Bröning, 2015; H. Unterrainer et al., 2017; Unterrainer et al., 2016; Zellner et al., 2011). On a neuroscientific level, this line of evidence is paralleled by recent

findings linking childhood trauma to disturbances of neurobiological structures related to emotion regulation. As outlined above, this includes the anterior cingulate, dorsal lateral prefrontal and orbitofrontal cortex, the corpus callosum and the hippocampus (Teicher and Samson, 2016), impairments in white matter fiber tracts, specifically in the cingulum and the superior longitudinal fasciculus (Daniels et al., 2013) and chronic hyperactivity of the corticotropin-releasing factor systems (Heim and Nemeroff, 2001).

Moreover, in line with recent epidemiological studies (Grant et al., 2016; Grant et al., 2015), our results indicate that male sex serves as a significant predictor of SUD symptoms (Fuchshuber et al., 2018a, 2019b). This finding might be explained in part by internalized gender specific customs, which make it more "desirable" for males to self-medicate negative emotions and symptoms of depression in order to avoid appearing "unmanly". What is more, social disapproval of drug and alcohol consumption in women might be stronger than in men (Fattore et al., 2008). In correspondence to this, our findings indicate that biological sex does not moderate the influence between primary emotions and SUD, but directly affects SUD vulnerability (Fuchshuber et al., 2019b). In contrast, our results were not able to replicate previous studies indicating female sex as a predictor for depression (Albert, 2015; Kessler, 2003). This unexpected finding might be the result of a self-selection bias within our sample. Male subjects might have been more likely to take part in this study, which was advertised as a survey about addiction and depression, if they were affected by depressive symptoms.

With regard to study one (Fuchshuber et al., 2018a), our results indicated that the underlying factors - primary emotions and personality organization - derogate the correlation between symptoms of depression and SUD. This is consistent with assumptions made in AN-theory (Solms et al., 2015; Zellner et al., 2011), assuming a common etiological core for both disorders. However, our findings suggest that Despair very precisely predicts depression, while its influence on addictive behaviors is diminished by deficits in personality organization. Therefore, addictive behaviors might be seen as a compensative strategy against gaps within a corrosive personality structure, as proposed by authors linked to ego-psychology (Khantzian, 2013; Mentzos, 2017). In contrast, our results highlight the fact that the influence of personality structure on depressive symptoms is repressed by the latent factor Despair, supporting the assumption that depression emerges due to hyperactive SADNESS and hypoactive SEEKING networks (Watt, 2000; Watt and Panksepp, 2009). Nevertheless, this

relationship might be more complex as both studies reviewed the above gathered evidence for a substantial interrelation between personality structure and primary emotion functioning (Fuchshuber et al., 2018a; Fuchshuber et al., 2019a), which is consistent with basic assumptions of AN-theory (Panksepp and Biven, 2012; Solms and Panksepp, 2012).

In correspondence to this, our second study (Fuchshuber et al., 2019a) was able to gather new insights regarding the relationship between attachment security, personality organization and primary emotion functioning. If computed in a single model, our results suggest that Kernberg's (Kernberg and Caligor, 2005) concept of personality organization, which is linked to object relations theory, predominantly predicts ANGER, while adult attachment attitude is related to emotional functioning in general. With regards to our results, it might be concluded that deficits in personality organization and insecure attachment foster increased negative primary emotion dispositions (ANGER, FEAR and SADNESS), while secure attachment plays an important role in increased positive primary emotion dispositions (SEEKING, PLAY and CARE). This is with the exception of "anxiety of being rejected", which predicted increased CARE. This finding corresponds to the relationship between this concept and the preoccupied or insecure ambivalent attachment style, linked to exuberant clinging to attachment figures in relevant literature (Ainsworth and Bell, 1970; Bartholomew and Horowitz, 1991). In conclusion, our results indicate empirical support for basic assumptions of object relations and attachment theory, assuming internalized object relations and attachment working models as crucial for the functional integration of affects (Jacobson, 1954; Kernberg, 2006b, 2015; Schore and Schore, 2008; Schore, 2015).

Interestingly, the finding that - compared to adult attachment - deficient personality organization is substantially related to increased ANGER, reflect theoretical differences between Kernberg's (1993) conceptualization of object relations theory and attachment theory. While his theoretical assumptions, which are strongly influenced by Kleinian-theory (Klein, 1946), emphasize the function of personality organization in the integration and neutralization of aggressive affects, aggression has considerably less significance in attachment theory (Fonagy, 2003).

What is more, in the study Fuchshuber et al. (2019a) we were able to shed new light on the relationship between adult attachment and personality organization. Thereby, results of the correlation analysis corresponded to previous research suggesting substantial links between

both concepts (Ainsworth, 1969; Fischer-Kern et al., 2010; Fonagy, 2003; Hiebler-Ragger et al., 2016). More specifically, the strength of the correlations between structural deficits and attachment security scales ranged from negative medium correlations with "Comfort with Dependence" to large positive correlations with "Anxiety of being Rejected" (Cohen, 1992), reflecting conceptual similarities of personality organization and attachment security.

Furthermore, additional analysis suggests that a predominance of primitive defense, which is linked to increased ANGER, might in part mediate the relationship between childhood trauma and the development of insecure attachment attitudes in adults. This finding might be explained by a mechanism which urges traumatized individuals to split contradictory representations of self and others into "good" and "bad" representations. This process might serve the function of protecting relatively unstable positive inner self and object images from contamination with intense negative and aggressive internalizations (Fonagy, 2003; Kernberg, 1993; Klein, 1946). However, a predominance of this mechanism might inhibit the development of stable and beneficial relationships and therefore reinforce the development of insecure attachment attitudes.

Study three (Fuchshuber et al., 2019b) further investigated the relationship between psychiatric disorders and primary emotions. In contrast to study one, which followed a confirmatory approach focusing on the role of despair (Zellner et al., 2011), study three applied path analysis to investigate the relationship between all primary emotion dimensions, SUD and mood disorders in a more exploratory manner. Our results suggest that SUD symptoms are associated with increased SADNESS and, to a lesser extent, with increased ANGER. This finding echoes previous results by Unterrainer et al. (2017), which indicated increased SADNESS, FEAR and ANGER dispositions in SUD inpatients. However, with regard to the overall explained variance, SUD might be less related to primary emotions than previously expected. This is particularly the case for SEEKING which, in line with Unterrainer et al (2017), did not show significant associations with SUD. This finding, which contradicts evidence from neuroscientific research (Alcaro and Panksepp, 2011; Koob and Le Moal, 2005; Volkow et al., 2016), might be explained by conceptual differences between functional aspects of the ML-DA or SEEKING system and the general disposition towards SEEKING measured by the ANPS. More specifically, with regards to its role in reinforcement learning, the ML-DA/SEEKING network is crucial in the development of SUD; however, this

might not be reflected in the individual's disposition towards decreased SEEKING. Furthermore, our results were gathered in the course of a cross-sectional study, hence it is impossible to infer causal conclusions based on our findings. Therefore, it is conceivable that many forms of SUD can be understood as dysfunctional coping strategies against a hypoactive SEEKING system as outlined by Zellner et al. (2011) and Solms (2015). Yet, owing to the cross-sectional study design, we might have been unable to detect this association, as problematic consumption of psychoactive substances may have artificially increased the SEEKING disposition of participants (Panksepp and Biven, 2012). Thus, to sufficiently investigate the relationship between SEEKING and SUD, it will be necessary to conduct longitudinal studies assessing SEEKING prior to the onset of problematic substance use. By contrast, our findings highlight the role of SADNESS and ANGER in SUD. In line with the results of Unterrainer et al. (2017), this partly supports assumptions of AN-theory (Solms et al., 2015; Zellner et al., 2011) and also reaffirms observations of object relations theory emphasizing the etiological role of aggression in SUD (Glover, 1932; Rosenfeld, 1960). This observation further supports the notion of substance abuse as a function of artificial affect regulation. By taking drugs the addicted individual tries to seal gaps in a deficient personality structure (Fuchshuber et al., 2018a), which is linked to increased negative affects (Fuchshuber et al., 2019a; Lenzenweger et al., 2001; Kernberg, 2015). Specifically, addictive behaviors seem to be associated with increased feelings of loneliness and isolation in addition to heightened feelings of rage and aggression, which are experienced as intensely unpleasurable and ultimately overwhelming (Panksepp, 1998; Panksepp and Biven, 2012). The observed significant relationship between SUD and SADNESS further highlights the conceptualization of addiction as attachment disorder, specifically linked to dysregulations within the endogenous opioid system (Coenen et al., 2011; Burkett and Young, 2012; Flores, 2004). Furthermore, the observed association between SUD and ANGER underlines psychoanalytic theories, which relate substance abuse to auto-aggressive behavior, which is presumably directed against malicious inner self and object representations (Glover, 1932; Kernberg, 1993; Rosenfeld, 1960). As observed in study two (Fuchshuber et al., 2019a), the connection between structural deficit and increased ANGER is linked to traumatic childhood relationships.

Moreover, our findings suggest a differential role of primary emotions in the development of psychiatric disorders (Fuchshuber et al., 2019b). Thereby, SADNESS seems to play a substantial role in all assessed forms of mood disorders (depressive symptoms, anxiety symptoms and somatization). However, in contrast to SUD, depressive symptoms were also predicted by decreased PLAY and SEEKING and increased FEAR, which is largely in line with findings from Montag et al. (2017). Additionally, a similar pattern was found for anxiety symptoms, which was associated with increased SADNESS, FEAR and decreased PLAY. Therefore, our results not only support Panksepp's (2004) hypothesis of the importance of the PANIC/GRIEF or SADNESS system in anxiety disorders but also highlight his emphasis on the clinical significance of PLAY, which has traditionally been neglected in psychiatric research (Panksepp, 2011; Panksepp and Biven, 2012). Likewise, this assumption is reaffirmed in the observed association between PLAY and somatization symptoms. Furthermore, the significant relationship between increased SADNESS and somatization might reflect the relationship between SADNESS and the endogenous opioid system, as a hypoactivity of mu and delta opioid network - correlated to increased SADNESS - is known to promote feelings of bodily discomfort (Burkett and Young, 2012; Panksepp, 2011).

Finally, it should be kept in mind that our results suggest substantial intercorrelations between SUD and symptoms of mood disorders, as well as between different dimensions of primary emotions. Therefore, the interplay between other psychiatric symptoms and primary emotions underlying SUD should be understood as an interdependent phenomenon.

General Conclusions, Limitations and Outlook

Following a neuroscientifically informed psychodynamic framework, the primary focus of this thesis was to gain new insights regarding the development and treatment of SUDs. Based on the research presented above, the following chapter will discuss general limitations of our findings and aims at providing an outline for future directions of research. Furthermore, this chapter will discuss several important conclusions regarding the development of SUDs, as well as corresponding implications for the treatment of this disorder.

Limitations

Notably, due to methodological restrictions the findings presented in this thesis do not allow for causal interpretation but are associative in nature. Therefore, the results might be

seen as groundwork for future studies utilizing longitudinal approaches. However, with regard to the treatment of this disorder, it might be ultimately irrelevant if the inter- and intrapersonal problems linked to SUD are the cause or consequence of substance abuse, or an interaction of both (Khantzian, 2015).

In correspondence to that, the presented studies exclusively tested linear models regarding the relationship between primary and higher order processes, as well as regarding their influence on the development of SUD. However, with respect to the non-linear assumptions of AN-theory (Dodds, 2013; Panksepp, 2004), future studies should investigate non-linear relationships to describe the complexity of these relationships in a more naturalistic manner (Scharff and Procci, 2002). This might be achieved in future studies by the estimation of non-recursive structural equation models.

Furthermore, it should be considered that the conclusions of this thesis are embedded within a specific (psychodynamic) discourse and do not claim to constitute an exclusive "truth", but rather present an attempt to approximate a model, which usefully describes reality inferred from empirical data, though this model is necessarily provisional.

In addition, with regards to a bio-psycho-social assessment of this disorder, social aspects, including socio-economic, political and legal issues, influencing the development of SUD have been largely neglected in the presented research. Therefore, future research might aim at developing a more comprehensive approach towards this disorder, by considering historical and societal conditions.

What is more, the validity of our findings is limited due to the assessment of psychiatric symptoms by self-rating measurements, which are vulnerable to distortions towards social desirability. Furthermore, it cannot be ruled out that some psychiatric symptoms and disorders were not detected in our sample due to a lack of self-reflection abilities, especially in participants suffering from psychotic disorders or severe personality disorders (Bateman and Fonagy, 2010). Hence future studies should consider applying structured clinical interviews to improve the assessment of psychiatric symptoms.

Similarly, in the studies presented above, the assessment of psychodynamic parameters relied on the use of self-rating measures, which reflect consciously available representations of concepts, at least partially hypothesized as unconscious. In order to strengthen the validity of our results, future projects should include other means of data collection. This includes

qualitative and semi structured interviews, which allow for the assessment of less conscious mental states.

Moreover, it should be considered that traumatic experiences in childhood are highly susceptible to splitting, dissociation or denial, and might therefore not be detectable to a full extent (Bremner and Marmar, 2002; Schimmenti and Caretti, 2016). Hence, it cannot be ruled out that our findings might have underestimated the relationship between childhood trauma and adult psychiatric symptoms.

Conclusions and Outlook

Despite these limitations, the findings presented in this thesis were able to generate several significant conclusions. In summary, our findings emphasize the importance of considering psychodynamic assumptions regarding the etiology of SUD. Taken together, the analyzed data indicates a rather specific pattern underlying SUD. This pattern relates addiction with substantial developmental deficits in predominantly secondary processes (Solms and Panksepp, 2012), especially with regard to the related concepts of personality organization and attachment style. In turn, these concepts seem to be crucial for the functional regulation of primary emotion systems (Fuchshuber et al., 2019a), indicating that SUD might be understood as an artificial and dysfunctional affect regulation strategy.

In correspondence to this, Fuchshuber et al. (2018a) were able to empirically validate fundamental etiological assumptions proposed in psychoanalytic theory, which assume early relationships as building blocks or tuning variables of adult personality structure, ultimately determining psychopathological developments (Bilitza, 2008; Kernberg, 2015, 1988; Scharff and Procci, 2002).

With regard to Kernberg's (1993; Kernberg and Caligor, 2005) conceptualization of personality organization, addiction treatment should thus focus on the development of more mature defense mechanisms, more coherent identity narratives and improved reality perception. Improvements in these areas might enable more autonomous and functional affect regulation abilities, which might be seen as a crucial factor in stabilizing the affected individual's process of weaning, abstinence and rehabilitation (Fonagy and Bateman, 2006; Fox et al., 2008).

Moreover, in line with a significant amount of research (Schindler et al., 2005; Schindler and Bröning, 2015; Unterrainer et al., 2017; Zellner et al., 2011) our results suggest

that addiction might be understood as a dysfunctional compensation strategy against an insecure attachment organization and associated increased SADNESS activity, which utilizes psychoactive substances as soothing and seemingly "secure" attachment figures (H. Unterrainer et al., 2017; Fuchshuber et al., 2019a; Fuchshuber et al., 2019b). This not only underscores the significance of patient-therapist relationships in addiction treatment, but also implies that targeting insecure attachment might serve as an alternative route in the treatment of addiction, supplementing cognitive-behavioral and classic psychoanalytic approaches (Flores, 2001; Unterrainer et al., 2017). This assumption is further underlined by the close relationship between attachment attitude and emotional functioning (Fuchshuber et al., 2019a). However, research regarding the effects of attachment-based interventions in SUD treatment is still sparse, thus future research addressing this issue is needed. What is more, future research should further investigate the role of adult attachment attitude in an inpatient treatment setting, as our results suggest that this relationship might be more complex than previously anticipated (Fuchshuber et al., 2018b).

Furthermore, it was possible to show tentative links between psychodynamic and neurobiological markers, including white matter integrity and oxytocin reactivity (Tatzer et al., Submitted; H. Unterrainer et al., 2017). In this context, the widespread impairments in white matter tracts of PUD patients particularly highlight the role of white matter integrity in behavioral dysregulation (Clark et al., 2012; Jacobus et al., 2013; Unterrainer et al., 2016; H. Unterrainer et al., 2017). Moreover, these findings resonated with studies linking similar structural changes in white matter to the effects of childhood trauma (Daniels et al., 2013), which additionally underscores the importance of childhood trauma in the development of SUD. Hence, our findings suggest that addiction might be ameliorated by supporting patients who are working through traumatic memories in a therapeutic setting.

In summary, it can be concluded that a neuroscientifically informed psychodynamic framework is able to contribute valuable insights regarding the underlying mechanisms of SUD development. However, many questions remain unresolved and future research should aim at expanding and refining the etiological model proposed in this thesis. In correspondence to this, the development of improved standardized measures and the progressive embedding of psychoanalytic theories within empirical neuroscience might be rewarding goals for future research initiatives.

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