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Impaired awareness of self and others: Exploring insight into illness and theory of mind in opioid dependent patients undergoing opioid maintenance treatment.

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PREFACE

This work is a cumulative dissertation based on empirical studies, thus the results have already been published as peer-reviewed publications. For this reason, certain sections, tables and figures of this dissertations are identical to these publications. These peer-reviewed publications are listed below.

Publication 1: Eidenmueller, K., Grimm, F., Hermann, D., Frischknecht, U., Montag, C., Dziobek, I., Kiefer, F. & Bekier, N. K. (2021). Exploring influences on theory of mind impairment in opioid dependent patients. *Frontiers in Psychiatry*, *12*.
The corresponding chapter in this dissertation is **Chapter 2 Study 1 Exploring influences on theory of mind in opioid dependent patients**.

Publication 2: Eidenmueller, K., Grimm, F., Hermann, D., Frischknecht, U., Kiefer, F., Dziobek, I., & Bekier, N. K. (2022). Exploring impaired insight in opioid addiction: The role of self-stigma. *Heroin Addiction and Related Clinical Problems*, *24*(2), 45-51.
The corresponding chapter in this dissertation is **Chapter 3 Study 2 Exploring impaired insight in opioid addiction**.

The personal contributions to each of the publications are listed in the table below:

Work steps	**Publication 1**	**Publication 2**
Conception (%)	80%	80%
Literature research (%)	100%	100%
Ethics proposal (%)	50%	50%
Data collection (%)	50%	50%
Data analysis (%)	100%	100%
Interpretation of results (%)	90%	90%
Writing the manuscript (%)	100%	100%
Revision (%)	100%	100%
Figures and Tables (%)	Table 1 (100%) Table 2 (100%) Table 3 (100%) Figure 2 (100%)	Table 4 (100%)

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LIST OF ABBREVIATIONS

ACC	Anterior Cingulate Cortex
ACT	Acceptance and Commitment Therapy
BCIS	Beck Cognitive Insight Scale
BOLD	Blood Oxygenation Level Dependent
CTQ	Childhood Trauma Questionnaire
DCCS	Dimensional Change Card Sort
DSM	Diagnostic Statistical Manual
EF	Executive Functions
HAIS	Hanil Alcohol Insight Scale
ICC	Intraclass Correlation Coefficient
ICD	International Classification of Diseases
ISMI	Internalized Stigma of Mental Illness
M	Mean
MASC	Movie for the Assessment of Social Cognition
mPFC	Medial Prefrontal Cortex
OMT	Opioid Maintenance Treatment
PTSD	Post Traumatic Stress Disorder
RMET	Reading the Mind in the Eyes Task
SAS	Substance Use Awareness and Insight Scale
SD	Standard Deviation
SST	Stop Signal Task
STS	Superior Temporal Sulcus
SUD	Substance Use Disorder
ToM	Theory of Mind
TPJ	Temporoparietal Junction

1 INTRODUCTION

1.1 Opioid dependence and opioid maintenance treatment

Opioid dependence is among the most common addictive disorders worldwide and is responsible for a large percentage of drug-related morbidity and mortality (Degenhardt et al., 2013). The International Classification of Diseases (ICD 10: World Health Organization, 2016) poses six diagnostic criteria for opioid dependence: a strong craving for opioids, impeded control over opioid use, experiencing withdrawal symptoms, drug tolerance, neglect of interests and alternative activities in favor of opioid use and continued opioid use despite harmful consequences. If three of those criteria are met concurrently within the previous 12 months, the diagnosis is applied. Similarly, the Diagnostic Statistical Manual (DSM V: American Psychiatric Association, 2013) defines opioid use disorder as a problematic pattern of opioid consumption leading to clinically significant impairment or distress. At least two of a total of eleven diagnostic criteria need to be observed within a period of twelve months. The criteria posed by the DSM include loss of control over drug intake (more or longer periods of intake than intended, unsuccessful attempts of reduction), spending excessive time attaining, using or recovering from opioids, intense craving, interpersonal problems, continued opioid use despite it causing problems, giving up important or meaningful activities, repeated opioid use in dangerous situations, continued opioid use despite awareness of negative health impacts, drug tolerance and withdrawal symptoms. While the same diagnostic criteria are applied to opioid dependence as to other substance use disorders (SUDs), distinctive features of opioids are their extremely rewarding effect, due to intrinsic properties of the opioid receptor, combined with highly aversive withdrawal symptoms once a physiological dependence has been established. A physiological dependence can emerge after as little as four to eight weeks of steady opioid use, constituting the highly addictive potential of opioids (Sharma et al., 2016).

In the most recent European drug report (European Monitoring Centre for Drugs and Drug Addiction, 2021), it is estimated that there were 1 million high-risk opioid users in the European Union in 2019, which corresponds to 0.35 % of the population, with Germany

among the four countries that account for more than two thirds of this number. 27 % of patients entering addiction treatment in Europe in 2019 were admitted because of opioid use. Regarding deaths due to drug overdose, opioids were present in three quarters of the cases. In Germany, the number of fatal opioid overdoses has increased in 2019. In the United States, the rising numbers of opioid abuse and opioid use disorders in the wake of an increase in opioid analgesics prescriptions has developed into a grave public health crisis (Volkow & Blanco, 2021). While different studies on the matter agree that Europe as a whole is not likely to be facing an opioid crisis comparable to the United States (Häuser et al., 2021; Pierce et al., 2021), rising numbers in opioid prescriptions and abuse have been reported in several European countries in recent years, including Great Britain (Pierce et al., 2021), the Netherlands (Kalkman et al., 2019) and Germany (Rosner et al., 2019).

For the treatment of opioid use disorders, opioid maintenance treatment (OMT) has manifested as the clinical gold standard (Kourounis et al., 2016). Patients are treated with full μ-opioid receptor agonists (i.e. methadone, levomethadone, retarded morphine), partial agonists (i.e. burprenorphine) or a combination with the opioid antagonist naloxone (i.e. suboxone) on a regular basis, not necessarily with the goal of eventual abstinence, but with the objective of harm reduction. In Germany, OMT was first established in 1987 and fully legalised in 1992 (Michels et al., 2007). As of July 2021, the Federal narcotics control board reported 81300 registered patients in opioid maintenance therapy in Germany (Bundesopiumstelle, 2022). Research on OMT in Germany has shown high retention rates, improvements in mental and physical health and reduction of morbidity, infectious diseases and mortality (Michels et al., 2007). High standard Cochrane reviews confirm the advantages of OMT (Mattick et al., 2009, 2014).

A study on a sample of more than 1000 heroin dependent patients engaging in OMT in a psychiatric hospital in Pisa showed that the majority of patients exhibited limited insight into their substance dependence and consumption behaviour (Maremmani et al., 2012). Given that with the exception of a depot buprenorphine injection, OMT requires patients to ingest their substitute on a daily basis to avoid unpleasant withdrawal symptoms and therefore confronts them with their pathology, this finding may seem surprising. However, having only limited awareness of their addiction is a phenomenon common in patients with

SUDs (Goldstein et al., 2009). In this dissertation, said phenomenon of impaired insight into illness will be defined and described in the context of SUDs. Potential influencing factors, with special regard to theory of mind, will be elucidated. Subsequently, two original research papers by the author exploring theory of mind and insight into illness in OMT patients will be presented and discussed.

1.2 Insight into illness

Insight can be defined as „a person's understanding of their own self and experiences" (Raftery et al., 2020, p. 1). In the context of psychiatry, insight refers to the extent of a patient's awareness of their disorder and its implication and is typically structured in three components: the awareness of suffering from a disorder, the attribution of symptoms to this disorder and the recognition of the need for treatment resulting from the disorder (David, 1990). A term often used synonymously to insight into illness is awareness of illness. Not a synonym, but rather a related concept is interoception, which can be defined as „the sense of the physiological condition of the entire body or as a generalized homeostatic sensory capacity that underpins a conscious representation of how we feel" (Goldstein et al., 2009, p. 8). Whether consciously perceiving interoceptive signals is sufficient or a necessity for insight is unclear (Goldstein et al., 2009). Three dimensions are suggested by Goldstein et al. (2009) for differentiating between interoception and awareness/ insight: Sensorimotor (perceiving a particular state, without necessarily having explicit knowledge of this state), emotional (comprehension of the implications of a situation, independent from factual knowledge) and cognitive (the conscious thought process, independent from the recognition or attainment of a goal state). Beck (2004) emphasizes the role of metacognitive processes in his definition of cognitive insight, describing it as the capacity to reflect on one's own experiencing and thinking which includes the ability to consider other people's views concerning said experiences and thoughts. Cognitive and clinical insight can be regarded as complimentary concepts (Riggs et al., 2012).

When referring to a patient's negation of or failure to acknowledge an illness, the severity of the disorder or the behavioral and social constrains and repercussions that come with it, the term impaired insight into illness (or synonymously unawareness of illness) is

used (Goldstein et al., 2009). Another term sometimes used to describe impaired insight into illness is denial - however, its meaning somewhat depends on the clinical context (Williams et al., 2015). In Freudian psychoanalyst theories, denial is viewed as a psychological defence mechanism, a normative part of the human psyche and, depending on the circumstances, can be either protective or maladaptive (Freud, 1924, 1925). Impaired insight, on the other hand, can be seen as the multidimensional and dynamic product of the interaction of the primary symptoms of the illness, the patient's cognitive style and neurocognitive deficits, with the dysfunction of the neural circuitry outweighing the functionality of denial as a psychological defence mechanism (Williams et al., 2015).

Naturally, insight is an important factor in facilitating a patient to deal with an illness. Impaired insight on the other hand can lead to patients prematurely terminating or not seeking appropriate treatment as well as non-compliance and can therefore have negative social and health-related repercussions (Bottlender & Hloucal, 2010). Within treatment, impaired insight may lead to frustration and negative reactions from clinical staff (Williams et al., 2015). In schizophrenia, the disorder accompanied by the largest body of research on impaired insight, unawareness of illness has been linked to poorer treatment outcomes (e.g. O'Connor et al., 2013; Saravanan et al., 2010; Schwartz, 1998). Correlations between impaired insight and treatment outcome have also been found in patients suffering from depressive episodes with psychotic symptoms (Gerretsen et al., 2015). Furthermore, impaired insight in schizophrenic patients was linked to reduced interpersonal functioning (Lysaker et al., 1998) and poorer work performance regarding personal presentation and cooperativeness. This association appeared to be independent from global intelligence and executive functions and may have a negative impact on rehabilitation (Lysacker et al., 2002). Indeed, a recent meta-analysis identified insight as a predictor for the outcome of vocational rehabilitation programs for patients with severe mental illness (Manoli et al., 2021). Thus, insight appears to be a relevant factor in treatment, functioning and well-being of individuals suffering from a psychiatric illness and can be regarded as an important subject for basic and clinical research.

1.2.1 Insight in substance use disorders

Conditions most commonly related to impaired insight are neurological disorders like strokes, malfunctions or neglects following traumatic brain injuries and dementia (Orfei et al., 2008), schizophrenia and psychosis (Aleman et al., 2006; Martin et al., 2010; Mintz et al., 2003), mood disorders (Colis et al., 2006; Engh et al., 2007), obsessive compulsive disorders (Himle et al., 2006) and SUDs (Goldstein et al., 2009).

The most research on insight in SUDs can be found for alcohol dependence. Raftery et al. (2020) pooled data from five studies examining insight in alcohol dependent individuals using the Hanil alcohol insight scale (HAIS) and found that 56.6% of the sample had poor insight, 36.4% had fair insight, and only 7% had good insight. A study assessing reported reasons for not seeking treatment found lack of insight to be the cause in 55% of participants with alcohol use disorder (Probst et al., 2015). Furthermore, in people who do engage in inpatient treatment for alcohol dependence, insight has been linked to readiness to change (K. M. Kim et al., 2007) and prolonged post-treatment abstinence (J. S. Kim et al., 2007; Willems et al., 1973). A recent study on a sample with different substance and behavioral addictions confirmed the relationship between higher levels of insight and treatment success (Lambert et al., 2022).

The SUD with the second largest body of insight research is cocaine addiction. Two studies using awareness of choice as a measure for insight found lower levels of insight in cocaine users compared to healthy controls who abstained from cocaine (Benedict, 2014; Moeller et al., 2010). Participants with poorer insight exhibited higher cocaine use and a higher preference for cocaine-associated images in a choice task (Moeller et al., 2010). Deficits in self-awareness regarding symptoms of frontostriatal dysfunction were found to be associated with more difficulties upholding treatment motivation in cocaine dependent patients (Castine et al., 2019).

In adolescent cannabis users, low problem awareness and the desire to solve one's problems without the help of others have previously been identified as the main barriers to seeking treatment (Fernández-Artamendi et al., 2013). Cannabis users appear to have poorer

insight into illness in comparison to other substance users (Kim et al., 2022), however, the research on insight in cannabis use disorder is extremely limited.

Only marginally more studies exist on insight in opioid use disorders. In the aforementioned study exploring insight into illness in heroin addicts entering OMT, the majority of the patients had low insight into their substance use behaviours (Maremmani et al., 2012). In a treatment study with opiate dependent patients, higher insight was associated with attending more treatment sessions (Giyaur et al., 2005). As Raftery et al. (2019) point out, the majority of studies on insight in SUDs have been conducted with patients in addiction treatment. Therefore, it is not clear to which extent acute withdrawal symptoms, which are often experienced in the beginning of treatment, play a role in measuring insight in addiction. For this reason, opioid dependent patients in OMT might be an especially interesting population to study, as they are engaged in an addiction treatment that does not require detoxification.

Regarding the relationship between insight and mental health variables in SUDs, better insight seems to correlate with poorer mental health status (Yen et al., 2008), more psychiatric comorbidities (Maremmani et al., 2012) and higher degrees of psychological distress (Raftery et al., 2019). In patients with comorbid schizophrenia and alcohol use disorder, insight into alcohol use disorder and insight into schizophrenia were correlated. Compared to schizophrenic patients without comorbid alcohol dependence, these patients seemed to have lower levels of insight (Yen et al., 2009).

Goldstein et al. (2009) propose a neural dysfunction in brain regions relevant to interoception, self-evaluation, behavioral monitoring and habit formation as the basis for impaired insight in drug addiction. In their review article, they identified abnormalities in the insula as a likely contributor to craving, reduced awareness of the severity of the addiction and impaired insight. Further, the authors propose an association of dysfunctions of the anterior cingulate cortex (ACC) with unawareness and disadvantageous decision-making expediting relapse. Both the insula and ACC have previously been identified as relevant components in the neurocircuitry of addiction (Koob & Volkow, 2016). Studies on patients with cocaine use disorders have since found functional abnormalities in the rostral ACC in

cocaine dependent individuals with impaired insight (Moeller et al., 2014) as well as hints towards the ACC and ventro-medial prefrontal cortex as a part of the circuitry underlying the failure to recognize the need to change problematic drug use (Moeller et al., 2020). Even though research on the neurobiology of impaired insight in addiction is scarce, these results seem to support the idea of the relevance of ACC and insula in impaired insight in substance addiction proposed by Goldstein et al. (2009). Even beyond neurobiology, research on factors influencing impaired insight in addiction is scarce. In the following chapter, possible influences on insight in opioid dependence will be outlined.

1.2.2 Possible influences on insight in opioid dependence

Few studies have examined which factors might have an influence on insight in SUDs. In alcohol dependent patients, having previously experienced withdrawal symptoms and sharing a living space with other people were shown to be associated with better insight (Hyun et al., 2013). A study on patients in opiate addiction treatment found impaired insight to be associated with a longer duration of heroin use (Giyaur et al., 2005). In contrast, Maremmani et al. (2012) found that impaired insight was correlated with a shorter history of heroin addiction and fewer events of past treatment seeking. In a sample of users of different illicit drugs who met the diagnostic criteria for harmful substance use or dependence, better SUD awareness correlated with greater severity of illness (Kim et al., 2022). Beyond these findings, there are factors that might have a relevant relationship to impaired insight in opioid dependence, but have not specifically been researched in this context. In the following paragraphs, possible influential factors and the research indicating their potential relevance will be presented.

In their research on insight in schizophrenia, Langdon and colleagues (Langdon et al., 2006; Langdon & Ward, 2009) describe three explanatory approaches to impaired insight: the deficit approach, the nondeficit approach and the cognitive neuropsychological perspective. The *deficit approach* views impaired insight as a result of the loss of critical neuropsychological functioning caused by the mental illness. The *nondeficit approach* frames impaired insight as a secondary consequence of the stigma of mental illness, describing it as the result of motivational processes, such as avoiding distress and low self-esteem that

would come with acknowledging the diagnosis. Langdon and Ward (2009) themselves propose the *cognitive neuropsychological perspective*, which puts deficits in social perspective taking and theory of mind at the centre of impaired insight in schizophrenia. While these three approaches were originally formulated for explaining impaired insight in schizophrenic patients, they can also function as valuable perspectives for thinking about influences on impaired insight in opioid addiction.

Beginning with the deficit approach, executive functions (EF) are a potentially relevant influence on insight in opioid dependence. EF describe a selection of top-down cognitive processes that "make possible mentally playing with ideas; taking the time to think before acting; meeting novel, unanticipated challenges; resisting temptations; and staying focused" (Diamond, 2013, p. 135). Core components of EF are response inhibition, interference control (cognitive inhibition and selective attention), cognitive flexibility (adapting to changed circumstances, shifting perspectives, thinking outside the box) and working memory (Diamond, 2013). EF impairments have previously been linked to impaired insight in patients with psychotic disorders (Aleman et al., 2006; Lysaker et al., 2006), with impairments in error monitoring and cognitive flexibility assuming an eminent role (Aleman et al., 2006). In bipolar patients poor insight is also associated with impaired EF, with inhibition, selective and divided attention being significant predictors (Camelo et al., 2019). Several studies have found EF impairments in opioid dependent individuals (Gruber et al., 2007; Loeber et al., 2012; Pau et al., 2002; Sanborn et al., 2020). Ersche and Sahakian (2007) found cognitive inhibition and feedback processing to be the most affected EF components in opiate users. EF impairments seem to be a long-term effect of opioid use rather than a short-term effect of opioid intoxication, as EF deficits remain stable after several years of abstinence (Ersche et al., 2006). As deficits in EF have been previously associated with impaired insight into illness as well as opioid addiction, EF might be a relevant factor for impaired insight in opioid dependent patients.

Another construct that is associated with insight in mental illness is self-stigma, which is interesting from the perspective of the nondeficit approach. Generally, patients with SUDs are victims of marginalisation more often than patients with other mental illnesses or physical disabilities and are stigmatised as potentially dangerous individuals who are to

blame for their substance dependence (Corrigan et al., 2009). Opioid users face especially strong stigmatisation (Brown, 2015; Frischknecht et al., 2011). Patients in OMT report to experience institutional stigma (Harris & McElrath, 2012). Public and institutional stigma may be internalized by the people affected by it, resulting in what is referred to as self-stigma. Corrigan and Rao (2012) describe self-stigma in consecutive stages: awareness of public attitudes towards the stigmatised people, agreement with these attitudes and the application of the stereotypes to oneself as a part of the stigmatised group, culminating in harm to the person. Self-stigma and insight are correlated in patients with severe mental illness (Hasson-Ohayon et al., 2012), schizophrenia (Cavelti et al., 2012; Pruss et al., 2012) and depression (Woon et al., 2020). A study on 100 patients with a variety of different mental health diagnoses, including 20% of patients with SUDs, also found an association between insight and self-stigma (Mishra et al., 2009). To date, only one study with a sample of alcohol dependent Korean men in inpatient addiction treatment specifically examined the relationship between insight and self-stigma in a SUD population. This study did not find a significant correlation (Lyu et al., 2017). More research is needed to understand the relationship between self-stigma and insight in SUDs.

When approaching the topic from the cognitive neuropsychological perspective, theory of mind (ToM) seems to be a factor that might be of relevance for impaired insight in opioid dependence, as stable findings associate poor ToM with impaired insight into illness in schizophrenia (Bora, 2017; Bora et al., 2009; Ng et al., 2015). This relationship appears to be unrelated to symptom severity and neuro-cognitive deficits (Konstantakopoulos et al., 2014). In obsessive-compulsive disorder, several studies link ToM impairments and poor clinical insight (Mısır et al., 2018; Tulacı et al., 2018; Yazici & Yazici, 2019). While no studies have previously examined the relationship between ToM and insight in addiction, evidence of ToM impairments across different SUDs exists (review article: Sanvicente-Vieira, Romani-Sponchiado, et al., 2017), including one exploratory study with a sample of opioid dependent patients that found significant ToM deficits compared to healthy controls (Gandolphe et al., 2018). As Goldstein et al. (2009, p. 8) point out, “social cognition impairments may be related to self-awareness compromises (e.g., through mechanisms shared by awareness to self and others)”. Insight into illness may require the metacognitive capacity to see oneself as seen by other people and think about one’s own mental health from the perspective of

others (Langdon & Ward, 2009), which would make ToM crucial for developing awareness of one's illness. In the following chapter, ToM as a construct, findings on ToM in SUDs and possible influences on ToM in opioid dependence will be elaborated on.

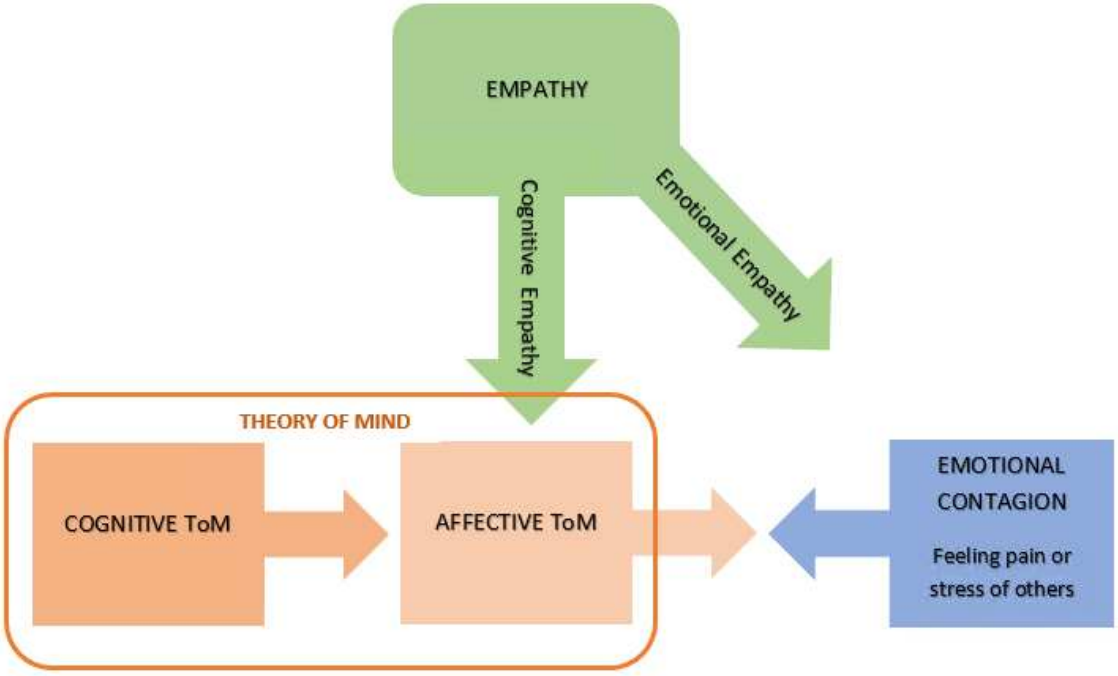
1.3 Theory of mind

The term *theory of mind* was first introduced by Premack and Woodruff (1978) and defines the attribution of mental states to oneself and others. It is somewhat of an umbrella term (Hynes et al., 2006) including the ability to make inferences about other people's thoughts, emotions, knowledge, expectations, desires, ideas and intentions. These social-cognitive processes play a huge role in human social interactions (Goldman, 2012) and have been proposed to be one of the key abilities differentiating between humans and other primates (Gallagher & Frith, 2003).

Other terms used when describing the process of inferring about the mental states of others are mentalizing, mind reading and empathy. Mentalizing, mind reading and ToM are often used synonymously, with mentalizing being the predominantly used term in the context of psychoanalytical work (Fonagy & Allison, 2012). Empathy and ToM are closely related constructs, with empathy focusing on the emotional aspects of mental states, describing the ability to recognize and also share other people's emotions (de Vignemont & Singer, 2006). As inferring about mental states is required for resonating with the emotions of others, ToM can be seen as the basis for empathy (O'Connor et al., 2007). While the affective resonation with the emotions of others is an aspect that distinguishes between empathy and ToM, some authors argue that the cognitive aspect of empathy can be equated to ToM, more specifically affective ToM (Walter, 2012). However, in a model by Shamay-Tsoory et al. (2010), it is proposed that rather than being a synonym for cognitive empathy, affective ToM integrates both cognitive and affective aspects of empathy (see figure 1).

Figure 1

Recreation of the model of the relationship between ToM and empathy as introduced by Shamay-Tsoory et al.



Note. Referring to Shamay-Tsoory et al. (2010), cognitive ToM is a precondition of affective ToM. Cognitive empathy is involved in affective ToM, e.g. in the sense of "I understand how you are feeling". Emotional empathy and emotional contagion interact with affective ToM.

ToM develops over the lifespan. The core phase of ToM development is at preschool age, between three and five years (Miller, 2012), but even in infancy, certain aspects of ToM can be detected. For instance, twelve month olds are able to understand the connection between other people's intentions and actions (Phillips et al., 2002). At the age of three, children have an understanding of the association between beliefs and actions in other people to a certain degree (Bartsch & Wellman, 1995). However, in false belief tasks, which require the understanding that someone will act according to their own beliefs even if the child themselves knows that belief to be incorrect, children under the age of four usually fail (Wellman et al., 2001). Even though the main ToM development unfolds in the preschool age, children's ToM abilities can further develop up to adolescence, e.g. if they are in an

environment that encourages perspective taking (Goldstein & Winner, 2012). In young adulthood, ToM is considered to be stable, whereas ToM abilities gradually decline in older adulthood (Miller, 2012).

Functional imaging studies have identified a core network of brain regions which are activated during ToM tasks, consisting of the medial prefrontal cortex (mPFC), the bilateral temporoparietal junction (TPJ), the precuneus and the temporal poles (Carrington & Bailey, 2009; Frith & Frith, 2003; Lavoie et al., 2016). A meta-analysis differentiating between different tasks for measuring ToM found distinct task-related activation profiles involving these brain regions (Schurz et al., 2014).

Being a highly complex and rather broad construct, ToM includes a variety of sub-processes. One of these processes is self-other distinction, as it is necessary to tell apart one's own mental states from those of others to be able to make appropriate inferences about the mental states of others. Self-other distinction was found to correlate with activation of the TPJ (Qureshi et al., 2020; Steinbeis, 2016), a component of the core-network associated with ToM (Schurz et al., 2014). Furthermore, to make inferences about mental states of others, one has to be able to process and interpret gaze, biological motion and gestures (Frith & Frith, 2003) as well as prosody (Chevallier et al., 2011). The direction of someone's gaze may contain information about their interests, what they want to obtain or do, whereas the quality of someone's movement may be an expression of the person's mood, e.g. being fearful, impatient or cheerful. And, on the macro level, inferences about a person's goals and intentions can be made from interpreting their actions (Frith & Frith, 2003). Brain regions associated with the processing of gaze, motion and agency are the temporal regions and the superior temporal sulcus (STS) (Frith & Frith, 2003). Another ability that can be seen as a sub-process of ToM is the assessment of social and psychological characteristics, which has been associated with activation of the mPFC, another area belonging to the core network of ToM (Schurz et al., 2014). However, not only what can be perceived from others, but also the context in which these perceptions are embedded is a relevant process for ToM. In order to infer from someone's behaviour to their psychological states, mental scripts of how one typically acts in different social situations need to be consulted. These processes have been shown to be associated with temporal pole activity

(Frith & Frith, 2003). Another important sub-process of ToM is mental imagery, which can be defined as the imagining of distinctive states that cannot be perceived explicitly. A brain area that was found to be associated with mental imagery is the precuneus (Schurz et al., 2014).

Apart from the aforementioned sub-processes contributing to ToM, distinct categories or levels of ToM can be differentiated within the construct. As mentioned earlier, one common distinction is to differentiate between cognitive and affective ToM, with cognitive ToM referring to the ability to infer about non-emotional mental states, i.e., thoughts, beliefs, knowledge and intentions, while affective ToM refers to inferences about other people's emotions (Kalbe et al., 2010; Shamay-Tsoory et al., 2010). Neuroimaging studies confirm the distinction between cognitive and affective ToM (Corradi-Dell'Acqua et al., 2014; Shamay-Tsoory & Aharon-Peretz, 2007). Furthermore, it is common to differentiate between different levels of complexity of ToM performance. First-order ToM refers to reasoning about mental states of others, for example "She wants to eat the apple". Second order ToM requires the ability to make inferences about other people's beliefs about another person's mental states, for example "She thinks that he wants to eat the apple". Third order ToM applies when inferences are made about other people's second order ToM, for example "She thinks that he believes that I want to eat the apple" (Verbrugge & Mol, 2008).

ToM impairments have been shown in several neurological and psychiatric disorders, including basal ganglia disorders (Bodden et al., 2010), Huntington's disease (Eddy et al., 2014), autism spectrum disorders (Baron-Cohen, 2001; Martinez et al., 2017), schizophrenia (Bora et al., 2009) and mood disorders (Bora & Berk, 2016; Montag et al., 2011). As ToM plays a relevant role in human social interactions (Goldman, 2012), it is not surprising that it has been connected to relevant outcome variables in mental health research. In severe mental illness, ToM was found to be a predictor for community functioning (Cook et al., 2013) and, in women, maternal sensitivity (Rigby et al., 2016). In patients with schizophrenia, impaired ToM is associated with limited social competence (Brune et al., 2007) and poor quality of life (Maat et al., 2012). In the following section, ToM impairments and their clinical relevance in SUDs will be outlined.

1.4 Theory of mind and substance use

In a review on ToM in SUDs, the authors conclude that "despite the lack of studies and the methodological limitations of the existing ones Theory of Mind seems to play a role in drug use conditions" (Sanvicente-Vieira, Romani-Sponchiado, et al., 2017, p. 127), with most evidence for ToM impairments being present in alcohol and stimulant addiction. A meta-analysis (Onuoha et al., 2016) confirms impaired ToM in alcohol dependent patients and finds the effect to be unaffected by IQ and level of education. Nandrino et al. (2014) found specifically affective ToM to be impaired in alcohol dependent individuals. Other research supports this finding, e.g. Onuoha et al. (2016), who found bigger effect sizes for studies using the "Reading the mind in the eyes"-test, a measure for affective ToM, and Maurage et al. (2016), who found affective, but not cognitive ToM to be impaired in alcohol dependent patients compared to healthy controls. In adolescents, affective ToM and binge drinking are correlated inversely, even after controlling for sex, age and level of education, indicating that affective ToM impairments may play a role in the onset of alcohol abuse (Lannoy et al., 2020). Another study examining the relationship between ToM and adolescent heavy drinking found that adolescents with poor ToM exhibited significantly more heavy episodic drinking when a high need for social conformity was present (Laghi et al., 2019). In alcohol dependent patients in an inpatient detoxification treatment, impaired ToM was shown to be associated with depressiveness (Thoma et al., 2013).

Regarding ToM and stimulant abuse, facial emotion recognition and ToM impairments have been detected in current methamphetamine abusers (Kim et al., 2011) and detoxified methamphetamine dependent patients after an average of six months of abstinence (Henry et al., 2009), indicating that ToM impairments exceed short term effect of methamphetamine intoxication. Furthermore, poor emotion recognition has been reported in individuals with non-medical methylphenidate consumption (Maier et al., 2015). For cocaine users, significantly poorer performance compared to healthy controls has been reported for emotion recognition (Hulka et al., 2013), while another study reported significant ToM impairments in cocaine dependent patients, but not recreational users, and correlation between poor ToM test score and high cocaine intake (Preller et al., 2014). In a sample of cocaine dependent women, ToM impairments regarding second order false belief

stories and reading negative mental states were detected, which correlated with substance use related variables (Sanvicente-Vieira, Kluwe-Schiavon, et al., 2017). A study with stimulant polysubstance abusers found impairments in emotional empathy, which were predicted by the number of abused substances (Kroll et al., 2018).

In cannabis users, differences to control groups regarding event related potentials during an emotional processing paradigm in which participants were shown faces with different emotional expressions (Troup et al., 2016) and changes in activation patterns of the precuneus, cuneus, right ACC and left parahippocampal gyrus during a ToM task (Roser et al., 2012) have been reported. Heavy cannabis users were shown to be slower in the identification of emotions on the basis of facial expressions compared to healthy controls, unrelated to generally slower reaction times (Platt et al., 2010).

As for opioid dependence, most ToM research focuses on aspects of affective ToM. Deficits in emotion recognition have been shown in abstinent opioid addicts and OMT patients (Kornreich et al., 2003; Martin et al., 2006; McDonald et al., 2013). The impairment seems to be less impactful than in alcohol dependent individuals (Kornreich et al., 2003). McDonald et al. (2013) also reported a reduced capacity to infer about social situations in OMT patients. Martin et al. (2006) found OMT patients to be generally slower at recognizing emotions compared to healthy controls, but with the exception of facial expressions of disgust, which OMT patients recognized with significantly higher accuracy. As the authors suggest, “this may reflect increased exposure to other people’s expressions of disgust and/or priming by the physical and social environments encountered by opiate-dependent individuals” (Martin et al., 2006, p. 1598). A study with patients who were simultaneously addicted to heroin and nicotine compared them after a minimum of three months of heroin abstinence with nicotine dependent patients and healthy controls and found decreased connectivity in the PFC during the Reading the Mind in the Eyes Task (RMET), a measure for affective ToM (Ieong & Yuan, 2018). To this date, only one study assessed ToM beyond its affective components in opioid dependent patients. Gandolphe et al. (2018) conducted an exploratory study, assessing ToM in 29 opioid dependent patients and an equal number of healthy controls both with a movie paradigm and a semi-structured interview. ToM performance in both measures was significantly lower in opioid dependent patients

compared to the control group. These impairments appeared to be unassociated with onset and duration of substance abuse or duration of abstinence.

1.5 Possible influences on theory of mind in opioid addiction

Few studies explore which factors might impact ToM performance and impairments in opioid dependence, or SUDs in general. In their review, Sanvicente- Vieira et al. (2017) suggest neuroadaptations in brain regions relevant for ToM (namely the insula and PFC) as a result of drug abuse as a possible neurobiological basis for ToM deficits in SUDs. The ventromedial and dorsomedial PFC as well as the anterior insula are brain regions which have also been associated with EF in meta-analytic studies (Wade et al., 2018). Similarly as in insight into illness, EF have been linked to ToM in multiple studies, spanning from developmental psychology to psychiatric research. In preschool children, the development of EF and ToM appear to be linked, with inhibitory control seemingly playing a central role (Carlson et al., 2015; Carlson et al., 2004; Carlson & Moses, 2001). In children with autism, a condition widely associated with impaired ToM, correlations between ToM and EF have been shown (Kouklari et al., 2018; Pellicano, 2007). In adults, age related changes in ToM also correlate with EF (Bailey & Henry, 2008; German & Hehman, 2006). Again, inhibitory control is indicated to be especially relevant to these changes in ToM (Bailey & Henry, 2008). On the other hand, studies with conflicting results exist, e.g. a study by Cavallini et al. (2013), in which EF were not a significant predictor for age-related differences in ToM. Furthermore, some studies on neurological conditions affecting ToM and/ or EF found ToM and EF to be unassociated in patients with multiple sclerosis (Batista et al., 2018), frontal lobe lesions (Rowe et al., 2001) as well as in a case study on a patient with amygdala damage (Fine et al., 2001). These conflicting findings can potentially be explained by the different cognitive mechanisms which are at work to varying degrees in different ToM tasks as shown in a study using various ToM tasks (Ahmed & Miller, 2011.) This could signify that the involvement of and correlation with EF somewhat depends on the specific task used to assess ToM in a study (Ahmed & Miller, 2011). In a review on the relationship between ToM and EF, the authors infer that “separable neurobiological mechanisms likely underlie ToM and EF, with shared mechanisms for domain-general processing that support both abilities” (Wade et al., 2018, p. 2119). EF impairments are not only linked to poor performance in ToM tasks, but, as

pointed out in chapter 1.2.2, opioid users exhibit EF deficits (Ersche & Sahakian, 2007; Gruber et al., 2007; Loeber et al., 2012; Pau et al., 2002; Sanborn et al., 2020), which appear to be a long-term effect rather than a temporary impairment caused by current drug abuse (Ersche et al., 2006). Some studies specifically point towards a relationship between EF and ToM in SUDs. Performance on several ToM tasks was positively correlated with EF in a sample of alcohol dependent patients (Thoma et al., 2013). Another study found associations between second order ToM performance and EF in alcohol dependence (Maqbool & Sengar, 2019). In opioid dependent patients with a comorbid nicotine dependence, emotion recognition was found to correlate with inhibitory control (Ieong & Yuan, 2018).

Another factor that might relate to ToM impairments in opioid dependence is childhood maltreatment. The term childhood maltreatment includes physical, emotional and sexual abuse as well as physical and emotional neglect (Teicher & Samson, 2013). Abuse and neglect in childhood cause a profuse stress response, which can be the source of structural, biochemical and functional cerebral alterations (Glaser, 2000). A robust body of research links childhood maltreatment to changes in social cognition. For example, children and adolescents who had previously been maltreated were shown to be delayed in the development of social perspective taking skills compared to peers who had not experienced maltreatment (Burack et al., 2006). Childhood maltreatment correlates with ToM alterations in children (Benarous et al., 2015) and adults (Germine et al., 2015). ToM deficits have been detected in female PTSD patients who had been traumatized in childhood (Nazarov et al., 2014). Rnic et al. (2018) examined childhood trauma and emotion recognition in young adults with clinical depression and healthy controls and found poor performance on the RMET to be correlated with emotional abuse in the clinical group and with physical abuse in the control group. Childhood neglect however was associated with better emotion recognition in both groups. In patients with chronic depression, activation of the amygdala during an affective ToM task was found to be modulated by childhood maltreatment, whereas the pathophysiological correlates of depressive symptoms did not seem to play a relevant role (Hentze et al., 2016). Experiencing maltreatment as a child poses an increased risk for developing a SUD later in life (Afifi et al., 2020; Douglas et al., 2010; Dube et al., 2003; Kendler et al., 2000; Kirsch et al., 2020). Compared to cocaine- and nicotine dependent

patients, opioid dependent patients most likely have experienced childhood trauma (Lawson et al., 2013). In a sample of OMT patients treated with buprenorphine, only 19.5% reported no form of maltreatment in childhood (Sansone et al., 2009). A recent study reported prevalences ranging between 16% for sexual abuse (in males) and 43% for emotional abuse in opioid dependent individuals (Santo et al., 2021). In a study with OMT patients, 29 % of the sample was diagnosed with PTSD. Even when controlling for PTSD diagnosis, depression and gender, trauma-related symptoms correlated with heavier drug abuse (Clark et al., 2001). A recent study observing an opioid-addiction-like phenotype in rats exposed to adversaries early in life also appears to attest to childhood maltreatment playing a part in increasing vulnerability to opioid dependence (Levis et al., 2021). As childhood maltreatment has been shown to be highly prevalent in opioid dependent individuals and has been linked to ToM impairments in multiple studies, it could be a relevant factor for the constitution of ToM in opioid dependence.

1.6 Aims and research questions

In summary, insight into illness and ToM share awareness as a common core and have been shown to be impaired in SUDs in general as well as specifically in opioid dependent patients. However, there is a lack of research examining both constructs and the potential influences on their impairment in opioid dependence. The previously presented body of literature indicates that impaired insight could possibly be associated with ToM deficits, as well as EF and self-stigma. As for ToM impairments in opioid dependent patients, EF and childhood maltreatment present themselves as possible influential factors when reviewing related literature.

The overarching scope of this dissertation is to gain a better understanding of processes of awareness of self and others in opioid dependent patients. Two studies will be presented in order to serve this purpose. The goal of the first study is to replicate findings of ToM impairments in opioid dependent patients and to explore potential influential factors on ToM in opioid dependence. The performance in a ToM task with high ecological validity in a sample of OMT patients was compared to data from healthy controls. Additionally, patients were assessed regarding EF, substance use related variables and self-reported

childhood maltreatment, in order to explore the relationships between these factors and ToM in opioid dependence. The second study of this dissertation aims to examine insight in opioid dependence and shed light on its relationship with potential influential factors representing the deficit and nondeficit approach as well as the cognitive neuropsychological perspective. Insight into illness was assessed in a sample of OMT patients and examined regarding its relationship to EF, self-stigma and ToM. Subsequently, the results of both studies will be discussed together regarding their theoretical and clinical implications as well as starting points for future research.

2 STUDY 1 Exploring influences on theory of mind in opioid dependent patients[1]

2.1 Abstract

Theory of mind (ToM) is an aspect of social cognition impaired in different addictive disorders, including opioid addiction. This study aimed at replicating ToM deficits in opioid dependent patients undergoing opioid maintenance treatment (OMT) and exploring the influence of substance use related variables, executive functions and childhood maltreatment on ToM in opioid dependent patients. 66 opioid dependent patients were tested using the Movie for Assessment of Social Cognition (MASC) and compared with the data of healthy controls. Furthermore, the opioid dependent patients underwent testing for executive functions and filled in the Childhood Trauma Questionnaire (CTQ). Performance on the MASC was significantly poorer in the opioid dependence group than in the control group, even when recent additional drug use and psychiatric comorbidities were controlled for. No correlations were found between ToM and substance use related factors. Aspects of ToM performance in opioid dependent patients correlated significantly with different EF domains. ToM correlated significantly with the CTQ scales for physical maltreatment. The results confirm impaired ToM in opioid dependent patients and highlight executive functions and childhood maltreatment as influential factors. The lack of associations between ToM and substance use related variables and the association with childhood maltreatment suggest that ToM impairments might be a risk factor predating substance abuse.

2.2 Introduction

Theory of Mind (ToM) describes the attribution of mental states to oneself and others. It includes the ability to make inferences about other people's thoughts, emotions,

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knowledge, expectations, desires, ideas and intentions. These social-cognitive processes play a huge role in human social interactions (Goldman, 2012). Impairments in ToM abilities have been shown in patients suffering from schizophrenia (Bora et al., 2009), bipolar disorder (Montag et al., 2010), autism spectrum conditions (Baron-Cohen, 2001; Martinez et al., 2017) and Huntington's disease (Eddy et al., 2014). So far, studies examining the relationship between impaired ToM and other outcome variables have mostly been conducted in the field of schizophrenia research. In schizophrenic patients, a limited ToM capability was shown to be the best predictor for poor social competence (Brune et al., 2007). ToM impairments have been associated with limited insight into illness (Bora et al., 2009) and poor quality of life (Maat et al., 2012) in schizophrenic patients. As demonstrated by these examples, ToM is a construct that may have an impact on health factors beyond social reciprocity and is therefore worth studying in other illnesses that affect the brain, e.g., psychiatric illnesses, other than schizophrenia. For patients with substance use disorders (SUDs), numerous studies demonstrate impairments in social cognition. For example, studies with cannabis users were able to show alterations in the physiological response in tasks requiring empathy and ToM (Platt et al., 2010; Roser et al., 2012; Troup et al., 2016). ToM deficits have been found in cocaine users (Hulka et al., 2013; Preller et al., 2014) and methamphetamine users (Henry et al., 2009; Kim et al., 2011). Studies researching patients with polysubstance abuse demonstrate correlations between ToM impairments and the number of consumed substances (Kroll et al., 2018) as well as structural alterations in the orbitofrontal cortex (OFC) and anterior cingulate cortex (ACC). Both are structures associated with ToM and empathy (Abu-Akel & Shamay-Tsoory, 2011; Meyerhoff, 2017). Patients in opioid maintenance treatment (OMT) exhibit impairments in social perception such as reading facial expressions (Kornreich et al., 2003; McDonald et al., 2013), a construct linked closely to ToM (Teufel et al., 2010). An exploratory study (Gandolphe et al., 2018) comparing ToM data from a semi-structured interview and a movie paradigm in 29 opioid dependent patients and an equal number of healthy controls found that opioid dependent patients' performance was significantly lower in both ToM measures. However, there is still a lack of research exploring ToM deficits in opioid dependence and which factors might have an impact on ToM performance in opioid dependent patients.

2.2.1 Executive functions

The relationship of ToM and executive functions has been studied in the field of developmental psychology as well as in regards to clinical populations. A recent meta-analysis (Thibaudeau et al., 2020) reported associations between ToM and executive functions in patients diagnosed with schizophrenia. Children with autism exhibit deficits in both ToM and executive functions, and those deficits appear to be associated (Kouklari et al., 2018; Pellicano, 2007). Studies conducted with healthy preschool children demonstrate a link in the development of ToM and executive functions. Specifically, a strong link between inhibitory control and ToM was shown (Carlson et al., 2015; Carlson et al., 2004; Carlson & Moses, 2001), with stronger correlations between ToM and conflict tasks, in which a dominant response had to be inhibited, compared to delay tasks, which required the delay of a response. Studies examining ToM in adults have found correlations between executive functions and age related changes in ToM performance in older adults, some also highlighting the relevance of inhibitory control (Bailey & Henry, 2008; German & Hehman, 2006). However, whilst the majority of publications suggest a link between executive functions and ToM, some studies show conflicting results. In a study by Cavallini et al. (2013), executive functions did not predict age related ToM differences. Studies examining specific neurological conditions have found a disconnect between ToM and performance in executive functions in affected individuals [amygdala damage: case study by Fine et al. (2001); frontal lobe lesions: Rowe et al. (2001); multiple sclerosis: Batista et al. (2018)]. Ahmed and Miller (2011) offer an explanation for the varying results. In their study examining the relationship between ToM and executive functions using different ToM tasks, they suggest that different ToM tests are using different cognitive mechanisms, which may indicate that the ToM test used has an influence on the involvement of different components of executive functioning. Research shows a link between opioid addiction and executive function impairments (Gruber et al., 2007; Pau et al., 2002). These impairments appear to be not just a temporary effect of current drug use, but indeed a long-term effect which is still detectable after several years of abstinence (Ersche et al., 2006). Opioid agonists used in OMT have been linked to impaired executive functions (Butler & Le Foll, 2019). The duration of opioid maintenance therapy and the consumption of additional substances have previously been identified as the main factors influencing

cognitive functioning, including executive functions, in opioid addicts (Loeber et al., 2012). As deficits in executive functions have been linked to ToM impairments as well as opioid addictions, we hypothesized that ToM performance is associated with executive functions in opioid dependent patients.

2.2.2 Childhood maltreatment

Childhood abuse and neglect are a potent source of stress and can lead to biochemical, structural and functional cerebral changes as a result of the stress response (Glaser, 2000). Numerous studies have examined the effects of childhood trauma on social cognition. In a study by Burack et al. (2006), children and adolescents who had experienced maltreatment exhibited delayed development of social perspective-taking abilities compared to non-maltreated peers. A link between childhood abuse and ToM impairments has been found in clinical and non-clinical samples. For example, women suffering from PTSD resulting from childhood abuse exhibit ToM deficits (Nazarov et al., 2014). In a study exploring ToM and childhood trauma in depressive patients and healthy controls, there was a correlation between ToM and emotional abuse in depressive patients and a correlation between ToM impairments and physical abuse in the control group. Childhood neglect however was positively associated with ToM in both groups (Rnic et al., 2018). In a sample of chronically depressed patients, amygdala activation during affective ToM tasks was largely modulated by childhood maltreatment and not by pathophysiological correlates of depressive symptoms (Hentze et al., 2016). In schizophrenic patients, ToM impairments have been associated with physical neglect during childhood (Mrizak et al., 2016) and childhood trauma has been related to alterations in brain functioning during a ToM task (Quide et al., 2017). In non- clinical groups, childhood maltreatment has been linked to ToM alterations in both children (Benarous et al., 2015) and adults (Germine et al., 2015). Adverse childhood events are a risk factor for substance dependence (Douglas et al., 2010; Dube et al., 2003; Kendler et al., 2000). Comparing nicotine-, cocaine-, and opioid dependent patients, the latter exhibit the highest prevalence of lifetime traumatic events (Lawson et al., 2013). In a sample of 150 patients in methadone substitution treatment, 29% of patients met the diagnostic

criteria for PTSD. Trauma-related symptoms were associated with more severe substance abuse (Clark et al., 2001). Regarding trauma and adversities occurring in childhood, there is a high prevalence of reported childhood maltreatment in opioid dependent patients (Conroy et al., 2009). In a sample of 113 opioid dependent patients undergoing buprenorphine treatment, only 19.5 % reported not having endured any form of childhood trauma (Sansone et al., 2009). Considering the high prevalence of childhood trauma in opioid dependent patients and the evidence indicating an association between childhood maltreatment and ToM, we hypothesized that ToM and experiences of childhood maltreatment are correlated in opioid dependent patient.

In this study, we aimed to gain a better understanding of ToM in opioid dependent patients undergoing opioid substitution treatment. Firstly, we wanted to see if the ToM deficits reported by Gandolphe et al. (2018) could be replicated in our sample. Furthermore, we wanted to explore potential factors influencing ToM in opioid dependent patients. With this goal in mind, we tested patients' performance in executive functions tasks and collected data on childhood maltreatment, measures of psychological well-being and substance use related factors.

2.3 Methods

2.3.1 Participants

A sample of 66 opioid dependent patients undergoing opioid maintenance treatment (OMT) were recruited from three psychiatric outpatient centers in Mannheim, Germany. Study participation was voluntary and all participants provided written informed consent prior to participation. The study was approved by the ethics committee of the Medical Faculty Mannheim, Heidelberg University, Germany (AZ: 2018-531N-MA).

In order to compare ToM performance between opioid dependent patients and healthy individuals, a control group was generated from the data sample of healthy controls provided by Montag et al. (2011) to match our sample of opioid dependent patients in age (+/– 3 years) and sex. For 17 out of 66 participants, it was not possible to

find a match that met the criteria. For those participants, the closest respective match was selected from the sample. The resulting sample did not significantly differ from our sample of opioid dependent patients in age [$t(130) = 0.96$, $p > 0.05$] or sex [$\chi^2(1) = 2.59$, $p > 0.05$). The groups differed significantly in the level of education (see Table 1). However, the level of education was not associated with ToM performances in neither [opioid dependent patients: $F(3, 62) = 2.72$, $p > 0.05$; healthy controls: $F(2, 55) = 2.82$, $p > 0.05$]. Therefore, we considered this an acceptable difference between opioid dependent patients and control group. Demographic data are presented in Table 1.

Table 1

Demographic characteristics of study participants

	OMT patients (*n* = 66)	Healthy controls (*n* = 66)	Value	*p*
Sex				
Male	68.2% (*n* = 45)	54.5% (*n* = 36)	$\chi2(1) = 2.59$	.08
Female	31.8% (*n* = 21)	45.5% (*n* = 30)		
Age	*M* = 43.38, *SD* = 8.62	*M* = 41.22, *SD* = 10.51	$t(130) = 0.96$	.34
School degree	15.2% no degree	0% no degree	$\chi2(3) = 41.38$	<.001
	51.5% Hauptschule[a]	13.6 % Hauptschule[a]		
	25.8 % Realschule[b]	30.6% Realschule[b]		
	7.6 % Abitur[c]	43.9% Abitur[c]		
Years of heroin abuse	*M* = 14.29, *SD* = 8.44	-		
Opioid substitution				
methadone	34.8 % (*n* = 23)			
polamidon	33.3 % (*n* = 22)			
buprenorphine	30.3 % (*n* = 20)			
retarded morphine	1.5 % (*n* = 1)			
Take home prescription[d]	72.7 % no (*n* = 48)			
	27.3 % yes (*n* = 18)			
Additional substance abuse				
none	12.1 % (*n* = 8)			
heroin	15.2% (*n* = 10)			
cocaine	9.1 % (*n* = 6)			
cannabis	34.8 % (*n* = 23)			
benzodiazepines	25.8 % (*n* = 17)			
alcohol	10.6% (*n* = 7)			

pregabalin	10.6% (*n* = 7)
amphetamine	7.6% (*n* = 5)
Relevant psychiatric comorbidities	
Borderline personality disorder	9,2 % (*n* = 14)
Bipolar disorder	1,3 % (*n* = 2)
Psychotic disorders	4 % (*n* = 6)

Notes.

a German high school degree attained after 9 years

b German high school degree attained after 10 years

c German high school degree attained after 13 years

d Patients with stable abstinence of any other substances than the prescribed OMT dose are eligible to visit the clinic only once per week and get a subscription for taking their daily dose at home. This is referred to as "Take Home".

2.3.2 Procedure

During a first appointment, opioid dependent patients were screened for psychiatric diagnoses using the German translation of the Structured Clinical Interview for the DSM (Wittchen et al., 1997). The screening was conducted by trained clinical staff. Patients were interviewed about current substance use and history of addiction. Additionally, substance use was regularly evaluated by urine screenings in the outpatient centers. Patients filled in the trauma questionnaire during this first appointment. The ToM task and neuropsychological assessments were conducted on a separate day to ensure that the appointment was not too long for patients to keep up their level of concentration.

2.3.3 Measures

ToM performance was tested using the Movie for the Assessment of Social Cognition [MASC: (Dziobek et al., 2006)]. The MASC consists of a 15 min long movie about four protagonists getting together for a dinner party. The video is paused 45 times and participants are presented with questions aiming at the protagonists mental states. The administration of the MASC took approximately 45 min per participant. The items cover

various aspects of social cognition, including emotions of different valence, thoughts, intentions, first and second order false beliefs, irony and faux pas. Participants have to take verbal content and intonation, facial expressions and body language into account, which contributes largely to the ecological validity of the MASC. The questions are posed in a multiple choice format with four answer options. For each question, the answer options are categorized in the following way: “correct ToM” (correct mental state inferences), “no ToM” (the answer is not related to mental states), “exceeding ToM” (overmentalizing; over-interpretative mental state inferences) and “low ToM” (insufficient, overly simplified mental state inferences). Six additional questions that are unrelated to ToM are used as an attention control. Scores for “cognitive ToM” (inferences about thoughts and intentions, 27 items) and “emotional ToM” (inferences about emotions, 18 Items) were calculated in addition to the total score. Chronbach’s α for the MASC is reported at 0.84 (Dziobek et al., 2006).

A short neuropsychological tests battery for examining executive functions was administered on a computer. Before each task, the examiner explained the task to the participant and was available to clarify any remaining questions to ensure participants’ understanding of the tasks. The administration of all tasks took approximately 15 min.

Delay Task: The five-trial adjusting delay task (Koffarnus & Bickel, 2014) is a short version of the delay discounting task. Participants were confronted with five choices between money available now and a larger amount of money available after a delay. Depending on the participant’s choice on the first trial, the time delay on the following trials is adjusted up or down. The dependent measure for this task is the discount rate k, which indicates how much the value is affected by the delay. A higher discount rate indicates a higher depreciation of delayed rewards.

Dimensional Change Card Sort [DCCS, (Zelazo et al., 2014)]: This task was implemented to test participants’ cognitive flexibility. Participants have to switch between sorting bivalent stimuli according to the criteria of shape and color using the left and right arrows on the keyboard. The resulting score is based on an algorithm taking both accuracy and reaction time into account. For detailed information on score calculation, see Zelazo et al. (2014). The DCCS has a good test-retest reliability at ICC = 0.85 (61).

Stop Signal Task [SST, (Sebastian et al., 2013)]: This is a task for measuring response inhibition. Participants were instructed to push the right arrow key as fast as possible when a square appeared on the screen and the left arrow key when a circle appeared on the screen. However, when the shape appeared and changed color from blue to orange after 300 ms, they were instructed not to press any key and had to suppress the initial motoric response. Of the 150 randomized trials, 30 were stop-trials. As outcome variables we used the number of false alarms (pressing the key in a no go trial) and the stop signal reaction time (SSRT). The latter is a measure for the latency of the stop process and is estimated by subtracting the mean stop-signal delay from the median reaction time on go trials. A meta-analysis found the reliability of the SSRT measure to be good with an average ICC of 0.71 (Congdon et al., 2012).

Childhood maltreatment was assessed using the German translation of the Childhood Trauma Questionnaire (CTQ), a self-assessment instrument with five scales differentiating between physical and emotional abuse and neglect as well as sexual abuse. The internal consistency for the CTQ is reported at Chronbach's $\alpha = 0.94$ (Wingenfeld et al., 2010).

2.3.4 Statistical Analysis

Statistical analyses were carried out as indicated in the results section using IBM SPSS Statistics 25 for Windows. Results were regarded as significant when the two-sided p-value was below 0.05. For the group comparison of ToM performance on the MASC, Mann-Whitney U-tests and multiple regression analyses were conducted. To explore associations between ToM performance, substance use related variables, executive functions and the CTQ, Pearson's correlations were administered. In this part of the analysis, only the data of the opioid dependent patients were analyzed, as the relevant data beyond MASC performance was not available for the control group.

2.4 Results

2.4.1 Group characteristics

Opioid dependent patients and control group did not differ significantly with regards to sex [$\chi^2(1) = 2.59$, $p > 0.05$] or age [$t(130) = 0.96$, $p > 0.10$]. The level of education differed significantly between the two groups [$\chi^2(3) = 41.38$, $p < 0.001$], with more participants of the control group having achieved higher educational degrees than of the opioid dependent group.

2.4.2 ToM performance

As MASC scores were not normally distributed in the control group, non-parametric tests were applied to analyze for group differences. To avoid alpha-inflation due to multiple testing, p- values were adjusted using the Bonferroni correction. Mann- Whitney U-tests revealed significantly lower MASC scores overall as well as for cognitive and emotional ToM scores and all three error scores (no ToM, exceeding ToM, low ToM) in the opioid dependent group (see Table 2).

Table 2

Descriptive statistics for MASC scores in opioid dependent patients and control group and group comparison with Mann-Whitney *U*-test. P-values were adjusted using Bonferroni correction.

MASC variables	Opioid patients (*n* = 66)		Healthy controls (*n* = 66)		Mann- Whitney- U- Test	
	M	SD	M	SD	U- value	p
Total score	27.29	5.21	33.64	3.65	781.5	<.001
Cognitive ToM	16.56	3.60	20.41	2.57	842	<.001
Emotional ToM	11.23	2.49	13.23	1.56	1185	<.001
Exceeding ToM	7.05	3.05	4.59	2.36	1315	<.001
Low ToM	6.58	3.34	4.41	2.44	1322.5	<.001
No ToM	3.59	2.63	2.02	1.32	1401	<.01

In a subanalysis, opioid dependent patients with comorbid diagnoses that might affect ToM, that is, bipolar disorder, borderline personality disorder, and history of psychotic disorders were excluded, as well as patients who might be under the influence of substances. Here we used clinical intoxication at the time of testing or urine test positive for benzodiazepines or pregabalin on the testing day. In this subanalysis the difference in MASC scores remained statistically significant ($p < 0.001$).

A multiple linear regression analysis was conducted to predict MASC total scores based on group (opioid dependent patients or control group), sex, age, level of education and the number of correct control questions in the MASC using the enter method. A significant regression equation was found [$F(5, 115) = 19.917$, $p < 0.001$]. The R^2 for the overall model was 0.46 (adjusted $R^2 = 0.44$), indicative for a high goodness-of-fit according to Cohen (1988). Group ($B = 2.51$, $p < 0.01$), age ($B = -0.12$, $p < 0.01$), level of education ($B = 1.34$, $p < 0.01$) and the number of correct control questions ($B = 1.36$, $p < 0.01$) all contributed significantly to the model. Sex did not contribute significantly to the model ($B = 1.3$, $p = 0.09$). A multiple linear regression using the forward selection method revealed that group (opioid dependent patients vs. healthy controls) was the predictor that could explain the most variance of MASC total scores on its own (adjusted $R^2 = 0.28$). See Table 3 for model summary.

Table 3

Multiple linear regression predicting MASC total scores using the forward selection method.

Model	Predictors	R^2	Adjusted R^2	Std. error of the estimate	*F*	*P*	β	Sig. of coefficients
1	Group	0.28	0.28	4.59	47.32	<0.001	0.53	<0.001
2	Group	0.36	0.35	4.36	33.52	<0.001	0.40	<0.001
	Correct control questions						0.31	<0.001
3	Group	0.41	0.40	4.19	27.82	<0.001	0.37	<0.001
	Correct control questions						0.32	<0.001
	Age						−0.23	0.001
4	Group	0.45	0.43	4.08	23.8	<0.001	0.25	0.005
	Correct control questions						0.30	<0.001
	Age						−0.20	0.005
	Level of education						0.23	0.008

2.4.3 ToM and variables related to substance abuse

There was no statistically significant difference in MASC total scores for the different substitution substances (methadone, polamidon, buprenorphine), $F(2, 62) = 2.02$, $p = 0.142$. It did not have a significant effect on MASC scores if patients consumed additional psychoactive substances ($U = 168$, $p = 0.54$), had a Take Home prescription ($U = 368.5$, $p = 0.36$) or which substances they consumed. Based on the calculated Pearson's correlation coefficients, there were no significant correlations between MASC scores and number of consumed substances ($r = 0.2$, $p = 0.15$), the number of years of heroin use ($r = -0.08$, $p = 0.55$) or the number of years in OMT ($r = -0.02$, $p = 0.89$).

2.4.4 ToM and executive functions

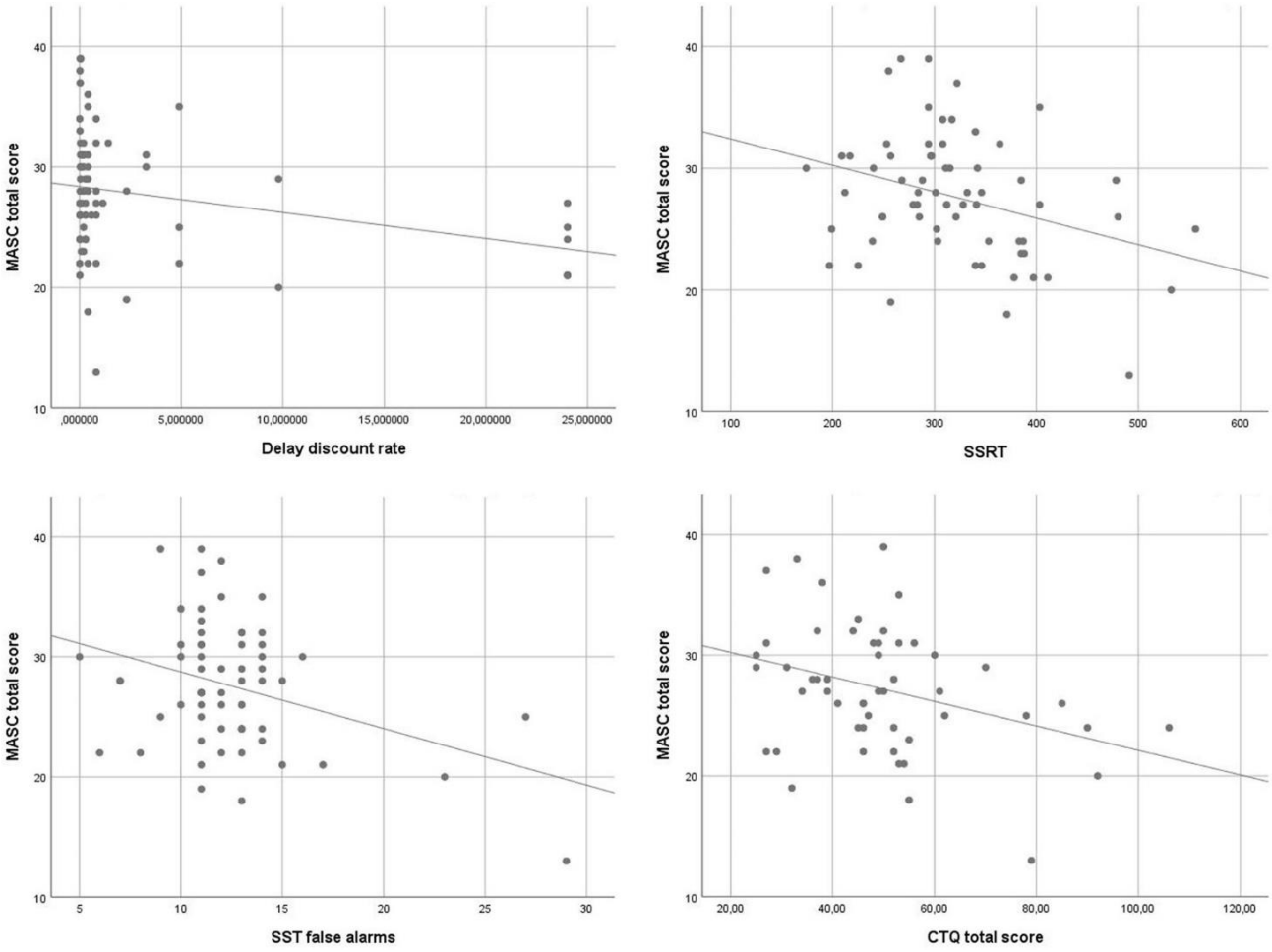
To identify associations of ToM and executive functions, an exploratory analysis using Pearsons correlations was performed. MASC total scores correlated inversely with the delay discount rate ($r = -0.27$, $p < 0.05$), SSRT ($r = -0.33$, $p < 0.01$) and the number of false alarms in the SST ($r = -0.35$, $p < 0.01$). Furthermore, the emotional ToM score correlated inversely with SSRT ($r = -0.40$, $p < 0.01$) and the number of false alarms ($r = -0.39$, $p < 0.01$). The cognitive ToM score correlated inversely with the delay discount rate ($r = -0.25$, $p < 0.05$). Scatterplots of the main findings are depicted in Figure 2.

2.4.5 ToM and childhood trauma

For the exploratory analysis of associations of ToM and childhood trauma also Pearsons correlations were performed. All p-values shown are corrected for multiple testing. The CTQ total score correlated inversely with the MASC total score ($r = -0.34$, $p < 0.05$) and the cognitive ToM score ($r = -0.35$, $p < 0.05$). The physical abuse scale correlated inversely with the MASC total score ($r = -0.27$, $p < 0.05$). The physical neglect scale correlated inversely with the MASC total score ($r = -0.30$, $p < 0.05$) and cognitive ToM ($r = -0.30$, $p < 0.05$). The remaining CTQ scales emotional abuse, emotional neglect and sexual abuse did not significantly correlate with the MASC.

Figure 2

Scatterplots of correlations between MASC score, executive functions and CTQ.



2.5 Discussion

The present study investigated ToM in opioid dependent patients undergoing OMT as well as possible influences on it. The first important result is the confirmation of poorer ToM performance in opioid dependent patients compared to healthy controls. This is in line with the findings of Gandolphe et al. (2018). As the group difference was stable when controlling for the influence of other substance consumption and comorbid psychiatric diagnoses that might affect ToM, it seems like the found ToM deficits are associated with opioid

dependence itself and not just due to the influence of intoxication or psychiatric comorbidities common in opioid users.

Substance use related variables like the substance used for OMT, duration of OMT, onset of opioid dependence, use and duration of use of non-opioidergic drugs, and eligibility for a Take Home prescription were not associated with ToM performance in the MASC in our sample. Again, this finding is reflected in the results of Gandolphe et al. (2018), who found no link between patients' ToM abilities and substance use related variables (duration of substance abuse, age at onset of substance abuse and duration of abstinence). The authors interpret this as an indicator for ToM deficits predating substance abuse, highlighting ToM impairments as a suspected risk factor for substance abuse. For example, it might be possible that ToM deficits lead to more interpersonal problems and social stress resulting in increased substance use. As Gandolphe et al. (2018) suggest, ToM deficits and their implication should be prioritized in the rehabilitation of opioid dependent patients.

The contribution of this study beyond the replication of previous findings is the exploration of possible influential factors on ToM in opioid dependent patients. Investigating the relationship between ToM and components of executive functioning, we found that MASC total scores correlated significantly with measures for delay discounting and response inhibition. The correlations were negative, indicating that opioid dependent patients who rejected delayed rewards at a higher rate and who had poorer inhibitory control exhibited weaker ToM. The DCCS score did not significantly correlate with any of the MASC scores, suggesting that set shifting does not play an important role in ToM performance. The SST variables correlated with the emotional ToM scale, whereas the delay discount rate correlated with the cognitive ToM scale. This result suggests that response inhibition plays a significant role in emotional ToM, but not in cognitive ToM. Furthermore, delay discounting appears to be associated with cognitive, but not emotional ToM. Different studies suggest a dissociation between cognitive and emotional ToM (Kalbe et al., 2010; Schlaffke et al., 2015; Shamay-Tsoory & Aharon-Peretz, 2007). Our findings seem to support the idea of different cognitive processes underlying cognitive and emotional theory of mind.

Regarding the relationship between ToM and childhood maltreatment, we found that the CTQ total score as well as both scales for physical maltreatment (physical abuse and physical neglect) were inversely correlated with the MASC total score. Higher scores on the CTQ and the aforementioned scales were associated with weaker ToM performance. This appears to be in line with the findings of Mrizak et al. (2016), who reported a link between physical neglect in childhood and ToM deficits in schizophrenic patients. The role of physical childhood maltreatment in the ToM performance of opioid dependent patients suggested by this result appears noteworthy. It may be an indication that ToM impairments in opioid dependent patients suffering from childhood maltreatment are not due to emotional neglect, i.e., less opportunities for practicing certain aspects of social cognition, but rather suggests that influences of physical abuse and neglect (e.g., violent impacts to the head, malnourishment) on brain development may be at the core of the relationship between childhood trauma and ToM. Another explanation might be that physical and emotional childhood abuse and neglect often occur together. It is hard to imagine that a child who is abused on a physical level is simultaneously receiving the necessary emotional care and attention to the full extent. This assumption is backed by research: Adverse childhood events have been shown to be interrelated, with adults who reported one form of adverse childhood experience were likely to have experienced other forms as well (Dong et al., 2004). Claussen and Crittenden (1991) found that most children experiencing physical maltreatment experienced psychological maltreatment as well and that the latter was a better predictor for negative outcomes than the severity of physical injury. Emotional abuse however is more likely to go under-identified by the person affected by it (Goldsmith & Freyd, 2005) as well as by other people (Claussen & Crittenden, 1991). In this light, it can be assumed that patients who reported physical abuse and neglect in the CTQ might also have experienced forms of emotional abuse and neglect, but may not have reported it in the questionnaire to the full extent. Therefore, it can be argued that the correlation between physical maltreatment and ToM in our sample of opioid dependent patients may not be due to the isolated effects of physical maltreatment, but also might be influenced by concurrent emotional maltreatment.

As childhood trauma can influence the development of executive functions (Zelazo, 2020), it can be hypothesized that the correlations we found between executive functions

and ToM in opioid dependent patients might be mediated by childhood maltreatment. A mediator analysis with a larger sample of opioid dependent patients investigating the relationship between ToM, executive functions and childhood maltreatment might help to bring further understanding of this matter. Furthermore, longitudinal studies examining the relationship between childhood maltreatment, executive functions, ToM and addiction would be an important step toward understanding how these factors play into each other.

In addition to executive functions, another relevant factor of cognitive functioning impacting ToM in opioid dependent patients could be intelligence. Correlations between measures of executive functioning and fluid intelligence have previously been reported (Diamond, 2013). Studies have linked ToM performance to general intelligence (Coyle et al., 2018), however, it is not fully clear how much of this association may be due to the language based nature of ToM tasks (Navarro et al., 2021). Further research examining the relationship between ToM, executive functions and intelligence are needed to gain a deeper understanding of influences on impaired ToM in patients with SUDs.

Another perspective for future research could be the examination of the relationship between ToM and substance use related factors, executive functions and childhood trauma in other SUDs. Bosco et al. (2014) found that the duration of alcohol abuse correlated negatively with ToM performance in alcohol dependent patients, suggesting brain damage due to the neurotoxic effects of alcohol to be a relevant factor for ToM impairment in this population. This differs notably from our finding, which might indicate different mechanisms underlying ToM impairment in opioid dependent patients and alcohol dependent individuals. Exploring and comparing influential factors on ToM in abusers of different substance groups in future research could be very beneficial to the understanding of the processes underlying social-cognitive impairments in SUDs.

The present study has some limitations that need to be mentioned. Firstly, the opioid dependence group and control group were not an identical match regarding age

and sex. However, those differences were not of statistical significance. Furthermore, the groups did significantly differ in education. As we found no significant association between the level of education and ToM in either group, we concluded that the intended comparison of ToM between the groups would still be valid. Aside from that, the participants of the control group were tested in a different institution a number of years before the testing of our sample of opioid dependent patients. As there is no literature reporting cohort effects of ToM or social cognition in general, we considered this not to be a hindrance to the comparison of ToM performance between the groups. Also, the fact that the outcome in this study reflects what Gandolphe et al. (2018) found in their sample points toward the validity of our group comparison. Therefore, we consider the group comparison of ToM between opioid dependent patients and healthy controls in this study to be cogent despite the described differences between the groups. Nonetheless, a comparison between ToM in opioid dependent patients and perfectly matched healthy controls in identical testing conditions would be desirable. Another potential limiting factor in this study is that a substantial percentage of the opioid dependent patients in our sample were also consuming substances other than opioids and/or had comorbid psychiatric diagnoses. One could therefore argue that group differences and correlations found in this study are not necessarily related to opioid addiction and opioid maintenance treatment per se, but might be related to other mental health and addiction variables. However, we did control for these factors in our group comparison analyses. Although it would have been possible to only recruit opioid dependent patients with no comorbidities and no additional substance use, these patients represent a minority of the population of opioid dependent patients. It was important to us to examine a representative sample of opioid dependent patients, which in our opinion enables more of a generalization of our findings to opioid dependent patients beyond our specific sample than it would be possible with the exclusion of comorbidities and other substance use.

In summary, the present study was able to confirm ToM deficits in opioid dependent patients in comparison with healthy controls and was the first to explore the influence of executive functions and childhood maltreatment on ToM in opioid dependent patients. And although there are certain limitations to this predominantly exploratory

study, it provides a step toward a better understanding of ToM in opioid addiction. The dissociation of ToM and substance use related variables in combination with the correlations between ToM and childhood maltreatment strongly suggest that ToM impairments are not the mere consequence of opioid use, but may predate substance abuse and pose a risk factor for the development of opioid addiction. The protruding role of physical maltreatment might be a hint toward neurological factors playing a part in the development of ToM impairments in this population. Further research is needed to analyze the directionality of the relationships found in this cross-sectional study, as this could potentially be of interest from a clinical perspective, e.g., for the development of prevention programs targeting victims of physical childhood maltreatment or interventions aiming at the improvement of theory of mind which might contribute to the prevention of opioid addiction.

3 STUDY 2 Exploring impaired insight in opioid addiction[2]

3.1 Abstract

Impaired insight into illness has been demonstrated in patients with different substance dependences, including patients in opioid maintenance treatment (OMT), and has been shown to be of relevance for treatment motivation and outcomes. While influences on insight have been studied in other psychiatric disorders, there is a lack of research into influences on insight in addiction. Our study aimed at exploring the influence of substance use related variables, executive functions (EF), theory of mind (ToM) and self-stigma in OMT patients.

Methods: 59 OMT patients' insight into illness was assessed using a modified version of the Hanil Alcohol Insight Scale (HAIS). Furthermore, patients completed a short EF test battery, a theory of mind test (MASC) and a modified version of the Internalized Stigma of Mental Illness Inventory (ISMI).

Results: 28.8% of participants had poor insight, 69.5% had fair insight and 1.7 % of participants had good insight according to the HAIS. Insight did not significantly correlate with EF, ToM or any substance use related variables. However, we found a negative correlation between self-stigma and intellectual insight in the HAIS. Stigma resistance on the other hand correlated positively with the HAIS total score and intellectual insight.

Conclusions: Our results suggest that the dominant mechanisms influencing insight in opioid dependence may differ from those in psychotic disorders. The relationship between insight and self-stigma and its implications for clinical practice and further research are discussed.

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3.2 Introduction

Impaired insight into (or synonymously unawareness of) illness in the context of psychiatric disorders is characterized by the phenomenon of a patient's denial of or failure to recognize the illness itself, impeded action control and/or social repercussions of the illness. Alongside various neurological conditions, schizophrenia and bipolar disorder, impaired insight is described in the context of substance use disorders (SUDs) (Benyamani & Stöver, 2012; Fischer & Stöver, 2012; Goldstein et al., 2009; Pacini et al., 2013; Rovai & Maremmani, 2011). Few studies linked impaired insight to factors relevant to substance use and treatment. Insight into illness in alcohol dependent patients is associated with readiness to change in the context of addiction therapy (K. M. Kim et al., 2007) and longer periods of abstinence following inpatient treatment (J. S. Kim et al., 2007). According to a study examining patients addicted to cocaine, individuals with impaired insight used more cocaine and exhibited a higher preference for cocaine- associated images in a choice task in comparison to patients with higher awareness of their illness (Moeller et al., 2010). Deficits in self-awareness regarding symptoms of frontostriatal dysfunction have been associated with difficulties upholding treatment motivation in cocaine addicts (Castine et al., 2019). In a study exploring insight into illness in heroin addicts seeking opioid maintenance treatment (OMT), the authors were able to show that the majority of the patients had low insight into their substance use behaviours and that impaired insight was associated with a shorter treatment seeking and addiction history (Maremmani et al., 2012). Considering that OMT requires patients to attend a medical centre at least on a weekly basis in order to receive opioid replacement, the prominence of impaired insight in this population seems especially remarkable. However, despite the various indications to the relevance of insight in addiction for treatment variables, there is a lack of data on what influences impaired insight in individuals with SUDs. In the following paragraphs, possible influential factors on insight into illness based on existing research will be outlined.

3.2.1 Insight and executive functions

In a meta-analysis conducted with data on psychotic patients (Aleman et al., 2006), insight was linked to executive functions (EF), with impairments in set shifting and error

monitoring assuming a special role. EF impairments have previously been linked to opioid addiction (Gruber et al., 2007; Loeber et al., 2012; Pau et al., 2002). These impairments appear to be long-term effects, which are still detectable after several years of abstinence (Ersche et al., 2006). As deficits in EF have been found to be associated with impaired insight into illness as well as opioid addiction, we hypothesized that impaired insight is associated with poor EF performance in opioid dependent patients.

3.2.2 Insight and theory of mind

Theory of Mind (ToM) describes the attribution of mental states to oneself and others. It encompasses the ability to make inferences about other people's emotions, thoughts, ideas, knowledge, expectations, desires, and intentions (Goldman, 2012). Studies with schizophrenic patients have found associations between ToM impairments and poor insight into illness (Bora et al., 2009). This association is unrelated to the severity of symptoms or neuro-cognitive deficits (Konstantakopoulos et al., 2014). ToM impairments have been shown in SUDs (e.g. methamphetamine (Henry et al., 2009; Kim et al., 2011), cocaine (Hulka et al., 2013; Preller et al., 2014) and alcohol (Onuoha et al., 2016)), including opioid addiction (Gandolphe et al., 2018). As impaired ToM has been shown in schizophrenia and opioid dependence and has been linked to impaired insight in schizophrenic patients, we hypothesized that ToM deficits may also play a role in impaired insight in opioid dependent patients.

3.2.3 Insight and self-stigma

Patients with SUDs are more marginalized than patients with other mental disabilities and are perceived as dangerous and blameworthy for their diagnosis (Corrigan et al., 2009). Within the group of SUD patients, in particular individuals who use opioids appear to experience strong stigmatization (Brown, 2015; Frischknecht et al., 2011). OMT patients are often subjected to institutional stigma (Harris & McElrath, 2012). Public stigma can be internalized by people with SUDs resulting in self-stigma. A stage model (Corrigan & Rao, 2012) describes the consecutive process of self-stigma starting with the awareness of public attitudes towards the stigmatised people, followed by agreement with this attitudes

and the application of this stereotypes to oneself as being part of this group resulting in harm to oneself, e.g. by reduced self- esteem. Associations between self-stigma and insight into illness have been shown in patients with severe mental illness (Hasson-Ohayon et al., 2012). In schizophrenia, self-stigma has been found to predict insight into illness (Pruss et al., 2012).

Given the presented interactions of EF, ToM and self-stigma with both insight into mental illness and opioid use disorder, we aimed to gain a better understanding of impaired insight in opioid dependent patients undergoing OMT by exploring the influence of EF, ToM, substance use related variables and self-stigma on insight into illness.

3.3 Methods

3.3.1 Sample

A sample of 59 opioid dependent patients in opioid maintenance treatment (OMT) were recruited from three psychiatric outpatient centres in Mannheim, Germany. Study participation was voluntary and written informed consent was given prior to participation. The study was approved by the ethics committee of the Medical Faculty Mannheim, Heidelberg University, Germany (AZ:2018- 531N-MA). Patients with psychotic disorders or bipolar disorder were excluded from the study. Demographic data are presented in Table 4.

3.3.2 Assessment

Insight into illness was assessed using an adapted version of the Hanil Alcohol Insight Scale (HAIS) (Kim et al., 1998). The HAIS is a self-report measure with 20 items in which participants are asked to respond to statements with “agree”, “not sure” or “disagree”. The items are grouped into seven subscales: “emotional insight”, “intellectual insight”, “acknowledgement of substance use problem”, “acceptance of loss of control”, “abstinence intention”, “social surrounding” and “recognition of treatment necessity”. The HAIS is the only questionnaire to date that was designed to specifically measure insight in substance

dependence (Raftery et al., 2020). Scores vary between -20 and 20 points and allow grouping participants into “poor insight” (-20 -3 points), “fair insight” (4-15 points) and “good insight” (16-20 points). As the HAIS is originally specific to alcohol use, we adapted it for drug abuse by replacing the word “alcohol” with “drugs” in each item. Cronbach’s alpha was 0.64 for this adapted version, the Guttman split-half coefficient was 0.72. “Intellectual insight” was the only subscale with Cronbach’s alpha above 0.6, therefore the other subscales were not considered in the analysis.

Table 4

Demographic characteristics of study participants (N = 59)

Sex	72.9% male (*n* = 43)
	27.1% female (*n* = 16)
Age	*M* = 43.8, *SD* = 8.6
School degree	16.9% no degree
	47.5 % Hauptschule[a]
	28.8 % Realschule[b]
	6.8 % Abitur[c]
Years of heroin abuse	*M* = 14.9, *SD* = 8.4
Agonist opioid treatment	Methadone 37.3 % (*n* = 22)
	Polamidon 32.2 % (*n* = 19)
	Buprenorphine 28.8 % (*n* = 17)
	Retarded Morphine 1.7 % (*n* = 1)
	Take Home prescription[d] 27.1 % (*n* = 16)
Additional substance use	None 13.6 % (*n* = 8)
	Heroin 13.6 % (*n* = 8)
	Cocaine 8.5 % (*n* = 5)
	Cannabis 37.3 % (*n* = 22)
	Benzodiazepines 23.7 % (*n* = 14)
	Alcohol 11.9% (*n* = 7)
	Pregabalin 10.2% (*n* = 6)
	Amphetamines 6.8% (*n* = 4)

Notes.

a German high school degree attained after 9 years

b German high school degree attained after 10 years

c German high school degree attained after 13 years

d Patients with stable abstinence of any other substances than the prescribed OMT dose are eligible to visit the clinic only once per week and get a subscription for taking their daily dose at home. This is referred to as “Take Home”.

A short neuropsychological tests battery was administered on a computer. The duration was approximately 15 minutes. The examiner explained each respective task to the participant before its initiation on the computer and was available to clarify any remaining questions throughout to ensure participants’ understanding of the tasks.

Stop Signal Task (SST) (Sebastian et al., 2013): This task assesses response inhibition. Participants were instructed to push the right arrow key as quickly as possible when a square came up on the screen and the left arrow key when a circle appeared on the screen. If the presented shape changed colour from blue to orange after 300 ms, participants were instructed not to press any key, thus suppressing the initial motoric response. 30 of the 150 randomized trials were stop-trials. Outcome variables were the number of false alarms (pressing a key in a no go trial) and the stop signal reaction time (SSRT). The SSRT is a measure for the latency of the stop process and is estimated by subtracting the mean stop-signal delay from the median reaction time on go trials.

Delay Task: The 5-trial adjusting delay task (Koffarnus & Bickel, 2014) is a short version of the delay discounting task. In five trials, participants had to choose between immediately available money and a larger amount of money available after a delay. Depending on the participant’s choice on the first trial, the time delay on the following trials was adjusted. The dependent measure for this task is the discount rate k, which marks how much the value is influenced by the delay. A higher discount rate signals a higher depreciation of delayed rewards.

Dimensional Change Card Sort (DCCS) (Zelazo et al., 2014): This task assesses cognitive flexibility. Participants have to switch between sorting bivalent stimuli according to the criteria of shape and colour by pressing the right and left arrow keys. The resulting score is based on an algorithm factoring in accuracy and reaction time. See Zelazo et al. (2014) for a detailed description of score calculation.

To assess ToM performance, we used the Movie for the Assessment of Social Cognition (MASC) (Dziobek et al., 2006). The MASC consists of a 15-minute movie following four protagonists through a dinner party evening. The video is paused 45 times and participants are presented with multiple choice questions about the mental states of the protagonists. Each question has four answer options which can be categorized in the following way: “correct ToM” (correct mental state inferences), “no ToM” (the answer is not related to mental states), “exceeding ToM” (overmentalizing; over-interpretative mental state inferences) and “low ToM” (insufficient, overly simplistic mental state inferences). Six additional questions that are unrelated to ToM are used to control for how closely the participants are paying attention to the movie’s plot. The items cover different aspects of social cognition (emotions of different valence, thoughts, intentions, first and second order false beliefs, irony, faux pas). As verbal content, intonation, facial expressions and body language have to be minded when answering the questions, the MASC is considered to be a ToM test with relatively high ecological validity. The administration of the MASC took approximately 45 minutes per participant. In addition to the total score, scores for “cognitive ToM” (inferences about thoughts and intentions, 27 items) and “emotional ToM” (inferences about emotions, 18 Items) can be calculated.

To measure self-stigmatization, we used the Internalized Stigma of Mental Illness scale (ISMI) (Ritsher et al., 2003) in an adapted version for drug addiction in German language (Frischknecht et al., 2011). The ISMI is a self-report questionnaire with 29 items asking participants to assess their agreement with statements on a Likert scale stretching from 1 (strongly disagree) to 4 (strongly agree). The five subscales of the ISMI are Alienation, Stereotype Endorsement, Discrimination Experience, Social Withdrawal and Stigma Resistance. As stigma resistance has previously been identified as a separate construct (Brohan et al., 2010), we did not include those items in the total score and regarded the scale separately.

3.3.3 Procedure

During a first appointment, patients were screened for psychiatric diagnoses by trained clinical staff using the German translation of the Structured Clinical Interview for

the DSM (Wittchen et al., 1997). Patients were interviewed about their history of addiction and current substance use. Substance use was regularly evaluated by urine drug tests. Participants were tested for alcohol intoxication before the assessment using a breath test.

3.3.4 Data Analysis

Statistical analyses were carried out as indicated in the results section using IBM SPSS Statistics 25 for Windows. All tests were performed with a 2-sided $p<0.05$. Due to the exploratory nature of the study, no correction for multiple testing was applied. As the HAIS scores were not normally distributed, non- parametric tests were used (Spearman correlations, Mann-Whitney U-Test).

3.4 Results

Participants' HAIS scores ranged between -8 and 16 points. The mean HAIS score was 5.8 points (SD = 5.6). 28.8% of participants were in the poor insight group, 69.5% were in the fair insight group and 1.7% of participants were in the good insight group. The HAIS score did not correlate with sociodemographic variables (age, sex, school education). There were no significant correlations between the HAIS and the number of years of heroin use, the number of years in OMT, number of abused substances, opiate craving, opioid medication dosage or number of past inpatient treatments. HAIS scores did not significantly differ between patients with different opioid medications, different additional used substances and patients with or without take home prescription eligibility (all $p >.10$). There were no significant correlations between the HAIS score and the performance on EF tasks. HAIS scores did not correlate with the MASC total score or its subscales. The HAIS total score correlated with the ISMI stigma resistance score ($r = .32$, $p<.05$). The intellectual insight subscale correlated with the ISMI total score ($r = -. 34$, $p<.05$) as well as with stigma resistance ($r = .31$, $p<.01$). A median split was performed for the HAIS total score. A Mann-Whitney-U-Test was calculated to determine if there was a significant difference in stigma resistance between the high versus low insight group resulting from the median split. There was a statistically significant difference between both groups, $U = 267.5$, $Z = -2.05$,

$p < .05$. The high insight group showed significantly higher stigma resistance compared to the low insight group.

3.5 Discussion

The present study explored influences on insight into illness in opioid dependent patients. Insight was not associated with sociodemographic variables, substance use related variables, theory of mind or EF in our sample of 59 opioid dependent patients. However, we found statistically significant correlations between domains of self-stigma and insight into illness. Internalized stigma correlated with the intellectual insight score. Stigma resistance correlated with intellectual insight and the HAIS total score.

The positive correlation between stigma resistance and insight indicates that OMT patients with higher stigma resistance exhibited better insight into illness. Additionally, better intellectual insight was associated with less internalized stigma. This coincides with findings of associations between insight and self-stigma in patients with serious mental illness (Hasson-Ohayon et al., 2012). Pruss et al. (2012), who found self-stigma to be a key predictor for insight in schizophrenia, propose that the capability to self-reflect and distance oneself from incorrect beliefs (cognitive insight (Beck & Warman, 2004a)) mediates the relationship between insight and self-stigma. The concept of cognitive insight was originally established for psychotic disorders, but has since also been shown to be applicable for non-psychotic populations (Van Camp et al., 2017). The correlations between self-stigma and intellectual insight in our sample seem to attest to the assumption of Pruss et al. (2012) of cognitive insight as a bridge between insight into illness and self-stigma, as the HAIS intellectual insight scale and cognitive insight seem to overlap. Further research into the role of cognitive insight and its relationship to self-stigma in opioid addiction would be of interest.

Research has shown that negative outcomes connected to insight in schizophrenia, such as low hope, self-esteem and social functioning, are moderated by internalized stigma (Lysaker et al., 2007). In this context, our results may suggest a somewhat self-protective nature of impaired insight in opioid addiction in the presence of internalized stigma. An

individual who has internalized stigmatizing beliefs about addiction will have trouble accepting their own substance dependence without substantially harming their self-esteem. In the stage model by Corrigan and Rao (2012), the stages stereotype awareness and agreement are followed by the stage application to oneself, which by definition requires awareness of illness. In the model, harm can occur as a consequence of application of stigmatizing beliefs to oneself. Impaired insight would hinder application of stereotypes to oneself and may prevent subsequent harm. Stigma resistance on the other hand seems to enable insight in opioid dependent patients. If an individual is resisting stigmatizing beliefs about addiction, it is easier to accept a diagnosis without having to apply negative stereotypes to themselves.

As insight has implications for treatment motivation and outcome (J. S. Kim et al., 2007; K. M. Kim et al., 2007) and stigma resistance appears to be a relevant factor for insight, treatment modules aiming at building stigma resistance and dismantling self-stigma may have a positive impact on insight and thereby treatment outcome. This possible implication for addiction treatment should be a topic for future research.

The absence of associations between insight and substance use related variables in this study contrasts in some points with the findings of other authors. Maremmani et al. (2012) found that insight was related to history of addiction, with polysubstance abuse and a higher number of past treatments among other factors being linked to having insight. In our study, no associations between number of abused substances or past treatments were detected. It is possible that the differences between the results of Maremmani et al. (2012) and the present study are rooted in methodological differences. Maremmani et al. (2012) assessed insight using a structured interview developed for their purposes and assigned participants to “with insight” and “without insight” groups according to interview data (Maremmani et al., 1996; Quilici et al., 2007), whereas we collected metric data using a psychometric questionnaire. Partially, the HAIS and the structured interview emphasize different aspects of insight. While the HAIS scale “social surrounding” assesses the attribution of substance use problems to the environment and participants’ empathy for people affected by their drug use, the interview questions reported by Maremmani et al. (2012) do not cover this aspect. As our sample was much smaller than that of Maremmani

et al. (2012) (N = 1066), it is also possible that a larger sample is required to detect the associations. Another striking result is that in our sample of opioid dependent patients, we did not find any significant correlations between insight and ToM or EF. This is interesting, as it proposes a difference in influential factors on insight between opioid addiction and schizophrenia, as both ToM and EF have been linked to insight in psychotic disorders (Aleman et al., 2006; Bora et al., 2009). Potentially, this may point towards different mechanisms underlying impaired insight in opioid addiction than in schizophrenia.

There are several limitations to the current study. Given the cross-sectional nature of this study, conclusions regarding causality cannot be drawn and alternative explanations of its findings remain possible at this point. We only included opioid dependent patients who were in OMT treatment at the time of recruitment. This means of course that we were only able to assess insight in patients who had already taken the step to get treatment and that our findings can possibly not be generalized for the general population of opioid users. Also, it may be problematic that self-report measures for insight like the HAIS inherently require a certain level of self-awareness for the answers to be representative of the participants' state (Raftery et al., 2020). To dissolve this issue in future research, we suggest the development of an implicit measure for insight, e.g. a variation on the Implicit Association Test (Greenwald et al., 1998). Another potential limiting factor is that a substantial part of our sample was using other substances on top of opioids and/or had comorbid psychiatric diagnoses. Thus, it could be argued that the findings of this study may not be related to opioid addiction and OMT itself, but might also be related to other addiction and mental health factors. However, we did not include patients with comorbidities known to affect insight and found no statistically significant associations between variables related to additional substance use and the target variables. Although it would have been possible to only recruit participants without comorbidities and additional substance use, these patients represent a minority of the population of OMT patients. We considered it crucial to examine a representative sample of OMT patients, which in our opinion facilitates more of a generalization of findings to OMT patients beyond the study's specific sample.

In conclusion, our data suggests that rather than substance use related variables and

neurocognitive processes like EF or ToM, motivational aspects associated with self-stigma seem to play a role in impaired insight in opioid addiction. This indicates that other mechanisms may be at the foreground of insight in opioid addiction compared to psychotic disorders. Furthermore, impaired insight in conjunction with self-stigma appears to be another point to be added on the list of harmful effects of the stigma of addiction. We consider further efforts to reduce and research into public and internalized stigmatization to be of significant importance.

4 GENERAL DISCUSSION

The main aim of this dissertation is to shed light on awareness of self and others in opioid dependent patients, specifically insight into illness and ToM, and to explore their relationships to factors that stand out in literature as possible influences. To serve this purpose, two studies were conducted on opioid dependent patients undergoing OMT in an outpatient setting.

In the first study of this dissertation, a sample of OMT patients completed the MASC to assess ToM, a short EF test battery and a self-report questionnaire on childhood maltreatment. In order to enable a comparison of ToM performance, data from healthy controls who had also completed the MASC in a different study was obtained. Previous reports of ToM impairments in opioid dependent patients were confirmed. No association between ToM and substance use related variables (duration of opioid dependence and OMT, substance used for OMT, take home prescription eligibility, use of non-opioidergic drugs and duration of use) were detected. Several significant correlations were found between ToM and EF measures. The delay discount rate correlated inversely with the MASC total score and the cognitive ToM scale, indicating that participants who discarded delayed rewards at a higher rate had poorer ToM, specifically cognitive ToM. Correlations between the performance on the SST and the MASC total score as well as the emotional ToM scale implied an association between poor inhibitory control and ToM deficits, specifically in affective ToM. No associations were found between ToM performance and cognitive flexibility measured in the DCCS. As for childhood maltreatment, the CTQ total score as well as the test scores for physical abuse and physical neglect correlated negatively with ToM performance on the MASC. Sexual abuse, emotional abuse and emotional neglect did not significantly correlate with ToM.

In the second study of this dissertation, insight into opioid addiction was assessed using an adaptation of the HAIS in a sample of OMT patients. In addition, participants completed the MASC, the same EF test battery as in the first study, and a questionnaire on internalized stigma. No associations between insight into illness and substance use related or

sociodemographic variables, EF components or ToM were found. Internalized stigma on the other hand did significantly correlate with insight into illness. The ISMI total score correlated inversely with intellectual insight in the HAIS. Stigma resistance correlated positively with intellectual insight as well as the HAIS total score. OMT patients with better (intellectual) insight into illness therefore seemed to have less internalized stigma and a higher resistance to stigma.

4.1 Integration of study results in previous findings and outlook on future research

4.1.1 ToM and substance use, EF and childhood maltreatment

The results of the first study confirm ToM impairments in opioid dependent patients in OMT. As the few previous studies on ToM in opioid dependence either only assessed affective ToM (Ieong & Yuan, 2018) or had a rather small sample size (Gandolphe et al., 2018), the replication of ToM deficits in OMT patients using the MASC, which allows a comprehensive and largely ecologically valid assessment of ToM, and with double the sample size of Gandolphe et al. (2018), is a relevant finding. Further, the results of the first study contribute to deepen the understanding of ToM impairments in opioid dependence.

Beyond the group differences in ToM performance to the detriment of OMT patients, the results also corresponded to those of Gandolphe et al. (2018) regarding the dissociation of ToM and variables related to substance use and history of addiction. In addition, something that did correlate with impaired ToM abilities was childhood maltreatment, a factor logically not caused by substance abuse and predating the substance dependence diagnosis in adulthood. Taken together, these results might suggest that ToM impairments in opioid dependent individuals are not a result of deterioration caused by the neurotoxic effects of opioids, but potentially predate opioid abuse and may instead be a vulnerability factor for developing opioid dependence. Gandolphe et al. (2018) suggest interpersonal problems and social stress due to poor ToM and subsequent maladaptive coping in form of substance abuse as a potential mechanism. Indeed, interpersonal conflicts have been identified as a main contributor to relapse in women with SUDs (Sun, 2007) and maladaptive interpersonal conflict tactics are a predictor for substance abuse in adolescents (Unger et al.,

2003). A recent study examining predictors of adolescent substance use and later substance abuse found deficient social skills in adolescence to be among the best predictors for substance abuse in adulthood (Allen et al., 2021). Associations between ToM abilities and the development of social skills have been shown in healthy children (Watson et al., 1999) and children with autism spectrum disorder (Adibsereshki et al., 2015). As affective ToM deficits and interpersonal problems have been shown to correlate in alcohol dependent patients (Kornreich et al., 2002), this relationship between ToM and social skills appears to be present in SUDs, too. Hill et al. (2007) found a reduced frontotemporal BOLD response during the RMET in non-alcohol-dependent participants from families with multiple cases of alcohol dependence compared to a control group. The authors conclude that this may be a manifestation of genetic susceptibility and vulnerability to developing alcohol dependence. In the light of these findings, ToM as a risk factor for substance abuse and dependence with poor social skills as a mediator seems plausible. Then again, there is also the possibility of a common origin for ToM impairments and substance abuse, e.g. in form of variations in the dopamine D4 receptor gene associated both with changes in ToM development in childhood (Lackner et al., 2012) and severity of substance dependence (Lusher et al., 2000). Longitudinal studies including participants with and without a family history of addiction periodically testing ToM and social functioning early in life as well as assessing substance use would be desirable to gain understanding of the role of ToM in addiction.

The detected correlations between childhood maltreatment and ToM in OMT patients are a contribution of the first study beyond the replication of ToM impairments and their dissociation from substance use related variables in opioid dependent patients. A potential common factor in the relationship between opioid dependence, childhood trauma and ToM might be the endogenous opioid system. The endogenous opioid system is relevant to different aspects of addiction (Trigo et al., 2010) and its responsivity was linked to prescription opioid abuse in patients with chronic pain in a recent study (Ballester et al., 2022). The μ-opioid system modulates affiliative and protective social behaviour by reinforcing these behaviours “in response to positive and negative social experiences with long-term consequences for social behavior and health” (Meier et al., 2021, p. 250). As childhood maltreatment constitutes, among other things, of the lack of affiliative and protective behavior from caregivers, it might lead to lasting changes in the μ-opioid system,

resulting in a heightened desire for social bonding and the effects of endogenous opioids or failing that the use of external opioids (Gerhardt et al., 2022). On top of being a potential link between childhood trauma and opioid dependence, the μ-opioid system might also play a role in the development of ToM abilities. The endogenous opioid system has been shown to promote the direction of visual attention towards faces and eyes (Chelnokova et al., 2016), which enables decoding of emotional facial expressions, a crucial component of affective ToM. An evolutionary theory of ToM proposes physical touch and restraint in breast feeding, which involves the release of endogenous opioids, as a possible origin for ToM development in humans (Tsoukalas, 2017). In this light, the endogenous opioid system might offer a conceivable explanation of the correlations between ToM impairments and childhood maltreatment in opioid dependent patients.

An aspect that stands out in relationship between childhood trauma and ToM in opioid dependent patients as detected in the first study is the protruding role of physical maltreatment. Participants who reported experiences of physical abuse and physical neglect in the CTQ exhibited poorer ToM abilities. This was not the case for emotional abuse and neglect. Similarly, physical neglect has previously been reported to correlate with ToM impairments in patients with schizophrenia (Mrizak et al., 2016; Vaskinn et al., 2021). The apparent importance of specifically physical forms of childhood maltreatment for ToM seem baffling at first glance. Intuitively, one might rather suspect emotional neglect and the accompanying lack of social interactions and opportunities for practicing ToM or changes to the endogenous opioid system due to a lack of affiliative and bonding behaviour at the core of the association between ToM and childhood trauma. However, these explanatory approaches can't be fully ruled out considering the frequent concurrence of physical and emotional maltreatment. Different forms of childhood maltreatment rarely occur in isolation, but are interrelated (Higgins & McCabe, 2000). Especially physical violence or neglect, e.g. not providing the necessary nutrition and hygienic care, while simultaneously giving a child everything it needs on an emotional level does not seem plausible. Indeed, the vast majority of children experiencing physical maltreatment are also subjected to forms of emotional maltreatment (Claussen & Crittenden, 1991). In a study analysing health insurance data, between 81% and 98% of adults who reported one form of maltreatment in their childhood had experienced at least one other form of childhood adversity (Dong et al.,

2004). Moreover, compared to physical forms of maltreatment, emotional abuse is less likely to be identified and reported by the social environment (Claussen & Crittenden, 1991) and the victims themselves (Goldsmith & Freyd, 2005). Therefore, it is not unlikely that experiences of emotional abuse and neglect were underreported by participants in study 1, skewing the statistical relationships between subscales of the CTQ and ToM. Another possible explanation for the correlation between ToM deficits and physical, but not emotional maltreatment could be the impact of physical abuse and neglect on neural development. Different forms of childhood maltreatment impact brain development in distinct ways (Kim-Spoon et al., 2021; McLaughlin et al., 2014). Neuropsychological profiles differ between children who experienced neglect without physical abuse and neglected children who also experienced physical abuse (Nolin & Ethier, 2007). Healthy adults with a history of physical neglect have been found to exhibit changes in white matter connectivity (Tendolkar et al., 2018) and reduced grey matter volume in the PFC (Frodl et al., 2010). Harsh corporal punishment in childhood seems to be linked to changes in the hemodynamic and paramagnetic properties of the putamen and right caudate (Sheu et al., 2010). It is possible that alterations in brain development due to physical maltreatment in childhood may lead to ToM impairments. More research on the neuronal and socio-cognitive consequences of different types of childhood maltreatment is needed to gain a deeper understanding of this matter.

Regarding the relationship between ToM and EF, the results of study 1 show an association between ToM abilities and response inhibition. The performance on the SST and also the delay discounting task, which is often used as a measure for impulsivity (da Matta et al., 2012), were significantly correlated with performance on the MASC. Cognitive flexibility or set shifting, on the other hand, appeared to be uninvolved in ToM in opioid dependent patients. This is in line with the findings of Ieong and Yuan (2018), who found associations between affective ToM and inhibitory control in opioid and nicotine dependent patients, but not with set shifting, working memory, processing speed or verbal fluency, as well as developmental psychology researchers who highlighted the role of inhibitory control for ToM (e.g. Bailey & Henry, 2008; Carlson et al., 2015; Carlson & Moses, 2001).

Furthermore, the results of study 1 are in support of the proposed functional dissociation of cognitive and affective ToM (Kalbe et al., 2010; Schlaffke et al., 2015; Shamay-Tsoory & Aharon-Peretz, 2007), as performance on the SST correlated only with emotional, the delay discount rate only with cognitive ToM. Despite the relative closeness of response inhibition and delay discounting, as both are related to impulsivity (Weafer & Fillmore, 2016), there are fundamental differences between the two measures. In contrast to the SST, in which the impulse to react to a stimulus has to be inhibited following the stop signal (Sebastian et al., 2013), the delay task also involves the aspect of reward (da Matta et al., 2012). A study finding response inhibition, but not delay discounting to be affected under the influence of diazepam suggests separate underlying mechanisms (Acheson et al., 2006). Therefore, the distinct correlations of emotional and cognitive ToM with the SST and delay discounting tasks can be interpreted in favor of a functional disconnect of affective and cognitive ToM.

Both childhood maltreatment and EF were associated with ToM in study 1. Previous studies have found childhood maltreatment and EF to be related (Letkiewicz et al., 2021; Zelazo, 2020). In their review article on childhood trauma and cognitive functioning in addiction, Edalati and Krank (2016) draw the conclusion that the relationship between childhood maltreatment and SUDs is at least partially mediated by EF deficits, which may constitute a vulnerability factor. It is possible that EF impairments in the wake of childhood maltreatment may also be a mediating factor between trauma and ToM in opioid dependence. The relationship between childhood maltreatment and EF was not covered by the hypotheses of study 1 and thus not a subject of the data analysis. However, examining interrelations of childhood trauma, EF and ToM in opioid dependent patients in a mediator analysis in a larger sample certainly poses an interesting subject for future research.

4.1.2 Perspectives on insight into illness

The second study of this dissertation explored the relationship between insight into illness in opioid dependent patients with factors representing the deficit approach (EF), the nondeficit approach (self-stigma) and the cognitive neuropsychological perspective (ToM). The deficit approach understands impaired insight as the consequence of compromised

neuropsychological functioning caused by the illness (Langdon et al., 2006; Langdon & Ward, 2009). No significant correlations were found between insight and any of the EF measures assessed in study 2. This result speaks against the applicability of the deficit approach on impaired insight in opioid dependence. While there exists evidence in favour of the deficit approach for schizophrenic patients (Aleman et al., 2006; Lysaker et al., 2006), the results of study 2 may be an indicator of different mechanisms determining insight in substance use and psychotic disorders.

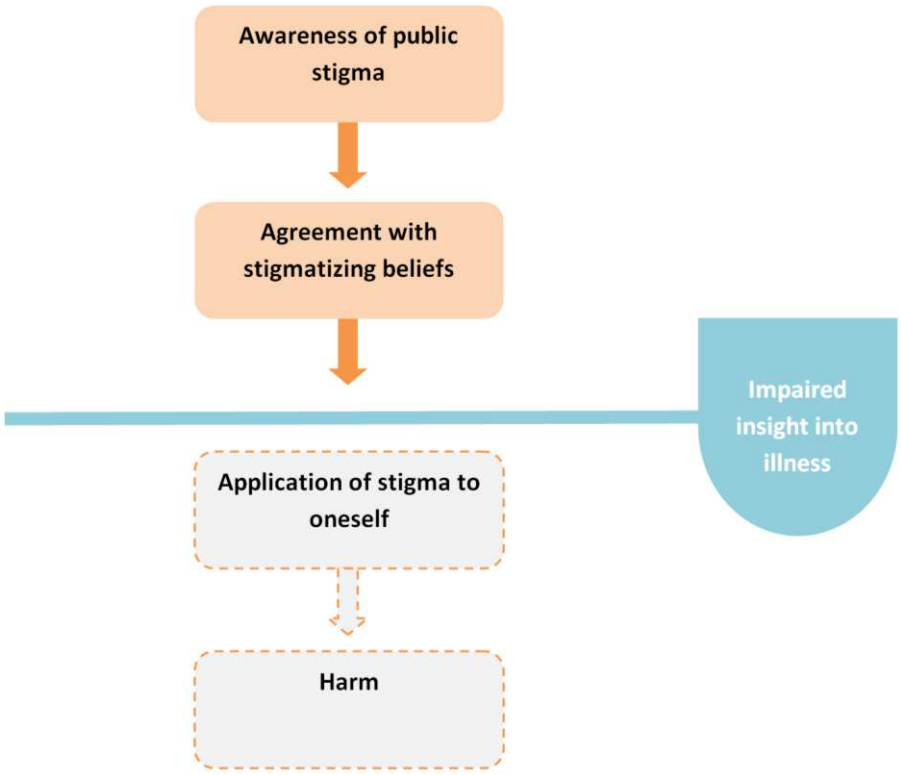
With the cognitive neuropsychological perspective, Langdon and Ward (2009) proposed that impaired insight stems from the failure to reflect on one's pathology from the perspective of others as a result of poor ToM abilities. Even though study 1 found ToM impairments in opioid dependent patients, the cognitive neuropsychological perspective could not be confirmed in study 2, as there was no association between impaired insight into illness and ToM in the study sample of OMT patients. Again, this differs from findings in schizophrenic patients (Bora et al., 2009) and indicates that the mechanisms underlying impaired insight in schizophrenia and opioid dependence are distinct from one another.

The nondeficit approach frames impaired insight not as deficit of competence, but as a subconscious motivational process aiming to avoid the distress of associating oneself with the stigma of a mental illness (Langdon et al., 2006; Langdon & Ward, 2009). In study 2, participants with higher stigma resistance had better insight into illness and a higher degree of intellectual insight was associated with less internalized stigma. These findings might be a testament to the nondeficit approach. A phenomenon that helps to put the idea of a motivational relationship between self-stigma and insight into perspective is the so-called insight paradox (Lysaker et al., 2007), a phenomenon which was well described in the context of psychotic disorders by Belvederi Murri and Amore (2019): "The acquisition of insight should be beneficial to the patient, but *paradoxically* leads to another problem. The insight paradox is often related to "post-psychotic depression," a phase of recovery when patients develop feelings of shame and sadness as they acquire insight" (p. 279). Insight into illness is related to poorer quality of life (Davis et al., 2020) and more suicidal ideations (Bornheimer et al., 2021) in patients with schizophrenia. Similarly, Maremmani et al. (2012) found that OMT patients classified as with-insight were significantly more likely to

experience suicidal ideation, which indicates that the insight paradox also applies to opioid dependence. But where does self-stigma come into play? In schizophrenia, self-stigma appears to be a moderating factor in the relationship between insight and negative outcomes (Lysaker et al., 2007). In patients with more internalized stigma, insight into illness was more strongly associated with depressiveness (Cavelti et al., 2012; Vidović et al., 2016), low hope, low self-esteem and poor social functioning (Lysaker et al., 2007). In the stage model of self-stigma introduced by Corrigan and Rao (2012), the third stage after stereotype awareness and agreement is the application to oneself, which subsequently leads to harm (e.g. low self-esteem). By logic, insight into illness is a perquisite for applying the stigma attached to a diagnosis to oneself. As illustrated in figure 3, impaired insight could intercept the sequence of the stages of self-stigma and thereby prevent arriving at the final stage of harm.

Figure 3

Modification of the stage model by Corrigan and Rao (2012) with the addition of impaired insight.



Against this background, the association of self-stigma with poor intellectual insight in OMT patients in study 2 could be interpreted in the sense of shielding oneself from the harmful consequences of identifying with a diagnosis that comes with attached (internalized) stigma. For a person who has internalized the public stigma associated with opioid addiction, labelling themselves as opioid dependent would come with the cost of damage to their self-esteem. This suggests an interpretation of impaired insight in opioid dependence which is closer to the Freudian understanding of denial as a defence mechanism (Freud, 1924, 1925).

Stigma resistance on the other hand seems to relate to better insight in opioid dependence. Stigma resistance can be defined as not being affected by stigmatizing beliefs (Ritsher et al., 2003) and actively challenging or deflecting stigma when encountered (Thoits, 2011). In severe mental illness, stigma resistance was found to be related to positive outcomes such as self-esteem, better social functioning and the use of problem centred coping strategies (O'Connor et al., 2018). A meta-analysis on the effects of stigma resistance in mental illness found associations with self-efficacy, quality of life, hope and recovery, all with strong effect sizes. In addition, there was a significant medium correlation between stigma resistance and insight into illness (Firmin et al., 2016), which is in line with the findings of study 2. It is possible that for a patient who is challenging and not accepting stigmatising beliefs about opioid dependence, insight into illness can be afforded without the cost of applying negative stereotypes to oneself and the harm that comes with that. Because of its apparent benefit for insight into illness as well as its association with a variety of desirable clinical outcome variables, there is a need for more research focusing on stigma resistance in SUDs in the future.

Another point that remains to be discussed is the role that specifically intellectual insight seems to play in the relationship between stigma and insight. The intellectual insight scale in the HAIS closely resembles what Beck and Warman (2004b) call *cognitive insight* when defining the ability to self-reflect and distance oneself from incorrect beliefs. The term was originally coined for patients with psychosis, but can also be applied for other clinical and nonclinical populations (Van Camp et al., 2017). In a study on schizophrenia, in which self-stigma was the best predictor for insight into illness, the relationship between insight and self-stigma was mediated by cognitive insight (Pruss et al., 2012). The results of study 2

suggest that cognitive insight may be an important aspect in the relationship between self-stigma and insight in opioid dependence, too.

4.1.3 Differences to findings in other SUDs

Some of the findings of the studies presented in this dissertation differ from results of studies on different substance dependences. Firstly, it seems noteworthy that the only other study to date examining the relationship between self-stigma and insight in a SUD found no association between self-stigma and insight into illness in alcohol dependent patients, using the same psychometric instruments as were used in study 2 (Lyu et al., 2017). This could be an indicator for a difference between opioid and alcohol dependent patients regarding the factors that contribute to impaired insight into illness. While the correlations between measures of internalized stigma and insight in study 2 speak for the nondeficit approach, this does not seem to be the case for alcohol dependence. A possible explanation for these differing findings could be the differences regarding the stigmatization experienced by alcohol- and opioid dependent patients. The stigma attached to alcohol differs from that of illicit drugs like heroin because alcohol is a legal substance (Schomerus, 2014). Compared to patients treated for alcohol dependence, heroin users were found to perceive more stigma in the sense of less acceptance and not being seen as potential partners (Chang et al., 2020). It is possible that the specifics of the public stigma of opioid use influence the relationship between self-stigma and insight in opioid dependent patients in a way that is not the case for the stigma of alcohol dependence. If for example stigmatizing beliefs attached to opioid dependence are more aversive, there might be a greater “need” for impaired insight as a shield from harmful consequences of self-stigma. There might be different mechanisms at play influencing impaired insight in different SUDs. To gain a deeper understanding of the relationship between insight and self-stigma, further research is needed assessing these factors in different SUDs as well as examining the respective public stigma attached to them.

Study 1 found no associations between ToM and substance use related variables (duration of opioid use and OMT, substance used for OMT, use of other substances, take home eligibility). Similarly, Gandolphe et al. (2018) found no correlations between ToM and

abstinence, duration of substance abuse or age at onset of substance abuse in OMT patients. However, studies on ToM in other SUDs did find relationship with substance use related variables. In alcohol dependent patients, ToM was shown to be associated with the duration of alcohol abuse (Bosco et al., 2014; Gizewski et al., 2013). The same is the case for cocaine users, with the addition of correlations between ToM and cumulative cocaine use and the concentration of cocaine/ norcocaine detected per hair analysis (Preller et al., 2014). These contrasting results might indicate different mechanisms underlying impaired ToM in opioid dependence compared to cocaine and alcohol use disorders. Moreover, there are other findings regarding ToM in alcohol dependence that differ from the findings of study 1. In the sample of OMT patients in this dissertation, both cognitive and emotional ToM were impaired in the MASC. Maurage et al. (2016), who also applied the MASC in a sample of alcohol dependent patients, found only emotional ToM to be impaired, while cognitive ToM appeared unobstructed. Also, while ToM deficits in OMT were associated with cognitive flexibility in study 1, ToM and cognitive flexibility did not correlate in a study with alcohol dependent patients (Thoma et al., 2013). Although different measures were used for the assessment of cognitive flexibility, these disparate findings could also be an indication of differences in the relationship between ToM and EF in alcohol and opioid dependence. More comparative research on ToM impairments in different SUDs is needed to further understand the mechanisms at play.

Overall, the differences between the findings presented in this dissertation and those reported on alcohol dependence and cocaine abuse indicate that processes of awareness of self- and others may not be the same in all SUDs, but may very well differ between different substance use populations. Further research analysing insight into illness as well as ToM in different SUDs would be beneficial for understanding the mechanisms underlying impairments in these constructs as well as commonalities and differences between substance dependences.

4.2 Limitations and further directions

There are several limitations to the studies presented in this dissertation. First of all, as both studies were cross-sectional, no conclusions about causality or directionality of the detected relationships can be made and alternative explanations of the findings are possible.

Some characteristics of the study samples present limiting factors that need to be addressed. A significant part of the participants also used additional substances other than opioids. Moreover, participants with psychiatric comorbidities beyond SUDs were included in the sample. Consequently, it could be argued that the study results can't be explicitly ascribed to opioid dependence, but might be rooted in other substance abuse or mental health factors. However, we did control for these variables when analysing group differences in study 1 and excluded participants with comorbid psychiatric diagnoses known to be connected to impaired insight. Furthermore, in both studies, no correlations between additional substance abuse and target variables were present, which indicates that the inclusion of participants who consumed substances other than opioids did not substantially alter the study results. Indeed, the recruitment of OMT patients who abused additional substances and/ or had other mental health issues was a deliberate choice, as this realistically reflects the population of patients that are treated in OMT centres. A representative sample of OMT patients was required in order to enable a generalization of study findings beyond the specific study sample, and this would not have been the case with the exclusion of patients with comorbidities or non-opioid substance abuse. Another limiting factor regarding the study sample is that only OMT patients were included, but no opioid dependent patients who were abstinent or using opioids but not in an OMT programme. This may have affected the results for both insight and ToM. It is plausible that insight into illness might differ between patients who have enrolled in OMT and opioid dependent individuals who have not taken that step. Also, there are indications that OMT and abstinence might be connected to differences in ToM abilities, as one study found OMT patients to have poorer social emotional skills than detoxified opioid dependent patients (McDonald et al., 2013). Further research with opioid dependent patients at different stages (OMT, no OMT, abstinence) and without confounding variables such as other substance use and

comorbidities could provide more clarity on the mechanisms influencing insight into illness and ToM in opioid dependence.

Another sample related limitation concerning study 1 is the control group, which did not perfectly match the clinical sample in age and sex (although the discrepancy was not significant) or the level of education. As none of those variables significantly correlated with the target variables, the group comparison was still regarded as viable. Furthermore, the groups' ToM abilities were assessed several years apart in different locations. However, no reports on cohort effects on ToM or social cognition in general exist that would suggest a problem for the group comparison. The reflection of the group differences in previous findings (Gandolphe et al., 2018) also speak for the validity of the group comparison in study 1. Still, a perfectly matched control group assessed under identical standardised test conditions would have been an advantage for the group comparison.

A limitation concerning both study 1 and 2 is that neither the number of social contacts in their daily lives, nor the number of members of participants' households was assessed. These variables could be relevant for social cognition and ToM and might also impact insight into illness, as the feedback of others in everyday life could be a potential source of insight.

Another variable which was not assessed in either study, but might have provided a further understanding of the mechanisms influencing ToM and impaired insight in opioid dependence, is intelligence. Fluid intelligence has been shown to correlate with EF (Diamond, 2013). In schizophrenia, insight into illness has been linked to premorbid intelligence in some studies (Gerretsen et al., 2013; Gerretsen et al., 2014), while others did not find an association (Ozzoude et al., 2019). ToM abilities have also been linked to general intelligence (Coyle et al., 2018), although it cannot be ruled out that this is due to the largely language based nature of the tasks used to measure ToM (Navarro et al., 2021). Further research on the role of intelligence in ToM, insight into illness and in the relationship between ToM and EF in opioid dependence is needed to understand how these variables interact.

Several limitations ought to be discussed regarding the measures that were used. The HAIS was used to assess insight into illness. It was originally developed for and only validated in alcohol dependence (Kim et al., 1998), but has proven to be applicable with modifications in opioid dependent individuals, too (Lambert et al., 2022). However, since study 2 was conducted, a new questionnaire has been published that could be a better fit for measuring insight in opioid addiction. The Substance Use Awareness and Insight Scale (SAS) was developed for the application in different SUDs and has been shown to meet quality standards of test and measurement theory in opioid dependent individuals (Kim et al., 2022). In addition, for further investigating the relationship between self-stigma and cognitive insight, the Beck Cognitive Insight Scale (BCIS) (Beck, 2004), which was shown to have good psychometric properties in a sample of substance abusers (Raftery et al., 2019), would be more specifically suited than the intellectual insight subscale of the HAIS. At the same time, self-report measures like HAIS, SAS and BCIS as well as interviews like the one used by Maremmani et al. (2012) have the inherent problem that they require the participants to have a certain level of self-awareness in order to correctly represent the construct they are supposed to measure (Raftery et al., 2020). An interesting approach to deal with this problem could be the development of an implicit assessment method for insight, e.g. an insight specific modification of the Implicit Association Test (Greenwald et al., 1998). As the contrasting results regarding the relationship of insight and history of substance abuse between study 2 and Maremmani et al. (2012) might also be an artefact of the different instruments used for insight, it seems crucial to conduct future studies using psychometric instruments validated for opioid dependent populations as well as implicit measures of insight in order to be able to thoroughly investigate and understand mechanisms underlying impaired insight in opioid dependence.

To measure stigma resistance, the corresponding subscale of the ISMI was used to in study 2. However, a meta-analysis reported a poor internal consistency for this subscale (Cronbach's alpha = .56) (Firmin et al., 2016). The Stigma Resistance Scale (Firmin et al., 2017) might have been a better choice for assessing stigma resistance. As it has five subscales, the implementation of the Stigma Resistance Scale in future research could allow to examine which aspects of stigma resistance are relevant for the relationship with insight into illness in opioid dependence.

Despite being a commonly used instrument in the assessment of childhood maltreatment, the accuracy of the results of the CTQ can be questioned, as it is a retrospective self-report measure. A recent meta-analysis discovered discrepancies in prospective and retrospective assessments of childhood maltreatment (Baldwin et al., 2019). Therefore, the results of the CTQ and consequently their correlations with ToM have to be interpreted with caution, as they may not represent participants' experiences of childhood maltreatment with full accuracy.

Lastly, the selection of EF tasks implemented in both studies may constitute a limiting factor, as they do not cover all components of EF. In order to not strain participants with overly long study assessments, only three EF tasks were administered. Working memory and feedback processing were not assessed. However, feedback processing, especially processing feedback of negative valence, has previously been shown to be impaired in opioid users (Ersche et al., 2006), and could potentially be relevant for insight into illness. In order to rule out or attest to the deficit approach, one would have to conduct a study with an extensive test battery covering all components of EF and analysing their relationship to insight into illness.

4.3 Clinical implications

As the results of study 1 as well as Gandolphe et al. (2018) suggest that ToM impairments might pose a risk factor for opioid abuse and dependence, therapeutic interventions training ToM abilities may be of value for recovery and prevention. In their review on ToM in alcohol dependence, Onuoha et al. (2016) point out the potential value of ToM interventions during addiction treatment for long term recovery by improving patients' social skills and reducing social difficulties and stress. Taking the correlation between impaired ToM and childhood maltreatment as well as the possibility of ToM impairments as a manifestation of a genetic vulnerability (Hill et al., 2007) into account, ToM interventions for addiction prevention could target individuals who have experienced childhood maltreatment or who have a family history of SUDs. While ToM trainings have not yet been established for SUDs, targeted interventions have been shown to improve ToM abilities in other populations. In childhood, the effectiveness of ToM trainings has been demonstrated

for children with autism spectrum disorder (Paschke-Müller et al., 2017) as well as for healthy children (Lecce et al., 2014). In adults with schizophrenia, ToM trainings have been shown to significantly improve patients' ToM abilities (d'Arma et al., 2021; Vass et al., 2018). Targeted ToM interventions mostly consisted of regular group sessions with vignettes, comic strips or video clips of social interactions as training materials for mental state inferences (Vass et al., 2018). Other concepts include the guided observation and analysis of facial expressions of other patients in the training group (Veltro et al., 2011) or add the imitation of facial expressions as an adjuvant element for mental state inferences (Mazza et al., 2010; Pino et al., 2015). Similar approaches could be feasible for the integration in treatment programmes for SUDs or in prevention programmes. Furthermore, recent results on the efficacy of a virtual reality based ToM training in which schizophrenic patients participate in simulated social interactions with avatars (Vass et al., 2021) indicate that this technology, which is also beginning to be established in addiction research and therapy (Mazza et al., 2021), could present a practicable option for developing ToM trainings to be used in the treatment and prevention of SUDs.

Since impaired insight into illness has been shown to negatively influence treatment seeking behavior and compliance (Bottlender & Hloucal, 2010) as well as treatment outcomes (O'Connor et al., 2013; Saravanan et al., 2010; Schwartz, 1998), insight is a relevant target for clinical interventions. Brief insight-focused therapy sessions in addition to treatment as usual can significantly improve insight into illness in alcohol dependent patients (Im et al., 2007; Jung et al., 2011), however, it was not assessed if this had an effect on treatment outcomes (Raftery et al., 2020). Moreover, in the light of the insight paradox (Lysaker et al., 2007), interventions focusing on insight might have aversive effects. As Belvederi Murri and Amore (2019) point out, "the cultural or individual stigmatization of mental illness may turn the acquisition of insight into a painful event and increase the risk of depression. Clinicians need to carefully evaluate and promote insight through a personalized approach to aid patient process of care and personal growth" (p. 277). The association between impaired insight and self-stigma found in study 2 indicates that this objection might be relevant for interventions targeting insight in opioid dependent patients. This issue could be addressed by incorporating self-stigma reducing and stigma resistance promoting elements into insight interventions for opioid dependent patients. Livingston et al. (2012)

conclude in their meta-analysis that there is (albeit limited) evidence that therapeutic interventions can reduce internalized stigma in patients with SUDs, highlighting acceptance and commitment therapy (ACT), motivational interviewing and positive stories about people with SUDs as effective approaches. More research exists on interventions targeting internalized stigma in severe mental illness, which have been found to have small to moderate significant effects according to a systematic review (Tsang et al., 2016). While the authors abstain from explicitly recommending one intervention strategy over others, they suggest psychoeducation as an effective approach on the base of the studies reviewed. Drapalski et al. (2021) recently published a nine week psychoeducational intervention programme targeting internalized stigma in psychosocial rehabilitation clients, which significantly increased stigma resistance and recovery orientation and decreased internalized stigma on the ISMI. However, at the six month follow-up these did not appear to be long-term effects. More research is needed on interventions reducing self-stigma and promoting stigma resistance in mental illness in general as well as specifically in SUDs. Moreover, developing interventions combining the promotion of insight into illness and the reduction of self-stigma would be of interest. Given the proposed self-protective nature of impaired insight in the presence of self-stigma, it should be examined if interventions successfully reducing self-stigma can also bring about improved insight without specifically targeting insight itself.

Interestingly, there is a therapeutic approach positively linked to the three constructs self-stigma, insight and ToM: mindfulness. Mindfulness has is origins in Buddhism and can be defined as “paying attention in a particular way: on purpose, in the present moment, and nonjudgmentally” (Kabat-Zinn, 1994, p. 4). In the last 20 years, mindfulness based interventions have increasingly become a research topic and staple in clinical practice in the mental health sector (Goldberg et al., 2018), including the treatment of SUDs (Sancho et al., 2018). Structural equation modeling of questionnaire data from psychiatric patients showed an association between mindfulness and stigma resistance (Chan et al., 2018). A systematic review of mindfulness based interventions showed that ACT, of which mindfulness is a core component, is a useful approach for reducing self-stigma (Stynes et al., 2022). Regarding insight into illness, a meta-analysis on mindfulness interventions for schizophrenic patients showed considerable improvements (g = 0.65) in awareness of illness (Hodann-Caudevilla et

al., 2020). Mindfulness based psychoeducation programmes for psychotic patients were shown to have positive effects on insight into illness, which were superior to those of conventional psychoeducation and were sustained at an 18 (Chien & Thompson, 2014) and 24 months follow-up (Chien et al., 2019). Especially the mindfulness components *observing* and *acting with awareness* were linked to enhanced insight (Chien et al., 2020), which could be an indicator that the "increased ability of noticing or attending to present-moment experiences" (Chien et al., 2020, p. 9) associated with mindfulness practice contributes to increased awareness of illness. Despite the results of study 2 that point towards different mechanisms underlying impaired insight in schizophrenia and SUDs, it seems plausible that mindfully attending to the present moment could also contribute to improved insight into illness in patients with SUDs. Regarding ToM, mindfulness based interventions have been found to improve ToM performance in psychotic patients (López-Navarro et al., 2022) and healthy controls (Trautwein et al., 2020), with even brief meditation sessions leading to significant improvements in a nonclinical sample (Tan et al., 2014). ToM deficits, self-stigma and impaired insight into illness are all relevant to opioid addiction, as covered in this dissertation, and mindfulness is associated with improvements in all three. In this light, the development and implementation of mindfulness interventions in the treatment of opioid addiction appears to be a relevant subject for future research.

5 SUMMARY

Insight into illness is relevant to treatment motivation and clinical outcomes in psychiatric disorders. Various studies have found insight to be impaired in patients with substance use disorders. Surprisingly, this includes patients in opioid maintenance therapy, who by the nature of their treatment are regularly confronted with their opioid dependence and thereby might be expected to have gained a certain level of insight into their substance use disorder. However, despite the clinical relevance of insight, there is a lack of research on mechanisms underlying impaired insight in substance use disorders. Literature on insight in mental illness reveals three explanatory approaches: The deficit approach suspects deficits in executive functioning at the core of impaired insight. The nondeficit approach frames impaired insight as the result of motivational processes connected to avoiding negative consequences of stigma. The cognitive neuropsychological perspective understands impaired insight as a consequence of poor theory of mind. Similarly to insight, theory of mind has been linked to clinically relevant factors and shown to be impaired in opioid dependent patients, but very little is known about influences on theory of mind impairments in this population. The aim of this dissertation was to gain a better understanding of insight into illness and theory of mind in opioid dependent patients and influencing factors on both.

In the first study, significant deficits in theory of mind were found in patients in opioid maintenance treatment. These deficits correlated with physical abuse and neglect in childhood and components of executive functioning, but not with variables related to substance abuse. This suggests that theory of mind impairments could be a risk factor predating substance abuse.

In study two, insight into illness was shown to be impaired in the majority of the sample of opioid dependent patients. Insight did not correlate with substance use related or sociodemographic variables. Neither executive functioning, nor theory of mind were associated with insight, hence the deficit approach and the cognitive neuropsychological perspective could not be confirmed for opioid dependent patients. Insight into illness was associated with stigma resistance and correlated inversely with self-stigma, which can be

interpreted as supporting the nondeficit approach for insight in opioid dependence.

In conclusion, there is a need for further research in order to better understand, firstly, the relationship between theory of mind, executive functions and childhood trauma; secondly, the relationship between insight into illness and self-stigma; and thirdly, the potential role of impaired theory of mind as a risk factor for substance abuse. Moreover, theory of mind, insight into illness and self-stigma are promising targets for clinical interventions for opioid dependent patients.

6 ZUSAMMENFASSUNG

Krankheitseinsicht ist relevant für Behandlungsmotivation und –Ergebnisse bei psychischen Erkrankungen. Bei Personen mit Abhängigkeitserkrankungen wurde eine eingeschränkte Krankheitseinsicht in zahlreichen Studien festgestellt. Überraschenderweise ist dies auch bei opioidabhängigen Patient*innen in Substitutionsbehandlung der Fall, obwohl die regelmäßige Konfrontation mit der eigenen Opioidabhängigkeit in der Natur dieser Behandlung liegt und man daher intuitiv vielleicht von einem gewissen Maß an Krankheitseinsicht ausgehen würde. Trotz der klinischen Relevanz von Krankheitseinsicht besteht jedoch bisher ein Mangel an wissenschaftlichen Studien zu den zugrundeliegenden Mechanismen eingeschränkter Einsicht bei Abhängigkeitserkrankungen. In der Literatur zu Krankheitseinsicht bei psychischen Erkrankungen finden sich drei Erklärungsansätze: Der Defizit-Ansatz vermutet Defizite in den exekutiven Funktionen im Kern eingeschränkter Krankheitseinsicht. Der Kein-Defizit-Ansatz versteht eingeschränkte Krankheitseinsicht als Konsequenz motivationaler Prozesse, die mit der Vermeidung negativer Auswirkungen des Stigmas der Erkrankung zusammenhängen. Die kognitiv-neuropsychologische Perspektive sieht eingeschränkte Krankheitseinsicht als Folge von Theory of Mind Defiziten. Ähnlich wie Krankheitseinsicht wird auch Theory of Mind mit klinisch relevanten Variablen in Verbindung gebracht und ist bei opioidabhängigen Patient*innen eingeschränkt. Dennoch ist bisher wenig über Einflussfaktoren auf Theory of Mind in dieser klinischen Population bekannt. Das Ziel dieser Dissertation ist es daher, ein tiefergehendes Verständnis über Krankheitseinsicht und Theory of Mind bei Opioidabhängigkeit sowie Einflussfaktoren auf beide Konstrukte zu gewinnen.

In der ersten Studie dieser Dissertation wurden signifikante Theory of Mind Defizite bei opioidabhängigen Patient*innen in Substitutionsbehandlung festgestellt. Diese Defizite korrelierten mit körperlichem Missbrauch und körperlicher Vernachlässigung in der Kindheit sowie mit Domänen der exekutiven Funktionen, jedoch nicht mit konsumassoziierten Variablen. Dies deutet darauf hin, dass Theory of Mind Einschränkungen einen dem Substanzmissbrauch vorausgehenden Risikofaktor darstellen könnten.

In der zweiten Studie zeigte sich Krankheitseinsicht bei der Mehrheit der Stichprobe opioidabhängiger Patient*innen als eingeschränkt. Einsicht korrelierte nicht mit soziodemografischen oder konsumassoziierten Variablen. Weder exekutive Funktionen, noch Theory of Mind waren mit Krankheitseinsicht assoziiert, weshalb sich der Defizit-Ansatz und die kognitiv- neuropsychologische Perspektive für Opioidabhängigkeit nicht bestätigen ließen. Krankheitseinsicht war mit Stigma-Resistenz assoziiert und korrelierte negativ mit Selbststigmatisierung, was zugunsten des Kein-Defizit-Ansatzes interpretiert werden kann.

Zusammenfassend lässt sich sagen, dass weiterführende Forschungsarbeiten erforderlich sind, um erstens die Beziehung zwischen Theory of Mind, den exekutiven Funktionen und Traumatisierung in der Kindheit, zweitens die Beziehung zwischen Krankheitseinsicht und Selbststigmatisierung und drittens die mögliche Rolle einer defizitären Theory of Mind als Risikofaktor für Substanzmissbrauch besser zu verstehen. Darüber hinaus sind Theory of Mind, Krankheitseinsicht und Selbststigmatisierung vielversprechende Ansatzpunkte für klinische Interventionen bei Opioidabhängigkeit.

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