Double Threat - Trauma and PTSD in Adolescents with Substance Use Disorders

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In accordance with §8 (1) of the doctorate regulations of the School of Science of Technische Universität Dresden, this dissertation has been prepared as a self-contained work. Chapters 2 to 6 of this dissertation consist of studies published or submitted for publication in peer-reviewed scientific journals:

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Details regarding, acknowledgements, grant funding and competing interests are presented in the relevant chapters. For the sake of consistency, all chapters, subsections, figures, tables, references and appendices were formatted in the same language (English) and citation style (APA Style Guide 7th edition). Select tables and figures were copied from the original publications. Since all studies have been published or are currently under review in open-access journals, no additional permission is needed to reprint the relevant figures and tables. None of the above publications have been or are intended to be used for other dissertations.

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Important Abbreviations

SUD – Substance Use Disorder

PTSD – Post-Traumatic Stress Disorder

SC – Symptom Cluster

TE – Traumatic Experience

MDMA – Methylenedioxymethamphetamine

DUDIT – Drug Use Disorder Identification Test

UCLA PTSD – The University of California at Los Angeles Post Traumatic Stress Disorder Reaction Index for DSM-IV

MINI-KID - The Mini-International Neuropsychiatric Interview for Children and Adolescents

DSM-5 - Diagnostic and statistical manual of mental disorders 5

DV – Dependent Variable

Abstract

Background: Substance use disorders (SUDs) are a great burden on adolescent patients and treatment of these patients is often not successful. One reason for this difficulty is the high rate of co-occurring disorders. One disorder that frequently accompanies SUDs in adolescence is a Post-Traumatic Stress Disorder (PTSD). In studies it has often been reported that a large number of patients fulfill diagnostic criteria for both disorders at the same time. Several explanations for this co-occurrence exist: i) A common etiological factor (genetic predisposition, similar neurobiological pathways) might underlie the development of both disorders. ii) Various lifestyle factors that go hand-in-hand with an adolescent SUD (risky sexual behavior, violent dark markets) might expose patients to circumstances that increase the rate of encountered traumatic experiences (TEs) and therefore PTSD. iii) The self-medication hypothesis, where it is posited that adolescents use drugs to medicate their PTSD symptoms, often in a very specific manner, such that particular substances are used to reduce explicit symptoms. One aim explored in this thesis is the relationship between SUD, TEs, and PTSD with regard to differences in SUD severity, patterns of substance use, the role of self-medication and the effects of SUD-specific treatment on PTSD symptomatology.

Methods: Five studies are presented in chapters 2 to 6 of this thesis. Chapter 2 contains a study in which the Drug Use Disorder Identification Test (DUDIT) was evaluated for use in a psychiatric adolescent patient population. This was the first study in which the DUDIT in relation to DSM-5 criteria was evaluated, in order to try to establish cut-off scores for the presence of a SUD in adolescents. In chapter 3 an evaluation is presented of the differences in SUD severity between adolescents with a SUD ('noTE' group), adolescents with a SUD and a history of TE but not PTSD ('TE' group) and adolescents with SUD and co-occurring PTSD ('PTSD' group). In the study presented in chapter 4 an investigation of the differences in substance use patterns between the three groups was undertaken, along with an evaluation of the associations between PTSD symptoms and use of specific substances. In chapter 5, the role coping motives play in the relationship between substance and PTSD symptoms was established. Finally, in chapter 6 the results of a pragmatic clinical trial are presented, in which the effects of a group-based treatment manual (the DELTA program) on SUD symptoms, substance use frequency and PTSD

symptoms are assessed.

Results: Across all included studies in this dissertation, an instrument for the assessment of SUD in adolescents was evaluated. This was used with other instruments, to establish a link between adolescent SUD and increased rates of PTSD and substance use. Furthermore, the connection between SUD and PTSD in adolescence seems to be related to a self-medication motive. Additionally we established a treatment program that reduced SUD symptoms but failed to influence the PTSD symptoms, which indicates treatment specific to one disorder is unlikely to support reductions in the co-occurring disorder. More specifically, the results presented in chapter 2 showed that the DUDIT has excellent discriminant validity and is a valid tool for the assessment of SUD severity in a clinical adolescent population. In chapter 3, it was shown that the prevalence of TEs and PTSD in adolescents with SUD is higher than in the general adolescent population. Furthermore, the PTSD group showed a significantly higher level of SUD severity than the other two groups. In contrast to our expectations, the TE group did not differ significantly with regard to SUD severity from the noTE group. In addition, SUD severity correlated positively with the number of PTSD symptoms in each symptom cluster. The study presented in chapter 4 showed that past-month substance use frequency was nearly the same across groups and across substances, with only the use of methylenedioxymethamphetamine (MDMA) being significantly more frequent and more prominent in the PTSD group compared to the other two. Participants in the PTSD group also reported a significantly earlier age of first substance use compared to participants in the other two groups. Moreover, in this study it was shown that the presence of the avoidance symptom cluster of PTSD was related to a more frequent past-month MDMA use. The findings presented in chapter 5, confirmed the pattern detected for past-month substance use in chapter 4. The PTSD group showed a more frequent MDMA use over the past-year compared to the other two groups. Additionally, the PTSD group reported using substances more frequently for coping reasons, and the frequency of coping use motives was positively correlated with the frequency of past-year MDMA use. In this study, evidence was provided that the relationship between group membership (noTE, TE, PTSD) and MDMA use frequency is in part mediated by the relationship both variables have with coping use motives. In chapter 6 medium-sized but non-significant reductions were shown in SUD symptoms and substance use frequency as a result of the DELTA intervention. Additionally, there was no indication that the

treatment program resulted in changes in PTSD symptomatology.

Discussion: Several important conclusion can be derived from the studies presented in this thesis. First, a co-occurring PTSD is more prevalent in SUD patients than in the general adolescent population and is associated with higher SUD severity. Second, patients with co-occurring PTSD and SUD are distinguished from SUD patients without PTSD through their increased use of MDMA. Third, the relationship between PTSD and MDMA use is partially mediated by a coping motive, supporting the self-medication hypothesis. Finally, the treatment of co-occurring PTSD and SUD seems to require therapeutic interventions specific for each disorder. The result that PTSD symptoms are not reduced after SUD-specific treatment can be interpreted as support for the self-medication hypothesis as well, in the sense that the treatment of the consequence (SUD) does not affect the preceding factor (PTSD). However, while the above interpretation is consistent with the data presented in this thesis on substance use itself, the associated data on the occurrence of SUDs indicates, that more factors than just self-medication are relevant for the development of a SUD. Furthermore, the results of this thesis do not imply that substance use motivated by self-medication motives is harmless or even beneficial, since there was no way of assessing if self-reported, coping-motivated substance use is successful in reducing symptoms or acute psychopathology. Consequently, in future projects focus should be on developing longitudinal research designs, in order to assess if and how PTSD symptoms develop over time with regard to substance use and how substance use trajectories develop in relation to PTSD symptomatology.

1. General Introduction

Adolescence is a developmental stage that occurs between the ages of 10 and 19, and marks the transition from childhood to adulthood (Plummer et al., 2017; Waltereit et al., 2018). This transitional period includes the development and onset of a large percentage of mental health disorders (Kessler et al., 2005). These early-onset disorders are often a heavy burden for adolescents and their presence is associated with a number of negative life outcomes in adulthood, such as educational failure, suicidality, social isolation, or criminal activity (Copeland et al., 2015). Furthermore, if a person is diagnosed with one mental health disorder, their risk for developing an additional disorder is increased for the next 15 years, but especially for the first year after diagnosis (Plana-Ripoll et al., 2019). Fulfilling the criteria for not just one, but two psychiatric disorders is an exceptional burden for adolescents and has a negative impact on normal age-appropriate development (Suntharalingam et al., 2021).

In this thesis, focus is placed on the co-occurrence of two widespread and debilitating mental health disorders: Substance use disorders (SUDs) and post-traumatic stress disorder (PTSD). A number of epidemiological studies have shown that these disorders frequently occur together (Brady et al., 2004). In North American adolescents this co-occurrence is often observed, with 20 – 54% of adolescents diagnosed with a SUD also fulfilling symptoms for PTSD (Turner et al., 2004; Williams et al., 2008). Similarly, German adolescents with a PTSD diagnosis fulfill SUD criteria at a rate of 30% (Essau et al., 1999). However, before the relationships between these disorders are explored further, a comprehensive description of each diagnosis is appropriate.

1.1 Substance Use Disorder

The use of psychoactive substances, while not pathological on its own, is the direct antecedent and requirement for the diagnosis of a SUD. According to the DSM-5 criteria, a SUD is always related to one of the following specific substances or class of substances: alcohol, caffeine, cannabis, phencyclidine, other hallucinogen, inhalant, opioid, sedative/hypnotic/anxiolytic, stimulants, cocaine, tobacco, or other substances (American Psychiatric Association, 2013). Based on this classification scheme it is conceivable that a patient can be diagnosed with several SUDs at the same time, if they use different substances. In

order to meet the criteria of a SUD diagnosis two out of eleven symptoms need to have been present at the same time over the past year, and a SUD can be classified as light (2-3 symptoms), moderate (4-5 symptoms), or severe (≥ 6 symptoms). All diagnostic criteria for a DSM-5 SUD are listed in Table 1-1.

Table 1-1. Symptoms of a DSM-5 substance use disorder

Substance Use Disorder symptoms according to DSM-5
1. Hazardous use
2. Social/interpersonal problems related to use
3. Neglect of major roles to use
4. Withdrawal
5. Tolerance
6. User of larger amounts or for a longer timeframe
7. Repeated attempts to quit or control use
8. A large amount of time is spent using it
9. Negative physical or psychological problems related to use
10. Activities given up to use
11. Craving

SUDs are prevalent disorders, with nearly 7% of adults fulfilling the criteria for at least one SUD in the past year (Seitz et al., 2019). In adolescents, these numbers tend to be even higher as seen in one study in which it was shown that up to 15% of adolescent participants reported a SUD over the previous year (Perkonigg et al., 2006). A large proportion of this prevalence is related to tobacco use disorder, without which the prevalence falls to around 3% for adults and 4% for adolescents (Perkonigg et al., 2006; Seitz et al., 2019). While a SUD in adolescences may induce developmental harm on its own (Kulak & Griswold, 2019), the presence of this disorder is also related to negative health outcomes such as an increased risk of accidents and violence (Eaton et al., 2012; Johnston et al., 2003), high-risk sexual behavior (Tapert et al., 2001), and chronic health problems (Mertens et al., 2007). The treatment of a SUD is a highly complex process, which can involve a number of different methods, approaches and settings (Pickard, 2020). Most treatment options for adolescents consist of counselling in early intervention services or clinical treatment in outpatient and inpatient settings (Winters et al., 2011), in addition to individual or group therapy (Weiss et al., 2004). While there is clear evidence that treatment can work, especially if cognitive behavioral therapy is used (Tanner-Smith et al., 2013), up to 50% of adolescents with SUD relapse during the first year after treatment (Deas & Thomas, 2001; Grella et al., 2004). One reason for this difficulty in successfully treating adolescent SUD patients (Deas & Thomas, 2001; Riggs, 2003) is related to the high rates of other psychiatric disorders present in this population (Deas, 2006). Up to 75% of adolescents

with a SUD report symptoms of a co-occurring psychiatric disorder (Kandel et al., 1999; Storr et al., 2012) such as depression, conduct disorder or attention-deficit hyperactivity disorder (Deas, 2006; Kandel et al., 1999; Storr et al., 2012). An additional disorder that often co-occurs to SUD is post-traumatic stress disorder (PTSD). One goal of this work is the exploration of this supposed connection between TEs and the occurrence of SUDs from the common etiology to the integrated treatment.

1.2 Post-Traumatic Stress Disorder

PTSD is a psychiatric disorder that, by definition, describes a pathological state resulting from an experience that involves death or the threat of death, serious injury, or sexual violence, namely a TE as defined by the DSM-5 diagnostic criteria (American Psychiatric Association, 2013). A PTSD can be diagnosed if a patient experiences intrusion symptoms (such as flashbacks, or recurrent distressing memories of the event), an avoidance of stimuli associated with the TE, negative changes in cognition and mood, and clear changes in arousal and reactivity (hyperarousal), after being exposed to a TE (American Psychiatric Association, 2013). However, a consistent finding from epidemiological studies is, that a large majority of people having a TE do not develop PTSD (Breslau, 2009). This is in line with studies showing that up to 26% of German adolescents have had TEs (Perkonigg et al., 2000). However, PTSD only occurs at rates of 1% to 2% in this population (Essau et al., 1999; Perkonigg et al., 2000; Salazar et al., 2013); this being slightly lower than the 3% to 7% for adults (Glaesmer et al., 2015; Kuwert et al., 2015). In the treatment guidelines for PTSD the use of psychotherapeutic approaches, such as cognitive behavioral therapy (CBT), have been recommended (Keane et al., 2006; Straud et al., 2019). These have been shown to be effective, with about 50% of PTSD patients improving after treatment (Bradley et al., 2005). However, these results were associated with patients with a singular diagnosis of PTSD and the co-occurrence of one or more disorder in addition to PTSD is related to worse treatment outcomes (Back, 2010; Back et al., 2009). One reason for this difficulty may be linked to findings, showing that early childhood trauma is related to higher rates of substance use and SUDs (Driessen et al., 2008; Dube et al., 2003), a stronger enjoyment of drug experiences (Carlyle et al., 2021) and worse treatment outcomes (Fitzpatrick et al., 2020; Karsberg et al., 2021).

1.3 Co-occurrence of SUD and PTSD

These findings highlighting a strong relationship between the presence of a PTSD and SUDs mark a starting point for the exploration of this co-occurrence. Specifically the question regarding the developmental etiology of these two disorders: Why would these two disorders develop concurrently? So far, three predominant explanations have emerged surrounding this discourse: i) The "common factor" hypothesis, where it has been suggested that both disorders may be an expression of an underlying common factor. Previous research has identified similar genetic factors that are related to an increased risk for the development of both disorders (Xian et al., 2000). Additionally, both disorders are related to similar dysfunctions in neurochemical pathways like the dopaminergic and noradrenergic systems (María-Ríos & Morrow, 2020).

ii) The "exposure" hypothesis, where it has been suggested that the TEs and PTSD may occur and develop after the onset of the SUD. This explanation rests on the idea that adolescents who engage in substance use may engage in more frequent high-risk behaviors, such as risky sexual behavior or violent confrontations (Baskin-Sommers & Sommers, 2006). These high-risk situations may lead to situations that develop into a TE, e.g. first-hand violence (Harford et al., 2013), and a subsequent development of a PTSD (Glaesmer et al., 2015; Strom et al., 2012). Additionally, people who use drugs may unintentionally overdose and non-fatal drug overdoses are traumatizing to experience as well as witness (Schneider et al., 2021).

iii) TEs and PTSD develop before substance use is initiated and subsequent use transforms into a SUD. Based on this explanation, TEs occur earlier than first substance use and this use fulfills the role of a coping mechanism for PTSD symptoms, and consequently develops into a SUD (Dworkin et al., 2018; Khantzian, 1997; McCauley et al., 2012). This "self-medication" hypothesis, has gained much empirical support (Chilcoat & Breslau, 1998; Sheerin et al., 2016) where it has been shown for example that 1/5th of PTSD patients use substances in an attempt to relieve PTSD symptoms such as hyperarousal, avoidance or intrusions (Leeies et al., 2010). Per definition, the self-medication hypothesis includes assumptions about the relative age of onset of PTSD and SUD namely, that SUD symptoms should develop following the PTSD symptoms. This pattern has been investigated and confirmed in previous studies, in which it was shown that anxiety disorders (Slade et al., 2015), conduct disorders (Guldager et al., 2012), and PTSD

(Wu et al., 2010) predate future SUDs. Moreover, in the self-medication hypothesis it is predicted that specific substances are used to deal with specific types of pathological states, as has been shown previously for alcohol use and hyperarousal symptoms (McCauley et al., 2012; Somohano et al., 2019). The main distinguishing factors between these three theories is timing. Specifically, the "common factor" theory suggests a similar timeframe for development of symptoms, the exposure theory assumes that PTSD develops after substance use has been initiated, and the self-medication hypothesis suggests that substance use is initiated as a consequence of PTSD symptoms, see Figure 1-1.

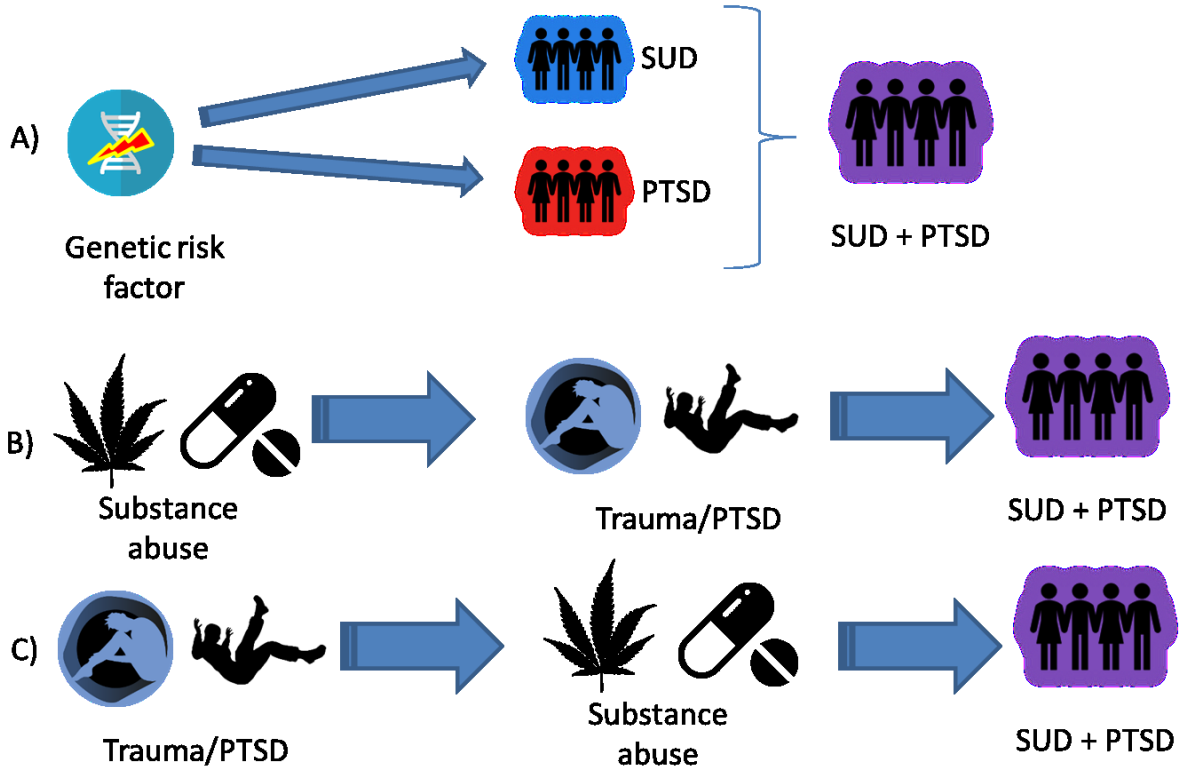

Figure 1-1. Timelines of the three developmental theories about co-occurring PTSD and SUD. A) Common risk factor hypothesis; B) Exposure hypothesis; C) Self-medication hypothesis. SUD, substance use disorder; PTSD, post-traumatic stress disorder.

Since both disorders (SUD and PTSD) include a first sign of symptoms in adolescence, focusing on this developmental period can help elucidate the potential connections between the two. Especially considering, that very little research has been focused specifically on adolescents and the issues they present with regard to co-occurring diagnoses. Furthermore, a more specific look is needed detailing differences between adolescents who develop PTSD after a TE and those who do not. This inclusion of all three groups (SUD only, SUD and TE but no PTSD, SUD and PTSD) happens rarely (Jaycox et al., 2004),

with most studies being focused on co-occurring SUD and PTSD (Davis et al., 2019; Driessen et al., 2008; Wieferink et al., 2017) or trauma in general (Bougard et al., 2016; Fitzpatrick et al., 2020; Simmons & Suárez, 2016).

1.4 Research Aims and Hypotheses

The main goal of this work was to better understand the pathogenesis of co-occurring SUD and PTSD in adolescence in order to improve psychiatric care and treatment of affected patients. More explicitly, the aim was to explore how co-occurring TEs and PTSD are related to SUD severity & to patterns of substance use. Specifically, three groups of participants were investigated: i) Adolescent SUD patients without trauma history (noTE group), ii) Adolescent SUD patients with a history of TEs but not PTSD (TE group), and iii) adolescent SUD patients with co-occurring PTSD (PTSD group). On the basis of this aim three hypotheses are presented:

1) SUD severity will differ between the three groups investigated in the work of this thesis (noTE, TE, PTSD), with the PTSD group showing the highest level of severity, and the noTE group the lowest, with all differences between groups being significant.
2) Across substances, the PTSD group will show the highest frequency of substance use and the noTE group the lowest, with all group differences being significant.
3) The explored differences in hypothesis two can partly be explained by participants in the PTSD group reporting an association between substance use frequency and self-medication motives.

1.5 Sample Population and Measurements

All studies presented in chapters 4-8 were conducted using data collected between November 2017 and December 2021 of treatment-seeking adolescents in Saxony, Germany. More specifically, the work presented in chapter 4 included patients from the general outpatient department and the specialized department for adolescent substance abuse at the Clinic for Child and Adolescent Psychiatry at the University Hospital C.G.C. Dresden. The work discussed in chapters 5-8 included patients drawn from the same department as well as patients from assisted-living communities offering inpatient rehabilitation

for adolescents with SUD. The demographic details of the participants will be presented in the relevant chapters.

In the frame of the presented studies a variety of psychometric instruments were applied. Most of these instruments were consistent across the studies, with different components of each instrument being analyzed in respective projects. A general overview over the assessment instruments is given in the following, with the specific dependent variables (DVs) analyzed in each study, presented in each chapter.

1.5.1 Sociodemographic Background

The applied sociodemographic questionnaire was a self-designed instrument consisting of 36 items, organized in three parts. The first part was used to assess education levels, income and the employment of caretakers. The second part included questions about the adolescent patient including age, gender, and educational achievement. The final part consisted of questions about the substance use history of the patient, which were not analyzed for this work.

1.5.2 Diagnostic Interview

The Mini-International Neuropsychiatric Interview for Children and Adolescents (MINI-KID, licensed according to invoice #20220315.1) (Sheehan et al., 2010) is a structured diagnostic interview used to evaluate the presence of a psychiatric disorder in children and adolescents. The interview uses screening and diagnostic yes/no questions to assess the presence of 32 psychiatric disorders, including all possible SUDs according to DSM-5 criteria. All interviews were conducted by psychologists working in the Department of Adolescent Substance Abuse using a German translation of the original MINI-KID (Plattner et al., 2012).

1.5.3 Assessment of PTSD and Trauma History

The University of California Los Angeles Post Traumatic Stress Disorder Reaction Index for DSM-IV (UCLA PTSD (Steinberg et al., 2004) is a self-report instrument that can be used to screen for exposure to TEs, and assess PTSD symptoms in school-age children and adolescents. It has been translated for, and used with German-speaking populations (Ruf et al., 2011). The instrument consists of a trauma history section, in which patients indicate the TE that afflicts them the most and the traumatizing features of the event (Criterion A). In the next section the frequency of the occurrence of PTSD symptoms during the past

month (rated from 0 = none of the time to 4 = most of the time) is assessed. The items map directly onto the DSM-IV intrusion/re-experience (Criterion B), avoidance (Criterion C), and hyperarousal (Criterion D) criteria. Scoring algorithms permit the tabulation of the UCLA PTSD total score, and A, B, C and D subscale scores. The DSM-IV diagnosis PTSD is given when all four criteria (Criterion A, B, C & D) are present (Steinberg et al., 2004).

1.5.4 Severity of Substance Use Disorders

The Drug Use Disorders Identification Test (DUDIT (Berman et al., 2005), German version from (EMCDDA, 2005)) is a self-report instrument composed of 11 items which is used to identify problems with the use of illegal drugs. Scoring of the DUDIT is two-fold: items 1 to 9 are scored on a five-point Likert scale, while items 10 and 11 are scored on a three-point scale (with the three items being score 0, 2 and 4 respectively). The overall score (DUDIT-total) is calculated by summing the scores of all items, the maximum score is 44. Since the questionnaire had been previously only evaluated for use in adult patient groups, in chapter 4 an evaluation is presented of the diagnostic accuracy of the DUDIT in a clinical adolescent sample.

1.5.5 Substance Use Motives

To assess use motives, a self-designed questionnaire was used in which twenty-two questions were asked that are answered on a scale with zero (“never applies”), one (“rarely applies”), two (“sometimes applies”), three (“mostly applies”) or four (“always applies”) points. The questionnaire had been designed to provide details about a patients substance use and allow for the extraction of three scores for different use motives: “coping” (4 items), “social motives” (3 items), and “other” (3 items). In order to determine if the theoretical structure of the questionnaire was empirically supported, a preliminary exploratory and confirmatory factor analyses were undertaken, the results of these are reported in chapter 7.

1.5.6 Substance Use Patterns and Frequency

The extent of substance use was assessed by clinical psychologists via a self-designed interview (Golub et al., 2021), in which it was specifically asked for the number of days each substance was used in the last 4 weeks as well as per month over the past year. Additionally, for each substance the interviewer

recorded the age of the patient when they first used the substance, as well as the route of administration (oral, nasal, smoked, intravenously). Furthermore, in the questionnaire the amount of each substance that was used on an average day was assessed, with the following units of consumption: nicotine (cigarettes), alcohol (standard drinks), cannabis (grams), MDMA/ecstasy (number of pills), amphetamine (lines or grams), methamphetamine (lines or grams), cocaine (lines or grams), hallucinogens (trips, micrograms, grams), ketamine (grams), and opiates (grams).

2. Assessment of SUD Severity

This chapter is based on the following publication:

Basedow LA, Kuitunen-Paul S, Eichler A, Roessner V and Golub Y (2021) Diagnostic Accuracy of the Drug Use Disorder Identification Test and Its Short Form, the DUDIT-C, in German Adolescent Psychiatric Patients. *Front. Psychol. 12:678819*. doi: 10.3389/fpsyg.2021.678819

In this paper, a report was presented about a psychometric evaluation of the DUDIT in adolescent patients with substance use disorders, including an analysis of receiver operating characteristics curves and area under the curve. Additionally, cut-off scores were established for adolescent psychiatric patients based on DSM-5 criteria. This is significant because previous psychometric assessments of the DUDIT were based on DSM-IV criteria and exclusively available for adult patients.

2.1 Background

As one of the main goals of this thesis is the assessment of differences in SUD severity between the three groups (noTE, TE, PTSD) a properly evaluated instrument for the use in adolescents was needed. One such instrument, available in 23 languages and for free from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 2005), is the Drug Use Disorders Identification Test (DUDIT). The DUDIT was developed in 2005 based on data from Swedish adults in the criminal justice system, addiction treatment centres and community samples (Berman et al., 2005). A review of 18 studies has shown that the DUDIT is a reliable and valid instrument for clinical use, with high internal consistency, sensitivity, and specificity (Hildebrand, 2015). However, only three international studies used the DUDIT within adolescent samples from Turkey (Evren, Ovali, et al., 2014), South Africa (Martin et al., 2014), and the Netherlands (Hillege et al., 2010); evaluating merely internal consistency and factor structure and thus making no judgement about applicability for clinical use. Consequently, DUDIT cut-off values for a SUD screening are available only for adults and are based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders-IV (DSM-IV) of substance abuse and substance dependence (American Psychiatric Association, 2000). According to these DSM-IV criteria, a DUDIT score >25 indicates dependence, independently of gender, while for men a DUDIT score > 5 and women > 1 indicates a large deviation from the mean in a general population sample (Berman et al., 2005).

To achieve the goal of a high diagnostic accuracy, the cut-off values of an instrument need to allow categorizing a patient correctly as having or not having a disorder (true positives and true negatives). At the same time the cut-off value should minimize the chance of categorizing someone with a disorder as

disorder free or vice versa (false negatives and false positives). A common tool to determine appropriate cut-off values is the Receiver Operating Characteristics (ROC) curve that plots sensitivity (true positive rate) against the false positive rate, which is calculated with 1 – specificity (the true negative rate). Using the ROC curve the area under the curve (AUC) serves as a global measure of discriminative power, while an index that maximizes sensitivity and specificity (Youden's Index) can be calculated to find a balanced cut-off point for a dichotomous diagnostic test (Fluss et al., 2005) such as the DUDIT.

In this study, we evaluated if the DUDIT can distinguish German adolescent, psychiatric patients with a SUD related to illicit drugs, from adolescent, psychiatric patients without a SUD. By assessing the ROC curve, evaluating the AUC, and calculating cut-off values based on Youden's Index, we assessed the suitability of the DUDIT as a screening instruments for a SUD related to illicit substances, among adolescent psychiatric patients. Cut-offs indicate the presence of a SUD of any severity according to DSM-5 criteria with a balanced combination of sensitivity (% of true positive subjects within the SUD group) and specificity (% of true negative within the no-SUD group) (American Psychiatric Association, 2013).

2.2 Methods

2.2.1 Participants

We recruited participants from the general outpatient department and the outpatient department for adolescent substance abuse of our Clinic of Child and Adolescent Psychiatry. This mixed sample was then divided into two groups based on their DSM-5 SUD diagnosis (presenting with at least 2 out of 11 criteria) established with the MINI-KID: Adolescent patients with SUD (*n* = 57 (20 female), mean age = 15.8 ± 1.4 years) and adolescent patients without a SUD (*n* = 67 (34 female), mean age = 15.4 ± 1.6 years).

2.2.1 Procedure

Between January 2019 and February 2021, we recruited adolescent patients, age 11-18 years, for participation in the study. Patients were approached for recruitment during their first appointment at our clinic. During this first appointment, next to standard clinical procedure a psychologist from our clinic provided an overview over the study and asked for informed consent. *N* = 294 patients were asked to

participate in this manner, of which *n* = 249 provided informed consent, meaning *n* = 45 declined to participate. If participants provided consent, we performed the data collection in the form of questionnaires and interviews with patients. The questionnaires were handed out during the first appointment to the participants without further instruction and the request to fill them out alone. The MINI-KID was conducted by a professional psychologist during a separate appointment at our clinic. We only included participants who had fulfilled out the DUDIT as well as participated in the second appointment for MINI-KID, leaving us with *n* = 128 participants (*n* = 48 from the general outpatient clinic and *n* = 80 from the department of substance abuse). The study was conducted in accordance with the Declaration of Helsinki. Patients as well as legal guardians were informed about the projects thoroughly and comprehensively. Written informed consent was obtained from all legal guardians. All procedures of this study were approved by the Institutional Review Board of the University Hospital C. G. Carus Dresden (EK 66022018).

2.2.1 Measures

2.2.1.1 DUDIT

See Chapter 1.5.4. The DV in this study was the total DUDIT score. Additionally, a group of senior psychotherapists and psychiatrist from our clinic adapted the language of the DUDIT to be more appropriate for the adolescent participants (e.g. changing the German formal version of you “Sie” to the more familiar form “Du”). *N* = 85 of our participants were asked to rate the quality and comprehensiveness of the adapted DUDIT questionnaire. The majority (66%) rated the DUDIT as a moderate to good questionnaire (a score of 5 or above on a 10-point scale), about 86% reported that the DUDIT is comprehensible (a score of 5 or above on a 10-point scale), and 96% answered that they understood the majority of the questions in the DUDIT. Consequently, it can be assumed that the DUDIT is well understood by and applicable for adolescents.

2.2.1.2 MINI-KID

See Chapter 1.5.2. Since the DUDIT only refers to illegal drugs, the main variables of interest was the presence and severity (mild, moderate, severe) of a substance use disorder (except alcohol or tobacco) according to DSM-5 criteria.

2.2.1 Statistical Analysis

We conducted the confirmatory factor analysis (CFA) with the lavaan package (Rosseel, 2012) in RStudio (RStudio Team, 2020). All other analyses were conducted with IBM SPSS Statistics 25.0. In case of missing values on the DUDIT, participants were excluded if they answered less than 80% of the questions. In cases were at least 80% of questions were answered, missing values were replaced by the mean value of the answered items (*n* = 10). Of *n* = 128 participants, *n* = 4 participants answered less than 80% of the questions, leaving us with *n* = 124 participants for our analyses. Participants were divided into two groups according to their SUD status for the past 12 months (any SUD vs. no SUD) based on the MINI-KID results. Descriptive group differences were t- or Chi-Square-tested.

In the next step, we created ROC curves to examine sensitivity and specificity at each possible cut-off value by plotting sensitivity (in %) at the y-axis vs 100 – specificity (in %) at the x-axis. We calculated the AUC (0-1 range, higher scores indicating higher discriminative power) to assess the overall diagnostic accuracy of the DUDIT. An AUC of 0.7 to 0.8 is considered as acceptable, 0.8 to 0.9 is considered to be excellent, and a value higher than 0.9 is outstanding (Mandrekar, 2010). The optimal cut-off point was determined by Youden's Index *J* (Sensitivity + Specificity – 1; 0-1 range, higher scores indicating higher effectiveness). Additionally, we repeated the analysis described above comparing only the participants with a mild or moderate SUD (n = 21) to the participants without SUD. All *p*-values < .05 were considered significant.

2.3 Results

2.3.1 Descriptive Statistics

The demographic and clinical characteristics of the sample are presented in Table 2-1. SUD and non-SUD patients did not differ significantly in mean age or sex. DUDIT score (*t-score* (122) = – 13.3, *p* <.001) was significantly higher in the SUD group than in the non-SUD group.

Table 2-1. Sample description

	Non-SUD patients (n = 67)	SUD patients (n = 57)	Test statistic	p-value	Total (*n* = 124)
Mean age in years (SD)	15.4 (1.6)	15.8 (1.4)	*t (*122) = – 1.4	.17	15.6 (1.5)

Sex	34 f, 33 m	20 f, 37 m	X^2 (1) = 3.1	.08	54 f, 70 m
Mean DUDIT-total score (SD)	2.0 (4.8)	17.7 (8.1)	*t* (122) = – 13.3	<.001	9.2 (10.2)
SUD diagnoses			X^2 (3) = 124.0	<.001	
No SUD	67	0			67
Mild	0	9			9
Moderate	0	12			12
Severe	0	36			36

Note: SUD diagnoses and severity were assessed on basis of the MINI Diagnostic Interview. *DUDIT*, Drug Use Disorders Identification Test; *SUD*, substance use disorder; *SD*, standard deviation; *f*, female; *m*, male

2.3.2 Area Under the Curve

The DUDIT raw values distribution and ROC curve are shown in Figure 2-1.

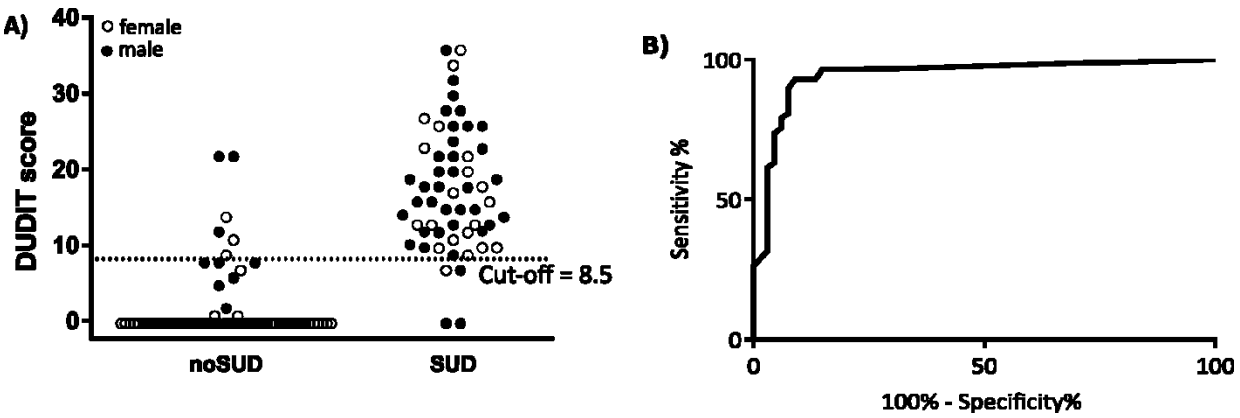

Figure 2-1. A) Raw values and cut-off for DUDT in total sample. Single dots represent the results from a single participant. A dotted line marks the optimal cut-off score based on Youden's Index J. B) ROC Curve for the DUDIT with sensitivity plotted against 100%-specificity.

The DUDIT AUC was larger than 0.9 with AUC = .95, 95% CI [0.90, 0.99]. Compared to the whole sample the AUC is slightly smaller when comparing only patients with mild and moderate SUD to participants without a SUD: AUC = .93, 95% CI [0.86, 1.0].

2.3.3 Cut-off Values

For the DUDIT-total the optimal cut-off was at a value of 8.5 (sensitivity = .93, specificity = .91, *J* = .84), meaning 93% of SUD patients were correctly classified as SUD patients, while 9% of non-SUD patients were falsely classified as SUD patients. In mild or moderate cases our analysis resulted in the same cut-off values as were determined for the complete sample: Based on Youden's Index *J* the optimal cut-off

value for distinguishing patients with a mild or moderate SUD from patients without a SUD is a DUDIT score of 8.5 (sensitivity = .95, specificity = .91, *J* = .86).

2.4 Discussion

In this study, we showed that the DUDIT has outstanding diagnostic accuracy for detecting SUDs regardless of severity, in German adolescent psychiatry patients based on DSM-5 criteria. Additionally, the DUDIT shows excellent diagnostic accuracy for detecting patients with mild or moderate SUDs. Finally, we determined a DUDIT cut-off value of 9 across all participants, meaning any patient with a DUDIT score higher than 8 is likely to fulfil the diagnostic criteria for a SUD. If only differentiating between patients without a SUD and patient with mild or moderate SUD the same cut-off value can be used.

Overall, the DUDIT is an instrument with excellent discriminative power, regarding adolescent psychiatric patients, and adolescent SUD patients, making it suitable for clinical practice. However, our cut-off values are based on Youden's Index, which aims for a balance between sensitivity (the ability to correctly identify SUD patients) and specificity (the ability to correctly exclude non-SUD patients). Yet, in adult SUD patients DUDIT cut-off values (based on DSM-IV), often have a higher sensitivity than specificity (see (Hildebrand, 2015) for an overview), which might reflect a desire to focus on the ability to correctly identify SUD patients. On the other hand, in a public health setting it might be more important to focus on specificity, excluding non-SUD patients correctly, to establish accurate estimates of prevalence. This focus on specificity might be relevant when trying to investigate local patterns of SUD distribution or when aiming to offer selected SUD-specific treatment options.

This study is the first published psychometric assessment of the German version of the DUDIT. While previous studies have used the DUDIT as a measure or screening tool (Dyba et al., 2019; Schäfer et al., 2017; Spencer et al., 2018), none have reported on the psychometric properties. Additionally, previous research has assessed the DUDIT on basis of the DSM-IV criteria for substance abuse and dependence (see Hildebrand et al. (2015) for an overview), which makes this study the first psychometric assessment using the updated DSM-5 criteria with three levels of SUD.

In addition to assessing the diagnostic accuracy for the whole sample, we investigated DUDIT

performance in a subsample consisting of patients with mild or moderate SUD. In these patients, the DUDIT cut-off value was related to a higher sensitivity but the same level of specificity, meaning that the DUDIT was more likely to correctly identify patients with a mild or moderate SUD, and had the same likelihood of incorrectly classifying non-SUD patients as having a mild or moderate SUD. Comparing our cut-off, sensitivity, and specificity values to previous research is of limited use, since previous studies did not use DSM-5 diagnostic criteria as a comparison (Hildebrand, 2015). Nonetheless, our cut-off values for any DSM-5 SUD are slightly lower than values for DSM-IV dependence (Durbeej et al., 2010) or any DSM-IV drug use disorder (Evren, Ogel, et al., 2014; Evren, Ovali, et al., 2014). This difference is likely due to these three studies sampling participants from criminal justice settings instead of a psychiatric care environment as we did. Unfortunately, no other cut-off values for adolescents have been established, which highlights the need for additional research into substance use specific instruments for adolescents.

2.4.1 Limitations and Future Research

First, we focused on a very specific sample, namely psychiatric patients. This subpopulation is pre-selected in so far, as they showed some disordered behaviour in the past that made them or their parents seek psychiatric care for their disorder. Therefore, our study fails to include a more general population of adolescents who might fulfil SUD criteria but are not affected enough to seek treatment.

Second, our focus was on screening for any level of severity of a SUD, thus any health care professional who wants to screen for a specific level of severity of SUD could not use the values we calculated. To screen for specific levels of severity, new cut-off values need to be determined. This issue also relates to the first limitation, since it highlights the need to establish cut-off values for each level of SUD severity separately.

Third, in our sample only few patients presented with a mild or moderate SUD, which means our results regarding the cut-off values in non-severe SUD patients should be considered preliminary. Since the sample size in that group was small, future research should take care to repeat a similar analysis with adolescent patients presenting only with a mild or moderate SUD.

Fourth, a considerable proportion of SUD patients were not classified as such (7%). While unfortunate, this is an expected proportion of failure that has been shown to occur at similar rates in the AUDIT

(Kuitunen-Paul et al., 2018). This non-diagnosis might be a result of a social desirability or recall bias, which are known to skew self-report data (Althubaiti, 2016).

Finally, while the majority our patients reported understanding the DUDIT well, *n* = 11 (14%) participants reported that they had problems understanding the DUDIT items and instructions (a score below 5 on a 10-point scale). It is possible that these participants misunderstood the questionnaire and did not answer it correctly. For example, they might have answered the questions while thinking of their use of legally available drugs like alcohol or nicotine.

2.5 Conclusion

This study is the first evaluation of the DUDIT in a German sample as well as a sample of adolescent psychiatric patients, based on DSM-5 criteria. We found that the DUDIT is an easily accessible, free-to-use, screening instruments for SUDs that has high diagnostic accuracy in a German adolescent, psychiatric population. We therefore considered the DUDIT an ideal instrument to compare SUD severity between our populations of interest (noTE, TE, PTSD).

2.6 Acknowledgements, Funding, Conflicts of Interest

During the past 36 months and unrelated to the presented analyses and data, SKP received author fees (Mabuse Verlag).) The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The Sächsische Aufbaubank -Förderbank-, (grant 100362999 to YG), funded this study. The funding body had no role in designing the study, data collection, analysis and interpretation of the data, or writing the manuscript.

3. SUD Severity and PTSD

This chapter is based on the following publication:

Basedow LA, Kuitunen-Paul S, Roessner V and Golub Y (2020) Traumatic Events and Substance Use Disorders in Adolescents. *Front. Psychiatry 11:559.* doi: 10.3389/fpsyt.2020.00559

This study contains an analysis of the differences in SUD severity between three groups of interest (noTe, TE, PTSD). Additionally, trauma characteristics and prevalence of TEs and PTSD in a sample of adolescent SUD patients were also assessed. It was found that adolescent SUD patients with PTSD reported more severe substance use problems than patients without PTSD—regardless of previous TEs.

3.1 Background

Previous research established the link between SUD and PTSD (Brady et al., 2004; Donbaek et al., 2014; Dworkin et al., 2018; McCauley et al., 2012). However, it remains to be explored if SUD severity is only increased in adolescents with co-occurring PTSD, or linked to the occurrence of TEs in general, providing an insight into the pathomechanisms of both disorders.

Here, we assess the prevalence of both lifetime TEs and PTSD according to DSM-IV criteria among German adolescents seeking treatment for a SUD and compare these prevalence rates with the general adolescent population. We compare three groups of SUD treatment-seeking adolescents: adolescents fulfilling DSM-IV PTSD diagnostic criteria ('PTSD' group), adolescents with a history of TEs but no PTSD ('TE' group) and adolescents with no TEs and no PTSD ('noTE' group).

We hypothesize that (1) adolescents with a SUD present with higher rates of current PTSD and past TEs than the general adolescent population. We predict that (2) SUD severity will be higher in the PTSD and TE group than in the noTE group and that (3) SUD severity is positively associated with the number of PTSD symptoms present in each symptom cluster.

3.2 Method

3.2.1 Participants

Between November 2017 and October 2019, *n* = 178 treatment-seeking adolescents at an outpatient clinic for adolescent substance abuse participated in the study. *N* = 64 adolescents (36%) did not complete all necessary questionnaires and were therefore excluded. In the final sample of *n* = 114 patients, the mean age was 15.8 years (*SD* = 1.3) with 43% (*n* = 49) females, see Table 3-1. Secondary

education levels were predominantly classified as low level (55%), while household income was predominantly classified as medium level (57%), see Table 3-1.

3.2.2 Procedures

Data collection was embedded into the standard diagnostic procedures at the outpatient clinic. Questionnaires were handed out to the patients and their legal guardians at the first consultation appointment in the outpatient department. The criteria for harmful use and dependence for all relevant psychoactive substances according to the ICD-10 guidelines (World Health Organization, 1992), were assessed in a personal interview by a trained clinical psychologist. Study assessments took place before any intervention started. The study was conducted in accordance with the Declaration of Helsinki. Patients as well as legal guardians were informed about the projects thoroughly and comprehensively. Written informed consent was obtained from all legal guardians. All procedures of this study were approved by the Institutional Review Board of the University Hospital C. G. Carus Dresden (EK 66022018) and registered at clinicaltrials.gov (NCT03444974). No reimbursement was offered to patients.

3.2.3 Measures

3.2.3.1 University of California at Los Angeles Post Traumatic Stress Disorder Reaction Index for DSM-IV

See Chapter 1.5.3. In the current sample, internal consistency was good for criterion A and B (α = .83 and .86, respectively), and acceptable for criterion C and D (α = .73 and .75, respectively). DVs for this study were the type of reported TEs and the presence of TEs (yes/no) and PTSD (yes/no)

3.2.3.2 DUDIT

See Chapter 1.5.4. In the current sample, internal consistency of the DUDIT was good with α = .87.

SUD diagnosis. DV was the total DUDIT score.

3.2.3.3 SUD Diagnosis

A clinical psychologist assessed criteria for harmful use and dependence syndrome for all relevant psychoactive substances according to ICD-10 (World Health Organization, 1992) in a personal interview with the patients. The SUD diagnosis was established in a consensus-based procedure by interviewing

psychologist and a board-certified child and adolescent psychiatrist

3.2.3.4 Sociodemographic Background

See Chapter 1.5.1. We analyzed the questions indicating age in years, gender, and education level (low, medium, high) of the patient as well as yearly household income (low, medium, high). Adolescents' educational levels and parental income levels were assessed according to previously established criteria (Robert Koch-Institut, 2018).

3.2.4 Statistical Analysis

All analyses were conducted with IBM SPSS Statistics 25.0. Based on UCLA PTSD results, patients were separated into three analysis groups: PTSD diagnosis ('PTSD' group), TE but no PTSD diagnosis ('TE' group), no TE and no PTSD diagnosis ('noTE' group). To investigate the relationship between SUD and PTSD symptoms, Pearson's correlation coefficient *r* was calculated between DUDIT score, the number of possible TEs, and the number of PTSD symptoms within each criterion cluster (Cluster A, B, C, and D). An analysis of variance (ANOVA) was performed to test for mean differences in DUDIT score between the three groups. To determine if the ANOVA is an appropriate procedure we checked the normality of the DV (DUDIT score) by means of the Shapiro Wilk test (Howell, 2002). Additionally, to check for homogeneity of variances, Levene's test was conducted. DUDIT score was normally distributed in the noTE group (W = .944; p = .072), the TE group (W = .956; p = .075), and the PTSD group (W = .952; p = .16). Further, Levene's test showed that the variance of DUDIT score was equal across groups, F (2, 111) = 0.8, p = .452. In cases were the F-test across groups was significant, post-hoc multiple comparisons using the Bonferroni correction were conducted to identify groups differing from each other regarding their mean DUDIT score. To detect demographic differences between the groups, χ^2-tests were conducted. Level of significance was defined as $p < .05$ (two-tailed). Since patients could present with harmful use or dependence for multiple substances, multiple univariate χ^2-tests were used to assess group differences in this variable. For this specific analysis, the level of significance was adapted according to the Bonferroni-procedure to $p < .05/3$. Effect sizes were classified according to Cohen (1988) into small effects ($|r| \geq .10$, partial eta-square $\eta_p^2 \geq .01$), medium effects ($|r| \geq .30$, $\eta_p^2 \geq .06$), and large effects ($|r| \geq .50$, $\eta_p^2 \geq .14$).

3.3 Results

3.3.1 Sociodemographic Characteristics and Substance Abuse

The majority of patients reported enough symptoms to qualify for cannabis abuse (80%), followed by alcohol abuse (39%) and stimulant (amphetamine, methamphetamine, or MDMA) abuse (44%), see Table 5-1. The three groups (PTSD, TE, and noTE) did not differ in any of the assessed sociodemographic characteristics nor in their SUD diagnoses, see Table 3-1.

Table 3-1. Sociodemographic characteristics of the complete sample, and the three subgroups**.**

		Analysis group			Group comparison		
Demographics	Total (*n* = 114)	noTE (*n* = 35)	TE (*n* = 47)	PTSD (*n* = 32)	Test statistic (df)	*p*	Effect size
Mean age (*SD*)	15.8 (1.3)	15.5 (1.3)	16.0 (1.3)	15.8 (1.2)	*F* (*113*) = 1.32	.271	η_p^2 = .023
Gender:					χ^2 (*2*) = 2.427	.297	φ = .15
Female (%)	49 (43)	12 (34)	27 (57)	17 (53)			
Male (%)	65 (57)	23 (66)	20 (43)	15 (47)			
Household income: # of patients in category (%), missing *n* = 60	(*n* = 54)	(*n* = 22)	(*n* = 21)	(*n* = 11)	χ^2 (*4*) = 1.525	.822	.17
Low income	9 (17)	4 (18)	4 (19)	1 (9)			
Middle income	31 (57)	11 (50)	13 (62)	7 (63)			
High income	14 (26)	7 (32)	4 (19)	3 (25)7			
Educational level: # of patients in category (%), missing *n* = 38	(*n* = 76)	(*n* = 22)	(*n* = 34)	(*n* = 20)	χ^2 (*6*) = 4.773	.573	.25
Low	37(55)	9 (41)	16 (47)	12 (60)			
Middle	20 (26)	6 (27)	11 (32)	3 (15)			
High	8 (11)	4 (18)	3 (9)	1 (5)			
Other	11 (14)	3 (14)	4 (12)	4 (20)			
Substance abuse: # of patients presenting with harmful use or dependence per substance (%), missing *n* = 2	(*n* = 112)	(*n* = 35)	(*n* = 47)	(*n* = 30)			
Alcohol	44 (39)	12 (34)	23 (49)	9 (30)	χ^2 (*2*) = 3.286	.193	.17
Cannabis	89 (80)	29 (83)	38 (81)	22 (73)	χ^2 (*2*) = 0.993	.609	.09
Stimulants (amphetamine, methamphetamine, or MDMA)	49 (44)	13 (37)	18 (38)	18 (60)	χ^2 (*2*) = 4.408	.110	.20

Note: *PTSD* = Post-traumatic stress disorder according to DSM-IV. *TE* = Traumatic event. *MDMA* = Methylenedioxymethamphetamine. A clinical psychologist performed the diagnosis of harmful use or dependence syndrome, and multiple diagnoses per patient were possible**.** For the differences in substance abuse, the p-value was adjusted according to the Bonferroni-procedure to $p < .02$**.**

3.3.2 Prevalence Estimates

The majority of patients (69%) reported at least one lifetime TE. Figure 3-1 illustrates that "non-domestic violence" followed by "sexual abuse" were the most-prevalent TEs categories, whereas "war" and "medical treatment" represented the least-frequent categories. Over one third of the patients with TE (41%) also fulfilled the DSM-IV diagnostic criteria for a PTSD according to the UCLA PTSD scale, resulting in a point prevalence of 28% for PTSD in the total sample.

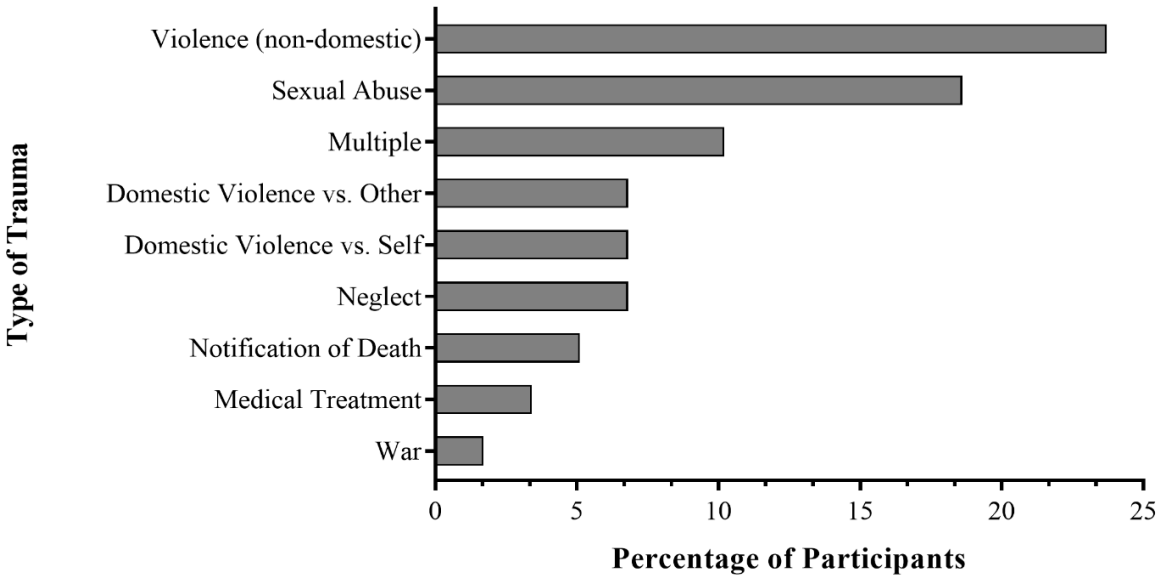

Figure 3-1. The percentage of patients (*n* = 59) that described a particular type of event as their most traumatizing experience. Total *n* = 114, with *n* = 35 reporting no traumatic experiences, and *n* = 20 not clearly identifying the most traumatizing experience.

3.3.3 The Relationship between TEs, PTSD Symptoms and SUD Severity

The number of symptoms in each PTSD symptom cluster (A = number of traumatizing features of TEs, B = intrusion, C = avoidance, D = hyperarousal) correlated positively with each other (all r = .23 to .56, all p < .038) and with DUDIT score (all r = .33 to .48, all p < .003) with an exception of DUDIT score and Cluster A (r = .20, p = .08). The correlations of DUDIT score and clusters B, C, and D can be classified as medium size effects (r =.30 to .49), see Table 3-2.

Table 3-2. Bivariate Pearson correlation coefficients between DUDIT score, the number of Traumatic events (TEs), and the number of symptoms present in Cluster A, B, C, and D of the UCLA PTSD Questionnaire

	DUDIT score	Number of TE	Sum Cluster A	Sum Cluster B	Sum Cluster C	Sum Cluster D
DUDIT score	__	.21*	.20	.33**	.35**	.48**
Number of TEs	.21*	__	.13	.34**	.27*	.16
Sum Cluster A	.20	.13	__	.45**	.27*	.23*
Sum Cluster B	.33**	.34**	.45**	__	.56**	.54**
Sum Cluster C	.35**	.27*	.27*	.56**	__	.47**
Sum Cluster D	.48**	.16	.23*	.54**	.47**	__

Note*: DUDIT* = Drug use disorders identification test. *PTSD* = Post-traumatic stress disorder according to DSM-IV. *Cluster A* = Traumatizing qualities of event. *Cluster B* = Intrusion. *Cluster C* = Avoidance*. Cluster D* = Hyperarousal. *SUD* = substance use disorder according to ICD-10, including substance abuse and substance dependence. *TE* = Traumatic event. *$p < 0.05$, **$p < 0.01$.The number of cases per cell varied due to presence of a PTSD between n = 79 and 114.

3.3.4 Group Differences in SUD Severity

The three patient groups (PTSD, TE, noTE) differed in their mean DUDIT score, F (2, 111) = 7.86, p = .001, η_p^2 = .124. Post-hoc multiple comparisons revealed that the PTSD group scored a significantly higher mean DUDIT score when compared to the TE group (t (77) = 3.812, p = .0008), and to the noTE group (t (65) = 3.33, p = .003). No difference was found between the TE and the noTE group (t (80) = .039, p = .969), see Figure 3-2.

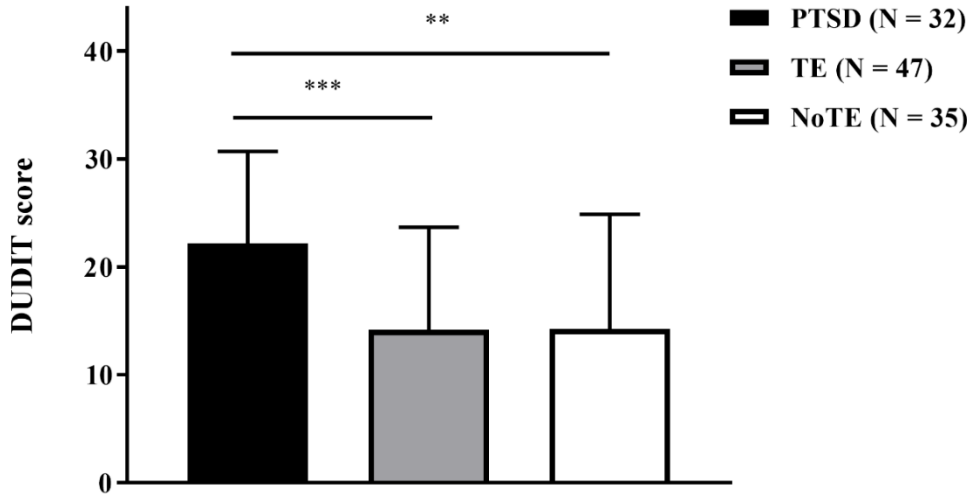

Figure 3-2. The mean DUDIT score for the PTSD group (n = 32), the TE group (n = 47), and the noTE group (n = 35). Mean differences were calculated through post-hoc multiple comparisons using the Bonferroni correction (**$p < 0.01$, *** $p < 0.001$).

3.4 Discussion

We investigated differences in SUD severity between three groups (PTSD, TE, noTE) of treatment-seeking adolescents at a German outpatient clinic for adolescent substance abuse. Additionally, we assessed the past-month-prevalence of PTSD and lifetime-prevalence of TE. In accordance with our hypothesis as well as earlier studies, our results indicate that adolescents with SUD were more likely to report TEs, more likely to suffer from PTSD following TEs, and more likely to fulfil the diagnostic criteria for PTSD compared to the general adolescent population (Essau et al., 2000). Contrary to our hypothesis, only the PTSD group displayed more severe SUD symptoms than the TE group and the noTE group. Additionally, we confirmed the hypothesis that SUD severity is positively associated with the number of hyperarousal, intrusion, and avoidance symptoms.

We were not able to delineate the reason for the positive relationship between the number of PTSD symptoms and SUD severity. Patients with stronger PTSD symptoms might self-medicate more heavily with psychotropic substances, and therefore develop more SUD symptoms (Dworkin et al., 2018; Khantzian, 1985; McCauley et al., 2012). Alternatively, when functional substance use develops into a SUD, PTSD symptoms might increase as a results of reduced overall mental health (Simmons & Suárez, 2016) . Additionally, the development of SUD-related withdrawal symptoms, such as anxiety or depression, might lead to stronger PTSD symptoms (Simmons & Suárez, 2016). Consequently, self-medication of PTSD symptoms with psychotropic substances should be seen as a risk factor, not only for a subsequent SUD, but also for an increase of PTSD symptoms later on. It remains to be explored, if patients with more severe PTSD engage in more substance use, if patients with heavier substance use are more vulnerable to develop PTSD following TEs, or whether a more complex bidirectional relationship exists. To assess these complex relationships, longitudinal studies are needed that frequently assess occurrence of TEs, PTSD symptoms, substance use, and SUD symptoms.

Our finding that TEs alone are not associated with higher SUD severity is supported by research examining the relationship between PTSD and SUD in adolescents and adults (Driessen et al., 2008; Kok et al., 2015; Reed et al., 2007). Reed et al. (2007) found that in adolescents, the presence of PTSD but not TEs without PTSD is associated with a higher risk for future substance abuse or dependence.

Furthermore, Driessen et al. (2008) observed that a PTSD diagnosis but not the number of TEs correlates with SUD severity. Finally, Kok et al. (2015) reported, that trauma-related variables do not add information about variation in drug use severity compared to PTSD symptoms. This line of research indicates that TEs are unrelated to SUD severity and the development of SUD symptoms.

Previous studies with adult SUD patients reported similar results to ours, insofar as all three symptom clusters correlated positively with SUD severity (Khoury et al., 2010; Kok et al., 2015).

3.4.1 Limitations

Our sample was limited to treatment-seeking adolescents with a SUD. Therefore, future research could investigate whether the presence of TE or PTSD influences the intensity of recreational substance use as well or if this influence is limited to SUD severity.

Our assessment of TEs and PTSD was based on self-report measures, which might be biased in the sense that patients might not recall all of their TEs. Additionally, all self-report instruments potentially suffer from response bias. Examples include misunderstanding of the items or a social-desirability bias (Rosenman et al., 2011). Furthermore, self-reports seem to underestimate trauma-specific cognitions, like intrusion symptoms (Takarangi et al., 2014). In future research it might be useful to use additional instruments such as standardized interviews to gain a more accurate picture of the PTSD symptoms clusters and number of TEs.

Furthermore, because we did not collect detailed data on substance use, we could not investigate the relationship between the use of specific substances and the number of PTSD symptoms in each cluster.

Finally, our cross-sectional study lacks a possibility to investigate the question of timing and causality concerning PTSD and SUD development. A prospective longitudinal study design is necessary in order to answer the question, which symptoms or disorders develop first, and if TEs precede substance use or vice versa. This line of research would help to clarify the hypotheses concerning the relationship between the two disorders. For example, the finding that substance use and SUD symptoms generally appear after a TE would support the self-medication hypothesis.

3.5 Conclusion

Adolescents with SUD reported 3-times higher rates of TEs, and a 5-times higher prevalence of PTSD following TEs, than the general adolescent population. SUD was more severe in adolescents with PTSD than in adolescents without TEs or with TE anamnesis but no PTSD symptoms. Finally, the level of SUD severity was positively correlated with the number of PTSD-related intrusion, avoidance, and hyperarousal symptoms.

3.6 Acknowledgements, Funding, Conflicts of Interest

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The remaining authors declare that the research was conducted in the absence of any conflict of interest. The Sächsische Aufbaubank -Förderbank-, (grant 100362999 to YG), funded this study. Open access funding by the Publication Fund of the TU Dresden.

4. PTSD and Patterns of Substance Use

This chapter is based on the following publication:

Lukas Andreas Basedow, Sören Kuitunen-Paul, Melina Felicitas Wiedmann, Veit Roessner & Yulia Golub (2021) Self-reported PTSD is associated with increased use of MDMA in adolescents with substance use disorders, *European Journal of Psychotraumatology, 12:1*, DOI: 10.1080/20008198.2021.1968140

In this paper, the authors investigated differences in substance use patters between three groups of interest (noTE, TE, PTSD). Additionally, they examined the relationship between use of specific substances and specific PTSD symptom clusters, and between group membership (noTE, TE, PTSD) and age of first substance use. It was found that participants in the PTSD group had a higher likelihood of past-month MDMA use. The use of MDMA was associated with reported avoidance symptoms. The first MDMA use was initiated after PTSD onset. It is unclear whether the association of MDMA use with avoidance symptoms is due to efforts to reduce these symptoms or a result of regular MDMA use.

4.1 Background

Even though, as shown in the previous chapter, the severity of adolescent SUD has been associated with a co-occurring PTSD, little is known with regards to use of specific substances and PTSD symptomatology in adolescents. Based on the self-medication hypothesis, the specific subjective effects of different substances might be perceived as relieving symptoms, symptom neutral or leading to stronger symptoms. Accordingly, adolescents with SUD and PTSD might use different substances to achieve a subjective relief from different PTSD symptom clusters (SCs). Thus, a patient who experiences strong hyperarousal symptoms might show a preference for substances with a relaxing effect, e.g. benzodiazepines, while a patient with avoidance symptoms might prefer stimulating substances, e.g. amphetamine. Previous studies in adults investigating how the use of psychoactive substances relates to the presence of specific PTSD symptoms reported conflicting results (Avant et al., 2011; Dworkin et al., 2018; Khoury et al., 2010; Tull et al., 2010). For instance, the presence of avoidance symptoms has been associated with alcohol, benzodiazepine, cocaine, and cannabis use (Avant et al., 2011; Dworkin et al., 2018; Khoury et al., 2010; Tull et al., 2010). The question of specific substance use in a relation to distinct PTSD symptoms is particularly important for the development of targeted therapeutic interventions. Additionally, substance use and subsequent SUDs should have a later onset compared to the disorder which is medicated (Khantzian, 1997). This pattern has been shown previously for adult patients (Berenz et al., 2017),

but not for adolescents. Furthermore, it is unclear if TEs alone might already predispose adolescents to increased substance use and SUD severity.

We conducted this cross-sectional, exploratory study with two aims: The primary goal was to investigate differences in frequency of substance use between subgroups of adolescent SUD patients (noTE, TE, PTSD) and to explore the relationships between substance use frequency and the three PTSD SCs (intrusion, hyperarousal, avoidance). The secondary goal was to explore differences in age of first substance use and if age of first substance use differed from the onset of PTSD symptoms.

4.2 Methods

4.2.1 Participants

Between November 2017 and November 2020, *n* = 234 treatment-seeking adolescents at a German outpatient clinic for adolescent substance abuse consented to participate in the study. From these participants, those who filled out the required questionnaires were selected, resulting in *n* = 121 (42% female) participants. These participants were divided into three groups based on whether they fulfilled PTSD criteria according to self-report ("PTSD"), reported a TE but did not fulfil PTSD criteria ("TE") or did not report any TE ("noTE"). Detailed demographic information of the study sample can be found in Table 4-1.

Table 4-1. Sample description

	Total	noTE	TE	PTSD	Group comparison			
					Test statistic	p-value	$\alpha_{Bonferroni-Holm}$	Effect size
N (female)	121 (51)	35 (7)	48 (22)	38 (22)	X^2 (2) = 11.2	.004	.006*	*V* = .30
Mean age in years (*SD*)	15.9 (1.3)	15.7 (1.4)	15.9 (1.3)	16.2 (1.2)	*F* (118) = 1.3	.285		
Number of participants divided by educational level (%) (*n* = 35 missing)					X^2 (10) = 10.3	.036	.008	*V* = .21
ISCED level 24	58 (48)	13 (37)	24 (50)	21 (55)				

ISCED level 25	7 (6)	4 (11)	0	3 (8)				
ISCED level 34	21 (17)	10 (29)	8 (17)	3 (8)				
Number of participants divided by yearly income of parental household (%) (*n* = 55 missing)					X^2 (10) = 9.3	.507	.025	*V* = .20
Up to 10.000€	8 (7)	4 (11)	3 (6)	1 (3)				
Up to 20.000€	16 (13)	5 (14)	5 (10)	6 (16)				
Up to 30.000€	22 (18)	7 (20)	8 (17)	7 (18)				
Up to 45.000€	8 (6)	1 (3)	4 (8)	3 (8)				
More than 45.000€	12 (10)	8 (23)	2 (4)	2 (5)				
Number of participants fulfilling criteria for a substance use disorder (%)								
Alcohol	31 (26)	6 (17)	14 (29)	11 (29)	X^2 (2) = 1.9	.395	.017	*V* = .13
Cannabis	49 (40)	12 (34)	23 (48)	14 (37)	X^2 (2) = 1.9	.393	.013	*V* = .13
MDMA	20 (17)	2 (6)	9 (19)	9 (24)	X^2 (2) = 4.5	.103	.010	*V* = .20
Amphetamine	7 (6)	1 (3)	4 (8)	2 (5)	X^2 (2) = 1.1	.565	.05	*V* = .10
Methamphetamine	16 (13)	0	8 (17)	8 (21)	X^2 (2) = 7.9	.020	.007	*V* = .23

Note*:* *statistically significant difference; *SD*, standard deviation; *MDMA*, 3-4,-methylendioxymethamphetamine; *noTE*, no traumatic experience group; *TE*, traumatic experience but no PTSD group; *PTSD*, post-traumatic stress disorder group; *ISCED*, International Standard Classification of Education; *ISCED level 24*, lower secondary education – general; *ISCED level 25*, lower secondary education – vocational; ISCED level 34, upper secondary education – general; differences in proportions (%) were tested via chi-square tests (corrected for multiple testing by Bonferroni-Holm procedure for eight tests) and differences in means were tested via ANOVA.

4.2.2 Materials

4.2.2.1 The University of California at Los Angeles Post Traumatic Stress Disorder Reaction Index for DSM-IV

See Chapter 1.5.3. DVs for this questionnaire were: age of first PTSD symptoms, probable presence of a PTSD, presence of a TE, and whether the criteria for the intrusion, avoidance, and hyperarousal SCs were fulfilled. In the current sample, internal consistency was good for criterion A and C (α = .82 and .81, respectively), and acceptable for criterion B and D (α = .77 and .76, respectively).

4.2.2.2 Substance Use

See Chapter 1.5.6. DVs for this study were days of past-month tobacco, alcohol, cannabis, MDMA, and amphetamine (specifically “speed”, but not methamphetamine, cocaine or other stimulants) use, as well as the age of first tobacco, alcohol, cannabis, MDMA, and amphetamine use.

4.2.2.3 SUD Diagnosis via MINI-KID

See Chapter 1.5.2. The DV of interest was the presence of a SUD according to DSM-5 criteria.

4.2.2.4 Sociodemographic Information.

See Chapter 1.5.1. We analysed the questions indicating age in years, gender, education level of the patient as well as yearly household income (“up to 10.000€”, “up to 20.000€”, “up to 30.000€”, “up to 45.000€”, “more than 45.000€”). Participants’ educational levels were assessed according to the International Standard Classification of Education (ISCED) (UNESCO, 2012).

4.2.3 Procedure

Data collection was embedded into the standard diagnostic procedures at our outpatient clinic. During the first appointment, the extent of past-year substance use was assessed, the questionnaires were handed out, and participants as well as legal guardians gave written informed consent to the study. The study was conducted in accordance with the Declaration of Helsinki. All procedures were approved by the Institutional Review Board of the University Hospital C. G. Carus Dresden (EK 66022018). Participants were not financially compensated for their contribution.

4.2.4 Statistical Analysis

All analyses were conducted with IBM SPSS Statistics for Windows, version 27.0 (IBM, 2020). Since our continuous DVs (number of days of tobacco, alcohol, cannabis, MDMA, and amphetamine use during previous month, age of first substance use) were all non-normally distributed across groups according the Shapiro-Wilk test (see Appendix Table A-1) we decided to use non-parametric tests for our group comparisons.

For the assessment of differences in socio-demographic characteristics between the three groups, we performed chi-square tests on the proportion of male and female participants, educational achievement, parental income and type of SUD. Age differences were assessed via an analysis of

variance.

For our main research question, we conducted chi-square tests to compare the prevalence of each substance across the three groups (noTE, TE, PTSD). Additionally, we performed a Kruskal-Wallis omnibus test to determine if our three groups differed in the five continuous DVs variables. If any of the omnibus comparisons was significant, we performed Mann-Whitney U follow up tests between all three groups. We used three Mann-Whitney U tests, limited to the TE and PTSD groups, to analyse if the presence of the three SCs (intrusion, avoidance, hyperarousal) was associated with the use frequency of substances whose prevalence differed between the groups.

For the analyses related to our secondary research question, we conducted a Kruskal-Wallis omnibus test and Mann-Whitney U follow up tests to investigate group differences in age of substance use onset. Additionally, we performed six paired sample t-tests to compare age of PTSD symptom onset with age of first substance use. The level of significance was set to $\alpha < 0.05$. To correct for Type 1 error through multiple testing we used the Bonferroni-Holm procedure (Holm, 1979) to assess significance of the chi-square tests, the non-parametric tests (Kruskal-Wallis, Mann-Whitney U) and the paired samples t-tests. Wherever we report p-values, we report the adjusted Bonferroni-Holm threshold for statistical significance ($\alpha_{\text{Bonferroni-Holm}}$) as well. Effect sizes were classified according to Cohen (1988) into small effects ($|d| \geq .20$, $|\eta^2| \geq .01$, $|V| \geq .10$), medium effects ($|d| \geq .50$, $|\eta^2| \geq .06$, $|V| \geq .30$), and large effects ($|d| \geq .80$, $|\eta^2| \geq .14$, $|V| \geq .50$).

4.3 Results

4.3.1 Sample Description

The three groups did not differ in the distribution of SUD diagnoses, level of education, or parental income. Between the three groups only the proportion of female participants differed significantly (X^2 (2) = 11.2, p = .004, $\alpha_{\text{Bonferroni-Holm}}$ = .006). The two gender groups did not differ in their age of first substance use (U = 1608.50, p = .199, $\alpha_{\text{Bonferroni-Holm}}$ = .01) their past-month tobacco (U = 1554.5, p = .101, $\alpha_{\text{Bonferroni-Holm}}$ = .008), alcohol (U = 1580.00, p = .259, $\alpha_{\text{Bonferroni-Holm}}$ = .017), cannabis (U = 1558.00 p = .215, $\alpha_{\text{Bonferroni-Holm}}$ = .013), MDMA (U = 1656.00, p = .285, $\alpha_{\text{Bonferroni-Holm}}$ = .025), or amphetamine

(U = 169.00, p = .419, $\alpha_{\text{Bonferroni-Holm}}$ = .05) use. The types of traumas reported by our participants are displayed in Table 4-2. Most common were traumas related to violence (26%) and sexual abuse (22%).

Table 4-2. Trauma types reported by participants in the TE and PTSD groups.

Trauma type	Total (n = 121)	TE (n = 48)	PTSD (n = 38)
Natural disaster (%)	11 (9)	10 (21)	1 (3)
Accident (%)	10 (8)	5 (10)	5 (13)
War (%)	3 (2)	0	3 (8)
Domestic violence vs. patient (%)	21 (17)	8 (17)	13 (34)
Domestic violence vs. others (%)	16 (13)	9 (19)	7 (18)
Non-domestic violence (%)	31 (26)	26 (54)	25 (66)
Sexual abuse (%)	27 (22)	12 (25)	15 (40)
Neglect (%)	16 (13)	5 (10)	11 (29)

Note*: TE*, traumatic experience but no PTSD group; *PTSD*, post-traumatic stress disorder group

4.3.2 Differences in Substance Use

We analysed differences in tobacco, alcohol, cannabis, MDMA, amphetamine use frequencies. While 13% of our sample fulfilled criteria for a methamphetamine use disorder, only n = 2 reported past-month use of methamphetamine, which is why we did not analyse methamphetamine use frequency. Furthermore, since none of our participants reported past-month use of cocaine, opioids, benzodiazepines or solvents we excluded these substances from the analyses as well.

The proportion of participants who had used MDMA in the last month differed between groups (X^2 (2) = 10.60, p = .005, $\alpha_{\text{Bonferroni-Holm}}$ = .010, d = .62) with the probable PTSD group reporting the highest proportion of past-month MDMA users. No difference in the use of other substances could be identified. Furthermore, across all three groups participants differed significantly in terms of the number of days of MDMA use in the last month (H (2) = 9.9, p = .007, $\alpha_{\text{Bonferroni-Holm}}$ = .010, η^2 = .07). The PTSD group had a higher past month frequency of MDMA use than the noTE group (U = 510.5, p = .016, $\alpha_{\text{Bonferroni-Holm}}$ = .025, η^2 = .04) and the TE group (U = 710.0, p = .010, $\alpha_{\text{Bonferroni-Holm}}$ = .017, η^2 = .04). The TE group did not differ from the noTE group in days of MDMA use in the past month (U = 839.5, p = .992, $\alpha_{\text{Bonferroni-Holm}}$ = .050, η^2 < .01). Both differences constitute small effects. Mean

scores, proportions and complete test results are displayed in Table 4-3, median scores and interquartile range (IQR) can be found in Appendix Table A-2.

Table 4-3. Mean scores and group comparisons

	Total (n = 121)	noTE (n = 35)	TE (n = 48)	PTSD (n = 38)	Group comparisons			
					Test statistic	p-value	$\alpha_{\text{Bonferroni-Holm}}$	Effect size
Number of participants (%) having used the substance in the past month								
Tobacco	112 (93)	30 (86)	45 (94)	37 (97)	X^2 (2) = 3.8	.153	.013	V = .18
Alcohol	67 (55)	19 (54)	28 (58)	20 (53)	X^2 (2) = 0.3	.860	.05	V = .05
Cannabis	70 (58)	22 (63)	24 (50)	24 (63)	X^2 (2) = 2.0	.366	.025	V = .13
MDMA	19 (16)	3 (9)	4 (8)	12 (32)	X^2 (2) = 10.6	.005	.010*	V = .30
Amphetamine	9 (7)	1 (3)	3 (6)	5 (13)	X^2 (2) = 2.9	.232	.017	V = .15
Mean number of days of substance use in the past month (SD)								
Tobacco	25.2 (9.7)	24.9 (10.6)	24.5 (9.9)	26.4 (8.8)	H (2) = 1.5	.468	.025	η^2 < .01
Alcohol	3.5 (6.4)	4.8 (8.2)	2.4 (3.9)	3.6 (7.1)	H (2) = 0.2	.890	.050	η^2 = .02
Cannabis	7.0 (9.7)	8.3 (10.6)	5.3 (7.9)	8.0 (1.6)	H (2) = 2.4	.297	.017	η^2 < .01
MDMA	0.33 (1.0)	0.14 (0.6)	0.29 (1.3)	0.54 (1.0)	H (2) = 9.9	.007	.010*	η^2 = .07
Amphetamine	0.49 (2.4)	0.23 (1.4)	0.7 (3.4)	0.47 (1.5)	H (2) = 2.7	.258	.013	η^2 = .01

Note*:* *statistically significant difference*; SD*, standard deviation; *MDMA*, 3-4,-methylendioxymethamphetamine; *noTE*, no traumatic experience group; *TE*, traumatic experience but no PTSD group; *PTSD*, post-traumatic stress disorder group; differences in proportions (%) were tested via chi-square tests and differences in means were tested via the Kruskal-Wallis procedure (both analyses corrected for multiple testing by Bonferroni-Holm procedure for five tests)

4.3.3 Relationship between MDMA Use and Specific PTSD SCs

The past month frequency of MDMA use across the TE and PTSD groups was significantly higher in the group of participants fulfilling the avoidance criterion compared to those that did not (U = 7.68, p = .008, $\alpha_{\text{Bonferroni-Holm}}$ = .017, η^2 = .73). For the other two SCs (intrusion, hyperarousal), no differences in frequency of MDMA use were detected, see Table 4-4. See Appendix Table A-3 for

median and IQR values.

Table 4-4. Mann-Whitney U tests assessing associations between MDMA use and PTSD symptom clusters in TE and PTSD participants

PTSD symptom cluster		*N*	Mean number of days of past month MDMA use (SD)	Group comparison			
				Test statistic	p-value	$\alpha_{\text{Bonferroni-Holm}}$	Effect size
Intrusion	present	62	0.38 (0.11)	U = 2.32	.184	.025	η^2 = .59
	not present	24	0.46 (0.35)				
Avoidance	present	43	0.52 (0.14)	U = 7.68	.008	.017*	η^2 = .73
	not present	43	0.28 (0.20)				
Hyperarousal	present	67	0.32 (0.10)	U = 0.13	.896	.050	η^2 = .51
	not present	19	0.68 (0.45)				

Note*: ** statistically significant difference *; MDMA*, 3-4,-methylendioxymethamphetamine; *PTSD*, post-traumatic stress disorder; differences were tested with Mann-Whitney U tests (corrected for multiple testing by Bonferroni-Holm procedure for three tests)

4.3.4 Age of Onset of PTSD and Substance Use

Across all three groups participants differed significantly with medium sized effects in terms of the age of their first substance use (H (2) = 11.3, p = .003, $\alpha_{\text{Bonferroni-Holm}}$ = .008 η^2 = .08). The PTSD group had a lower age of first substance use than the noTE group (U = 372.0, p = .001, $\alpha_{\text{Bonferroni-Holm}}$ = .025, η^2 = .14) and the TE group (U = 653.5, p = .022, $\alpha_{\text{Bonferroni-Holm}}$ = .017, η^2 = .06), with the effect being considered large and moderate respectively. The TE group did not differ from the noTE group in their age of first substance use (U = 705.0, p = .206, $p_{\text{Bonferroni-Holm}}$ = .050, η^2 = .02). All post hoc comparisons were controlled for multiple testing by applying the Bonferroni-Holm procedure for three tests. The age of PTSD onset was significantly lower than the age of first MDMA use (t (26) = -2.89, p = .008, d = -.56). All other differences were not significant (all $p > \alpha_{\text{Bonferroni-Holm}}$ corrected for five tests). Detailed tests results can be found in Table 4-5 and visual presentation of results in Appendix Figure A-1.

Table 4-5. Mean differences and test results for PTSD symptom onset and onset of substance use.

Difference from age of PTSD symptom onset	N	Mean difference in years (SD)	Test statistic	p-value	$\alpha_{Bonferroni-Holm}$	Effect size
First age of tobacco use	31	.07 (3.79)	t (30) = 0.95	.925	.050	d = .02
First age of alcohol use	32	-0.44 (3.58)	t (31) = -0.69	.494	.025	d = -.12
First age of cannabis use	33	-1.10 (3.72)	t (32) = -1.64	.111	.017	d = -.29
First age of MDMA use	27	-2.19 (3.93)	t (26) = -2.89	.008	.010*	d = -.56
First age of amphetamine use	16	-2.19 (3.25)	t (15) = -2.69	.017	.013	d = -.67

Note: * statistically significant difference; *MDMA*, 3-4,-methylendioxymethamphetamine; differences were tested via paired-t tests (corrected for multiple testing by Bonferroni-Holm procedure for five tests)

4.4 Discussion

In this study, we aimed to investigate if adolescent SUD patients with co-occurring probable PTSD are more likely to use specific substances than adolescent SUD patients without PTSD, and how the use of these substances relates to PTSD symptoms. We found that adolescent SUD patients with probable PTSD start using substances at an earlier age, are more likely to use MDMA, and use it more frequently than adolescents with a SUD and a history of TEs but no PTSD, or adolescents with only a SUD. Additionally, we observed that in adolescent SUD patients with TE history, the use of MDMA is associated specifically with the presence of the avoidance SC. Finally, we report that adolescents with a history of TEs start using MDMA after the first occurrence of PTSD symptoms.

The self-medication hypothesis posits that substance use and subsequent SUDs may be the result of an attempt to self-medicate co-occurring psychiatric disorders (Dworkin et al., 2018; Khantzian, 1997; McCauley et al., 2012). This hypothesis postulates that the preference for a specific substance may be the result of their ability to reduce acute symptomatology (Khantzian, 1997). In terms of co-occurring PTSD, the self-medication hypothesis implies that a co-occurring SUD occurs because the substance of choice has specific PTSD-symptom-relieving effects. In fact, this pattern has been shown repeatedly in the context of alcohol use and PTSD, suggesting that after encountering TEs a common response is engaging in drinking to cope (Hawn et al., 2020; Wu et al., 2010).

In the context of the self-medication hypothesis, the increased use of MDMA in adolescents with co-occurring PTSD and SUD is not surprising. Since MDMA use in adolescents has been generally

associated with a self-medication motive (Moonzwe et al., 2011), and MDMA- assisted psychotherapy has recently been shown to reduce PTSD symptomatology (Thal & Lommen, 2018), adolescents in our sample with PTSD and SUD may show increased use of MDMA because it decreases their distress induced by the different PTSD SCs. Our results indeed show, that a higher prevalence of MDMA use is specifically related to the presence of the avoidance SC. Symptoms of the avoidance cluster include "feeling of detachment" or "restricted range of affect" which might be associated with MDMA use since MDMA has been shown to induce heightened empathy (Carlyle et al., 2019), increased pro-social behavior (Borissova et al., 2020; Stewart et al., 2014) and is often used in social settings (McElrath & McEvoy, 2002). On the other hand, side effects of MDMA such as increased body temperature (Liechti, 2014) and increased blood pressure (Vizeli & Liechti, 2017) might explain why MDMA use is not associated with hyperarousal, since the increased activation of the sympathetic nervous system might exacerbate negative aspects of hyperarousal. Furthermore, acute detrimental effects of MDMA on memory (de Sousa Fernandes Perna et al., 2014; Kuypers & Ramaekers, 2005) could explain why the intrusion SC is not associated with its use: if memory is impaired, intrusive memories might also be suppressed. In light of the unique effects of MDMA, it seems plausible that it is used by adolescents with a PTSD to reduce their avoidance-induced distress, and that this self-medication use might continue unchecked and eventually develop into a SUD.

This proposed association between MDMA use and avoidance symptoms might have clinical implications. As demonstrated by our results, a higher level of MDMA use might indicate the presence of other, untreated disorders such as PTSD. This point is especially important since the self-medication hypothesis is not entirely without fault. Lembke (2012) argues that the picture might be more complicated and that psychiatric symptoms not only contribute to substance use, but the reverse might also be possible: the use of psychoactive substances might lead to an increase in psychiatric symptomatology through the occurrence of withdrawal symptoms or adverse pharmacological effects.

Indeed, another explanation for our observed results could be that frequent MDMA use has negative psychopathological consequences that worsen sub-clinical PTSD symptoms, leading to a

fully developed PTSD. This conclusion is supported by evidence showing that MDMA users show increased psychopathology in the Symptom Checklist-90-R compared to poly-substance users without MDMA use (Morgan et al., 2002). Additionally, MDMA use has been associated with psychiatric symptoms such as depression (P. McGuire, 2000), prodromal psychotic symptoms (Wiedmann, Kuitunen-Paul, et al., 2022) or depersonalization (P. McGuire, 2000; Thomasius et al., 1997) which often go hand in hand with PTSD (Auxéméry, 2018; Brady et al., 2000). Moreover, regular MDMA use might impair memory (Wunderli et al., 2017), disturb sleep (Schierenbeck et al., 2008) or diminish interest and excitement (Parrott, 2015) which could negatively influence the developmental process of PTSD. Finally, illicit MDMA use may further increase the risk of negative consequences, because of contamination with other psychoactive substances. For example, powder or pills sold as MDMA often contain synthetic cathinones (Oliver et al., 2019) with harsher side effects than MDMA (Karch, 2015; Papaseit et al., 2016). Nevertheless, we found that adolescents use MDMA on average two years after the first onset of PTSD symptoms, which is in line with research showing that adolescent MDMA use occurs later than mental health symptoms (Falck et al., 2006). This pattern of symptoms first – use later, can be considered further support for the self-medication hypothesis, suggesting that adolescent PTSD patients discover MDMA in their adolescence, and start using more frequently and subsequently develop a SUD in an effort to reduce their symptoms. Additionally, our findings of an earlier age of first substance use in patients with co-occurring SUD and PTSD might indicate an early exploration of self-medication options.

4.4.1 Limitations

First, this study consists of cross-sectional, retrospective data, which means we cannot investigate how the use of psychoactive substances, especially MDMA, changes during the developmental course of a SUD or PTSD. Second, we based our calculations on past-month use of different substances, which represents only a snapshot of a participant's use history. Third, most of our measures, including our assessment of PTSD diagnosis, are based on self-report which might lead to social desirability or recall bias (Althubaiti, 2016), which could lead to an underreporting of substance use and the true proportion of substance use in this population to be larger. Additionally, this procedure might overestimate the proportion of PTSD diagnoses in our sample. Future research

would be well advised to include standardized instruments and more long-term measures of use, e.g. the use over the past year, or lifetime exposure. Fourth, in assessing the age of PTSD symptom onset and substance use we could only include few participants, limiting the validity of our results regarding this topic and leading to our study having a low power to detect potential effects. Fifth, our sample consisted of a specific and limited convenience sample only including adolescent, treatment-seeking SUD patients. Therefore, we are not able to make any conclusion about the role MDMA use might play in adolescents with only a PTSD diagnosis. Sixth, because of the need to use non-parametric testing it was not possible to control for socio-demographic confounders during our main analysis. Fortunately, gender differences between the groups were not mirrored in our substance use outcomes. Finally, we conducted a large number of tests increasing our likelihood of reporting false-positive results. As a countermeasure, we only considered results statistically significant if they survived a correction with the Bonferroni-Holm procedure.

4.5 Conclusion

This study showed that adolescent SUD patients with co-occurring probable PTSD are more likely to have used MDMA in the past month, and use it in higher frequency, than adolescents with only a SUD, regardless of additional TE. This finding might reflect an attempt to self-medicate, specifically to deal with the SC of avoidance. On the other hand, the greater MDMA use might have facilitated the development of more severe avoidance symptoms. Independent of directionality, these results should be taken into account by clinicians encountering this high vulnerability patient group. Particular care should be taken to comprehensively assess if substances (like MDMA) are used as a form of self-medication.

4.6 Acknowledgements, Funding, Conflicts of Interest

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5. MDMA use, Coping Motives, and Self-Medication

This chapter is based on the following publication:

Basedow, L.A., Wiedmann, M. F., Roessner, V., Golub, Y. & Kuitunen-Paul, S. (Submitted) Coping motives mediate the relationship between PTSD and MDMA use

In this study, the aim was to test whether substance use in three groups (noTe, TE, PTSD) is related to an attempt to self-medicate PTSD-related mental distress. In adolescent SUD patients, there was found to be an association of current PTSD and lifetime traumatic experiences with higher MDMA use that could be partially explained by substance use being motivated by a coping motive. This indicated a self-medication process involved specifically in MDMA use compared to the use of other psychoactive substances, possibly due to the unique psychoactive effects of MDMA.

5.1 Background

While previous research has focussed on adult patients with PTSD and SUD who reported coping motives with regard to their substance use (Read et al., 2014), or on adolescents without SUD or PTSD (Lammers et al., 2013) little research has been conducted to directly explore the relationship between adolescent PTSD, substance use, and coping motives. In two studies with adult participants drawn from the general population, it has been shown that coping motives act as mediator in the relationship between TEs and problematic substance use (Shin et al., 2020; Ullman et al., 2013). In contrast, one study in adolescent SUD patients has shown that coping motives are increased in participants with co-occurring SUD and PTSD, instead of TEs alone (Staiger et al., 2009). In the present study, we aimed to explore the relationship between adolescent PTSD and SUD in the context of the self-medication hypothesis. To do so we investigated differences in reported coping motives between adolescents with a SUD (noTE), adolescents with a SUD and TEs but no PTSD (TE), and adolescents with a SUD and PTSD (PTSD). Additionally we explored differences in past-year substance use between these three groups and aimed to understand the connection between these three variables (PTSD group, coping motives, and substance use frequency) through a mediation analysis. Given the substance-specific psychoactive effects that might interact with PTSD symptoms, we conducted analyses for several substances, but restricted the mediation analyses to those substances whose use differed between groups.

5.2 Methods

5.2.1 Participants

Between November 2017 and April 2021, *n* = 303 treatment-seeking adolescents at a German outpatient clinic for adolescents with SUD consented to participate in the study. From these participants, those who filled out the use motives questionnaire were selected for exploratory and confirmatory factor analyses, resulting in *n* = 162 (41% female) participants. For the main analysis, participants were selected who had answered at least 80% of the items in the relevant questionnaires (*n* = 111, 43% female). Participants were divided into three groups according to their trauma status resulting from the PTSD questionnaire: no history of traumatic experiences ('noTEs'), a history of traumatic experiences but no PTSD ('TEs'), and past-year PTSD ('PTSD').

5.2.2 Materials

5.2.2.1 Trauma Assessment

See Chapter 1.5.3. DVs for this questionnaire were presence of a PTSD (yes/no) and presence of a TE (yes/no).

5.2.2.2 Use Motive Questionnaire

See Chapter 1.5.5. To determine if the theoretical structure of the questionnaire is empirically supported, we perform preliminary exploratory and confirmatory factor analyses. The main DV is the combined score of the "coping" items, with a maximum score of 16, and a higher score indicating more frequent substance use because of coping motives.

5.2.2.3 Additional Diagnoses via MINI-KID

See Chapter 1.5.2. DVs were the presence of any psychotic, mood (major depression or bipolar disorder), anxiety (general anxiety disorder, panic disorder, agoraphobia, separation anxiety disorder, social phobia, specific phobia), behavioural (attention deficit hyperactivity disorder, conduct disorder, oppositional defiant disorder) or obsessive-compulsive disorder (OCD).

5.2.2.4 Substance Use Interview

See Chapter 1.5.6. DVs from this assessment were days of past-month tobacco, alcohol, cannabis, methylenedioxymethamphetamine (MDMA), and amphetamine (specifically "speed", but not

methamphetamine, cocaine or other stimulants) use, as well as the age of first tobacco, alcohol, cannabis, MDMA, and amphetamine use.

5.2.3 Procedure

Data collection was embedded standard diagnostic procedures. During the first clinical appointment, participants as well as legal guardians were asked to provide written informed consent to the study. Questionnaires were handed out and substance use was evaluated by the hospital staff member (therapist, psychologist, or physician). The MINI-KID was conducted approximately 1-4 weeks later. The study was conducted in accordance with the Declaration of Helsinki and all procedures were approved by the Institutional Review Board of the University Hospital C. G. Carus Dresden (EK 66022018).

5.2.4 Statistical Analysis

5.2.4.1 Exploratory Factor Analysis

To account for the non-normal distribution of motive items (Shapiro-Wilk test for each questionnaire items $p < .001$), we used factor analysis extraction methods. The number of latent factors were explored with Scree plot, Kaiser-Guttman criterion, the revised MAP test as well as Parallel Analyses with principal components and raw data permutation (Ledesma & Valero-Mora, 2019). Possible item-factor assignments (factor structures) were deducted with exploratory factor analyses (EFA) in IBM SPSS Statistics 27.0 using Principal Axis extraction with Promax-rotation (kappa = 4).

5.2.4.2 Confirmatory Factor Analysis

The adequacy of factor structures was tested for the given empirical data with confirmatory factor analysis (CFA) using the lavaan package (Rosseel, 2012) in RStudio (RStudio Team, 2020). We tested the theoretical model (the three factors, “coping”, “social motives” and “other” consisting of distinct items), the empirical model build upon the results from the EFA, and the combined model that integrates theoretical considerations into the empirical model using the diagonally weighted least-squares (DWLS) method of estimation to account for non-normality within the categorical items. A good absolute model fit would be indicated by a X^2 to degrees of freedom ratio < than 2 (a

ration between 2 and 3 is acceptable), a Comparative Fit Index (CFI) ≥ .95 (.90 - .94 acceptable), a standardized root mean square residual (SRMR) ≤ .05 (.05 - .10 acceptable), and a root mean square error of approximation (RMSEA) ≤ .05 (.05-.10 acceptable) (Schermelleh-Engel et al., 2003).

5.2.4.3 Main Analysis

All the following analyses were conducted with IBM SPSS Statistics 27.0. In cases were at least 80% of questions were answered, missing values were replaced by the mean value of the remaining items ($n = 9$). Categorical demographic variables (presence of anxiety, mood, behavioural disorders, presence of OCD, gender) were chi-square tested. For our continuous sociodemographic variable 'age', we conducted an analysis of variance.

Since all our continuous main outcomes (coping score, use frequency for tobacco, alcohol, cannabis, MDMA, and stimulants) did not fulfil the criterion for normality (see Appendix Table B-1), non-parametric testing was applied. To predict the presence (yes/no) of past-year tobacco, alcohol, cannabis, MDMA, and stimulant use, five binary logistic regressions were calculated with group membership (noTEs, TEs, PTSD), and sociodemographic variables (other mental disorders, gender, age) that differed between the three groups as predictors, and the presence of past-year use of each substance as outcome. To control for differences in sociodemographic variables regarding the continuous outcomes (coping score, use frequency for tobacco, alcohol, cannabis, MDMA, and stimulants) differences in these outcomes were calculated with the Mann-Whitney U tests. If the Mann-Whitney U test was non-significant, group (noTEs, TEs, PTSD) differences in substance use frequency were calculated with a Kruskal-Wallis test. In case the Mann-Whitney U test detected significant differences for sociodemographic variables, Quade's test (Conover, 1999) was used to perform a non-parametric test while controlling for a covariate. Additionally Spearman's correlation coefficient ρ was calculated for the association between coping score and use frequency for each substance for which significant group differences could be detected. Mediation analyses for all substances for which significant group differences were detected, were performed with the PROCESS macro (Hayes, 2018). PROCESS provides both a significance test and an effect size estimate with 95% confidence interval for the mediational effect of mediator variable M ("coping score") on the relationship between a predictor X ("group membership") and an outcome Y

("substance use frequency"). This indirect effect (ab) describes by how much the relationship between X and Y (c') is affected by the relationship between X and M (a), and the relationship between M and Y (b), see Figure 5-1. The significance level for all analyses were set to α = .05

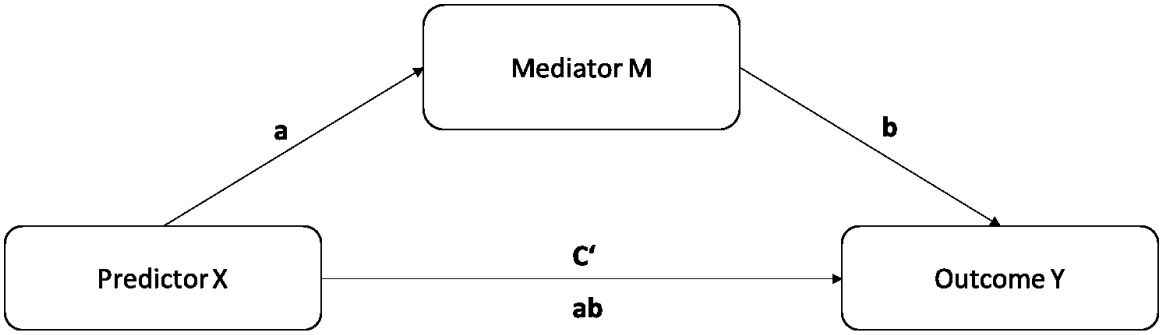

Figure 5-1. Exemplary mediation model

5.3 Results

5.3.1 Sample Description

Between-group differences in sociodemographic variables and the presence of mental disorders are shown in Table 5-1. Females were significantly underrepresented in the noTE group (X^2 (2) = 14.2, $p < .001$) while several co-occurring mental disorders were overrepresented in the PTSD group (X^2 (2) = 14.0, $p \leq .007$). Based on group differences in the presence of OCD we excluded the n = 5 participants with an OCD diagnosis from the analysis, leaving n = 106 participants. Based on the sociodemographic differences we controlled for gender and presence of anxiety disorder in our main analysis.

Table 5-1. Demographic information about the three samples

	Total	noTEs	TEs	PTSD	Group comparison	
					Test statistic	*p*-value
N (female)	111 (48)	31 (5)	42 (20)	38 (23)	X^2 (2) = 14.2	< .001*
Age (*SD*)	16.0 (1.3)	16.0 (1.3)	16.0 (1.2)	16.1 (1.3)	*F* (108) = 0.8	.923
N with psychotic disorders (%)	4 (3%)	0	1 (2%)	3 (8%)	X^2 (2) = 3.4	.187
N with anxiety disorders (%)	20 (18%)	2 (6%)	4 (10%)	14 (37%)	X^2 (2) = 14.0	< .001*
N with mood	62 (56%)	15 (48%)	20 (48%)	27 (71%)	X^2 (2) = 5.4	.067

disorders (%)						
N with behavioural disorders (%)	57 (51%)	13 (42%)	19 (45%)	11 (29%)	X^2 (2) = 2.2	.341
N with obsessive-compulsive disorder (%)	5 (5%)	0	0	5 (13%)	X^2 (2) = 10.1	.007*

Note: * significant at the 0.05 level; *anxiety disorders*; general anxiety disorder, panic disorder, agoraphobia, separation anxiety disorder, social phobia, specific phobia; *mood disorders*, major depression and bipolar disorder; *behavioural disorders*; attention deficit hyperactivity disorder, conduct disorder, oppositional defiant disorder; *OCD*, Obsessive-Compulsive disorder.

5.3.2 Confirmation of the Use Motive Questionnaire

Data from the use motive questionnaire was suitable for factor analyses with Kaiser-Meyer-Olkin coefficient = .83, a significant Bartlett test with $p < .001$ and a measures of sample adequacy coefficient of .80. In the exploratory factor analysis, items had satisfying communalities after extraction. The only exception was an item from the "social motives" scale (h^2 = .041) that was therefore not used within the following CFA analysis. Solutions with either two factors (indicated by Parallel Analysis and MAP test) or three factors (indicated by Kaiser-Guttman criterion) were suggested. The two-factor model explaining 63% of variance and producing one cross-loading item was deemed improper for further analysis as it collapsed all but the "social" items into one large factor. The "empirical" three-factorial model was selected for further CFA testing given that it was more theoretically sound by reproducing most of the theorized item assignments and that it explained variance to a rather large degree (67%). However, it deviated from the "theoretical" three-factor model by having two "coping" items with cross-loadings on the third factor, and one "other" item loading on "coping" only. A "combined" model was defined for further CFA analysis based on the "empirical" model; however, the "other" item was therein assigned to the "other" scale in order to have all scales more theoretically sound.

In the CFA, the "combined" model was deemed appropriate within our sample due to mostly acceptable model fit values, with X^2/df-ratio = 2.05, CFI = .94, SRMR = .05, but RMSEA 90%CI = .08-.18, see Appendix Table B-2. Fit indices for the theoretical and empirical models were in comparable ranges, but less advantageous. Therefore, we assume that all four items theorized to measure a

common construct (presumably "coping") indeed measure a common construct that differed from what other motive items measure. However, two of those items covering substance use due to stressful events, or substance use due to inner tension, were also cross-loading on another factor.

5.3.3 Substance Use

The logistic regression models showed that the presence of past-year MDMA use (*b* = 0.66, *p* = .034, *OR* = 1.94) was significantly predicted by group membership (noTEs, TEs, PTSD) when controlling for sex and presence of anxiety disorders, while there were no relationships between group membership and the presence of tobacco use (b = - 0.19, *p* = .721, OR = 0.83) alcohol use (*b* = 0.40, *p* = .289, *OR* = 1.49), cannabis use (*b* = -0.38, *p* = .392, *OR* = 0.68), or stimulant use (*b* = 0.42, *p* = .196, *OR* = 1.52). The presence of anxiety disorders was not associated with the frequency of past-year use of tobacco (*U* = 685, *p* = .746, η^2 = .001), alcohol (*U* = 402, *p* = .687, η^2 = .002), cannabis (*U* = 395, *p* = .193, η^2 = .018), MDMA (*U* = 407, *p* = .080, η^2 = .026), or stimulants (*U* = 225, *p* = .240, η^2 = .015). Similarly, both genders did not differ in past-year tobacco use frequency (*U* = 1005, *p* = .161, η^2 = .011), alcohol use frequency (*U* = 867.5, *p* = .351, η^2 = .010), cannabis use frequency (*U* = 967, *p* = .703, η^2 = .002), MDMA use frequency (*U* = 897, *p* = .197, η^2 = .014), or stimulant use frequency (*U* = 609, *p* = .561, η^2 = .004).

The past-year frequency of MDMA use differed between the noTEs, TEs and PTSD group (*H* (2) = 7.2, *p* = .027, η^2 = .058), but no differences were detected regarding the past-year frequency of tobacco (*H* (2) = 1.6, *p* = .457, η^2 = .004), alcohol (*H* (2) = 2.8, *p* = .256, η^2 = .008), cannabis (*H* (2) = 4.9, *p* = .085, η^2 = .033), or stimulant (*H* (2) = 1.3, *p* = .512, η^2 = .009) use. Details regarding the patterns of substance use in the different groups are displayed in Table 5-2.

Table 5-2. Group differences in substance use and coping

	Total	NoTEs	TEs	PTSD	Group comparisons		
	(*n* = 106)	(*n* = 31)	(*n* = 42)	(*n* = 33)	Test statistic (*SE*)	*p*-value	Effect size
Mean coping score (*SD*)	5.4 (5.6)	3.2 (4.0)	5.1 (5.3)	7.6 (5.6)	*F* (103) = 5.77	.004	η^2 = .101

Number of participants having used the substance in the past

year

Tobacco (*n* = 14 missings)	89 (83%)	25 (80%)	36 (86%)	29 (88%)	*b* = - 0.19 (0.38)	.721	*OR* = 0.83
Alcohol (*n* = 13 missings)	75 (81%)	20 (69%)	32 (89%)	23 (82%)	*b* = 0.40 (0.38)	.289	*OR* = 1.49
Cannabis (*n* = 12 missings)	82 (87%)	26 (90%)	32 (86%)	24 (86%)	*b* = -0.38 (0.45)	.392	*OR* = 0.68
MDMA (*n* = 12 missings)	41 (44%)	7 (23%)	18 (49%)	16 (59%)	*b* = 0.66 (0.31)	.034*	*OR* = 1.94
Stimulants (*n* = 11 missings)	32 (34%)	5 (17%)	17 (44%)	10 (37%)	*b* = 0.42 (0.32)	.196	*OR* = 1.52
Number of days of substance use per month over the past year (*SD*)							
Tobacco (*n* = 14 missings)	25.0 (10.1)	23.0 (11.7)	26.2 (8.4)	25.3 (10.1)	*H* (2) = 1.6	.457	η^2 = .004
Alcohol (*n* = 11 missings)	7.6 (10.1)	6.0 (9.3)	7.4 (10.6)	9.6 (10.4)	*H* (2) = 2.8	.256	η^2 = .008
Cannabis (*n* = 10 missings)	15.7 (12.1)	17.1 (12.9)	17.7 (11.8)	12.4 (11.5)	*H* (2) = 4.9	.085	η^2 = .033
MDMA (*n* = 9 missings)	2.3 (5.2)	0.9 (2.5)	1.6 (2.5)	4.4 (8.1)	*H* (2) = 7.2	.027*	η^2 = .058
Stimulants (*n* = 28 missings)	3.7 (8.0)	4.6 (9.0)	2.3 (6.1)	4.3 (9.0)	*H* (2) = 1.3	.512	η^2 = .009

Note: * significant at the .05 level. *MDMA*, methylenedioxymethamphetamine, *SD,* standard deviation; *OR,* Odds ratio.

5.3.4 Coping Score

While the presence of anxiety disorders was not associated with differences in coping score (U = 613.5, p = .340, η^2 = .008), the two sexes showed a significant difference in coping score (U = 993, p = .012, η^2 = .057); making it necessary to control for this variable in calculating the association between group membership (noTEs, TEs, PTSD) and coping score. While controlling for sex, the three groups differed significantly in terms of coping scores (F (103) = 5.77, p = .004, η^2 = .101), with level of reported coping motive being highest in the PTSD group and lowest in the noTEs group. Additionally, the frequency of past-year MDMA use correlated significantly and positively with

coping score (ρ = .287, p = .004).

5.3.5 Mediation Analysis

The mediation analyses for the effect of group membership (noTEs, TEs, PTSD) on past-year MDMA use frequency resulted in an indirect effect of coping score (b = 0.61, 95% CI [0.29, 1.58], p = .145), see Figure 5-2. Although the p-value is larger than the α-level of .05, the CI not including zero indicates a true effect. That is, coping motives mediate how the presence of TEs and/or PTSD is associated with the past-year frequency of MDMA use in adolescents treated for SUD.

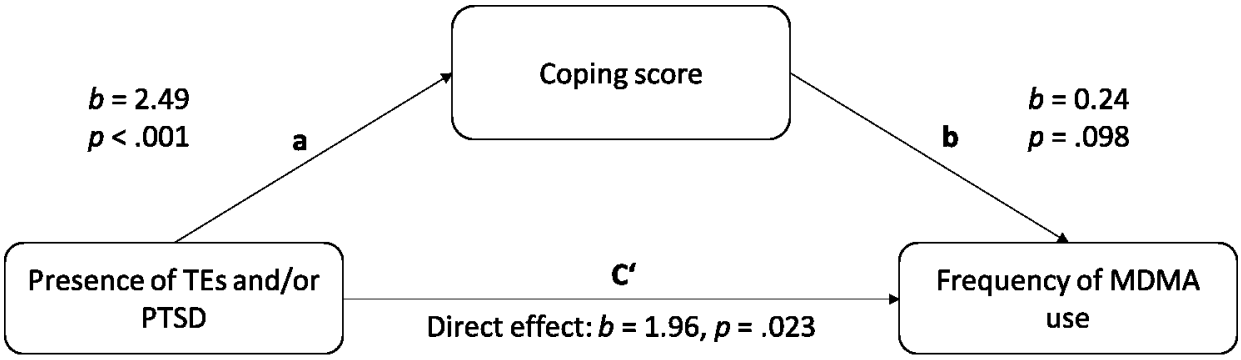

Figure 5-2. Mediation of the relationship between PTSD and MDMA use frequency by coping. *TE*, traumatic experience; *PTSD*, post-traumatic stress disorder; *MDMA*, methylenedioxymethamphetamine

5.4 Discussion

In the present study, we investigated the relationship between lifetime TEs and current PTSD diagnosis, substance use frequency and coping motives related to substance use in German adolescent SUD patients. We found that adolescents with co-occurrence of SUD and PTSD reported stronger coping motives and, in turn, a higher frequency and likelihood of MDMA use in the past year. Associations were specific to MDMA; they did not exist for tobacco, alcohol, cannabis, or stimulants.

Similarly to the study presented in the previous chapter, a co-occurrence of PTSD and SUD was associated with a higher frequency of past-year MDMA use in adolescents seeking treatment for SUD. Previous research supports our finding in so far as MDMA use has been associated with the presence of general psychopathological symptoms (Verheyden et al., 2002), use of multiple

psychoactive substances (Schifano et al., 1998) and with higher rates of PTSD (Lieb et al., 2002). However, in studies with adults, PTSD has mostly been associated with the use of alcohol (Dworkin et al., 2018; Hawn et al., 2020; Subbie-Saenz de Viteri et al., 2020) when compared to non-using populations. Since our sample showed high levels of alcohol use (amongst other substance use) as well, it might be more accurate to say that we showed MDMA use to be associated with PTSD when controlling for other substance use.

A first possible explanation for this relationship between MDMA use and PTSD might be a detrimental effect of MDMA use on PTSD development. Specifically, a more frequent MDMA use might lead to an escalation of sub-clinical PTSD symptoms until the criteria for a PTSD diagnosis are fulfilled. Support for this line of argument could be found in previous research that has shown that psychopathological symptoms like depression or aggression might develop after MDMA use (Lieb et al., 2002; Verheyden et al., 2002). Another explanation, supported by the results of our mediation analysis, suggests that an increased use of MDMA is observed in patients with PTSD symptoms because of stronger self-medication motives, i.e. to cope with PTSD-related symptoms. Our analysis has shown that part of the effect of TEs/PTSD on MDMA use frequency is explained by the level of reported coping motives for substance use. Plainly, if a higher frequency of coping motives was reported by a patient, the effect of PTSD on MDMA use frequency was increased as well. This finding is in line with the hypothesis that substance use might serve as a form of self-medication (Khantzian, 1985, 1997). This specific self-medication of PTSD symptoms with MDMA has been shown previously (Jansen, 1999; Moonzwe et al., 2011; Scott et al., 2013), while MDMA use in recreational non-pathological users is mainly related to enhancement or expansion motives instead of coping (Boys et al., 2001). Specifically, Jansen (1999) described a case report of a patient with PTSD who unambiguously ascribes his symptom relief to the acute effects of MDMA. Further, Scott et al. (2013) have shown that higher levels of coping motives are related to higher levels of MDMA use which is in line with our correlational analysis as well. Additionally, their research and one other study support our conclusion, that it are PTSD symptoms specifically that are related to increased MDMA use (Staiger et al., 2009), not TEs in general (Scott et al., 2013; Ullman et al., 2013). Furthermore, Moonzwe et al. (2011) showed in great detail how, for young adults, MDMA use has

been described as particularly effective in terms of coping with negative consequences of TEs. However, the authors also point out that this relationship is present only in participants who did not receive satisfactory mental health treatment, while in well-treated participants, MDMA use was not related to a significant coping effect (Moonzwe et al., 2011).

It remains speculative why specifically MDMA was involved in coping activities as compared to other substances with anxiolytic and sedative effects such as alcohol (which is known from adult studies) or opiates with their potentially more symptom-relieving properties (Klee & Reid, 1998). One issue is that alcohol is more available and more commonly used among adolescents in the study region compared to MDMA (Wiedmann, Atzendorf, et al., 2022). Its use might simply be much too high and prevalent in our sample, resulting in a ceiling effect that prevents us from detecting self-medicating patterns due to high use in non-self-medicating adolescents. Opiates, on the other hand, may not have been encountered by these patients, may have been less available compared to MDMA or more difficult to afford on a regular basis in the study region. In fact, only 3 of 201 adolescent patients in our institution reported any opiate use in the 12 months before admission (Wiedmann, Atzendorf, et al., 2022).

While at first glance it might seem like self-medication is beneficial for these patients, this practice is also related to a variety of negative outcomes. Specifically, the relief from distress is thought to act as a negative reinforcement, increasing the likelihood for further use in the future and increasing the risk for the aetiology of a MDMA use disorder according to current learning theories related to SUDs (Müller & Schumann, 2011; Redish et al., 2008). Likewise, reporting coping motives for substance use during adolescence is associated with higher rates of SUDs later in life (Patrick et al., 2011), indicating that the patients we saw in our study, might go on to develop more severe patterns of substance use later on. Further, a coping motive is not equivalent to a successful symptom reduction. For example, some participants report that MDMA use is more of a temporary break from PTSD symptomatology instead of having any substantial effect beyond the acute high (Moonzwe et al., 2011). Finally, a reduction in substance is made much more difficult as long as a self-medication behaviour is in place, leading to higher rates of relapse in patients with this use pattern (Staiger et al., 2009).

5.4.1 Limitations

First, we did not use a validated measure to assess substance use motives. Our measure was based on a self-designed questionnaire that was available in our research group, which did assess use motives but was not specifically designed for this purpose. Consequently, our coping score might not reflect a measure of coping motives but instead might represent another unclear factor related to PTSD presence and MDMA use frequency. However, we did provide exploratory and confirmatory factor analyses for the questionnaire providing some preliminary support for it being psychometrically sound.

Second, our sample consisted entirely of treatment-seeking patients, which does not allow for generalizations of the relationship between MDMA use, coping motives, and TEs for MDMA substance users outside this clinical setting.

Third, our cross-sectional design does not allow for conclusions about causal relationships. While we argue that patients take MDMA to reduce PTSD symptoms and might therefore facilitate a development of a SUD, this is mere association. To determine a causal chain in this relationship longitudinal studies are needed.

Fourth, the three groups in our sample differed in terms of gender distribution and the presence of mental disorders. However, we controlled for these factors in our main analysis, and examined if they were associated with our main outcomes. Based on these analyses we concluded that the gender and psychopathological differences did not influence our main outcomes.

Finally, our argument for a self-medication effect rests on MDMA relieving PTSD related symptoms. However, we did not ask participants to report coping motives specific for PTSD. Instead, participants reported general coping motives dealing with the relief of negative emotional states. Future research should take care to include measures that specifically ask if substances were used to reduce PTSD symptoms specifically.

5.5 Conclusion

This study in German adolescent psychiatric patients showed that a co-occurring PTSD and SUD is

related to higher MDMA use compared to patients without a co-occurring PTSD. This use was increased even when controlling for other substance use, sex, and co-occurring disorders. Additionally, we showed that the effect of PTSD on MDMA use frequency is mediated by the level of coping motives, indicating that MDMA use might be higher in this population, partly because of a self-medication motive.

5.6 Acknowledgements, Funding, Conflicts of Interest

Regarding the past 36 months, the authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. The Sächsische Aufbaubank –Förderbank- (grant 100362999 to YG), funded this study.

6. Treatment of co-occurring disorders

This chapter is based on the following publication:

Basedow, L. A*., Kuitunen-Paul, S.*, Wiedmann, M. F., Roessner, V., & Golub, Y. (Submitted). Evaluation of the Multimodal DELTA Therapy for Adolescents with Substance Use Disorders: A waiting-list-controlled pragmatic trial. ***** denotes shared first-authorship

In this paper, the results were reported of a pragmatic waitlist-controlled trial assessing the efficacy of the DELTA group program for adolescents with chronic substance use. The differences were assessed between the intervention and control group with regard to changes in SUD symptoms, substance use frequency, and co-occurring psychopathologies including PTSD. The results indicated that the DELTA program might be beneficial for reducing SUD symptoms and substance use frequency but not PTSD symptoms.

6.1 Background

Treatment options for adolescent SUDs in Germany are currently mostly limited to inpatient detoxification and outpatient drug counselling (AWMF, 2021; SLS, 2019). That is, we lack specific treatment options tailored for adolescents with SUD in outpatient care. Those few programs specifically designed for adolescents provide guidance only for the treatment of specific SUDs (Hoch et al., 2014), require a day clinic settings (Obert et al., 2017) or are not available in German (Himelstein & Saul, 2015; Obert et al., 2017).

Available treatment guidelines for SUDs recommend that interventions should include the treatment of co-occurring mental disorders, given that they have been repeatedly shown to influence the therapy outcomes (Kuitunen-Paul, Roessner, et al., 2021; Welsh et al., 2017). A promising approach that has been shown to be moderately helpful when disorders other than SUDs are treated in adolescents is integrative group therapy (Boege et al., 2020; Godley et al., 2010; Kaminer, 2005).

Given this lack of adolescent-specific, integrative programs, we have developed the “Dresden multimodal therapy for adolescents with chronic substance use” (German abbreviation: DELTA) (Golub et al., 2021), a 16-week group and individual therapy for SUD. Besides showing that DELTA can be feasibly conducted in adolescent patients with SUD, our primary aim was to show that DELTA is associated with a stronger reduction in SUD severity and substance use as compared to a waiting-list control group (WL). Our secondary aim was to show that DELTA is associated with a stronger

decrease in symptoms of co-occurring psychopathologies. We hypothesized that a in comparison to WL leads to reductions of 1) depressiveness, 2) other depression-related pathologies (anxiousness/depressive, social withdrawal), 3) PTSD-related symptoms, 4) aggressive and dissocial pathologies, as well as 5) enhancement of life satisfaction over the course of the 16-week intervention. Reductions in nicotine use, psychotic prodromal symptoms and attention problems are additionally explored, although DELTA does not focus on these problems.

6.2 Methods

6.2.1 Procedures and design

Participants were recruited between November 2017 and September 2021 from several settings (our outpatient department for adolescent substance abuse and three cooperating youth welfare institutions). For an overview of study flow, see Fig. 6-1. We included adolescents qualifying for any SUD (notwithstanding nicotine use disorder) aged between 12.00-17.99 years, applying the following exclusion criteria: Pre-existing neurological diseases; diseases of or with involvement of the central nervous system; intelligence quotient < 70; diseases concerning the adrenal gland, pituitary gland or hypothalamus; acute viral diseases. Participants from the outpatient department received a treatment recommendation (either DELTA, inpatient detoxification, or external drug counselling) after a multidisciplinary team of clinical expert reviewed their case. Those who agreed to participate but did not want to join the DELTA intervention were assigned to the WL condition. Participants living in a youth welfare institutions were cluster-randomized to either WL or DELTA. In accordance with recommendations for clinical trials in small populations (Parmar et al., 2016), we increased the number of DELTA participants by re-randomizing WL participants in youth welfare institutions to receive DELTA after a 16-week waiting period. Therefore, this evaluation study enabled WL controls with a delayed intervention. First, baseline assessments (BL) were conducted, including paper-pencil questionnaires for participants and legal guardians, and structured interviews on substance use and mental disorders. After completion of the DELTA group sessions or passing at least 16 weeks to fulfil the WL condition, a similar follow-up assessment (FU) was

conducted. Depending on the availability of participants, the FU measures were taken on average at 26.3 weeks (SD = 6.7 weeks, range = 15.0 – 53.1 weeks) after BL, i.e. approx. eight weeks after the last DELTA session. Both patients and legal guardians agreed to study participation by written consent after a comprehensive verbal and written information. Patients did not receive reimbursements for participation in the group sessions, which were carried out in the outpatient setting. Blinding was not possible for participants or personnel administering the intervention. All procedures were conducted in accordance with the Declaration of Helsinki and were approved by the local Institutional Review Board (EK 66022018), see also clinicaltrials.gov registry entry NCT03444974.

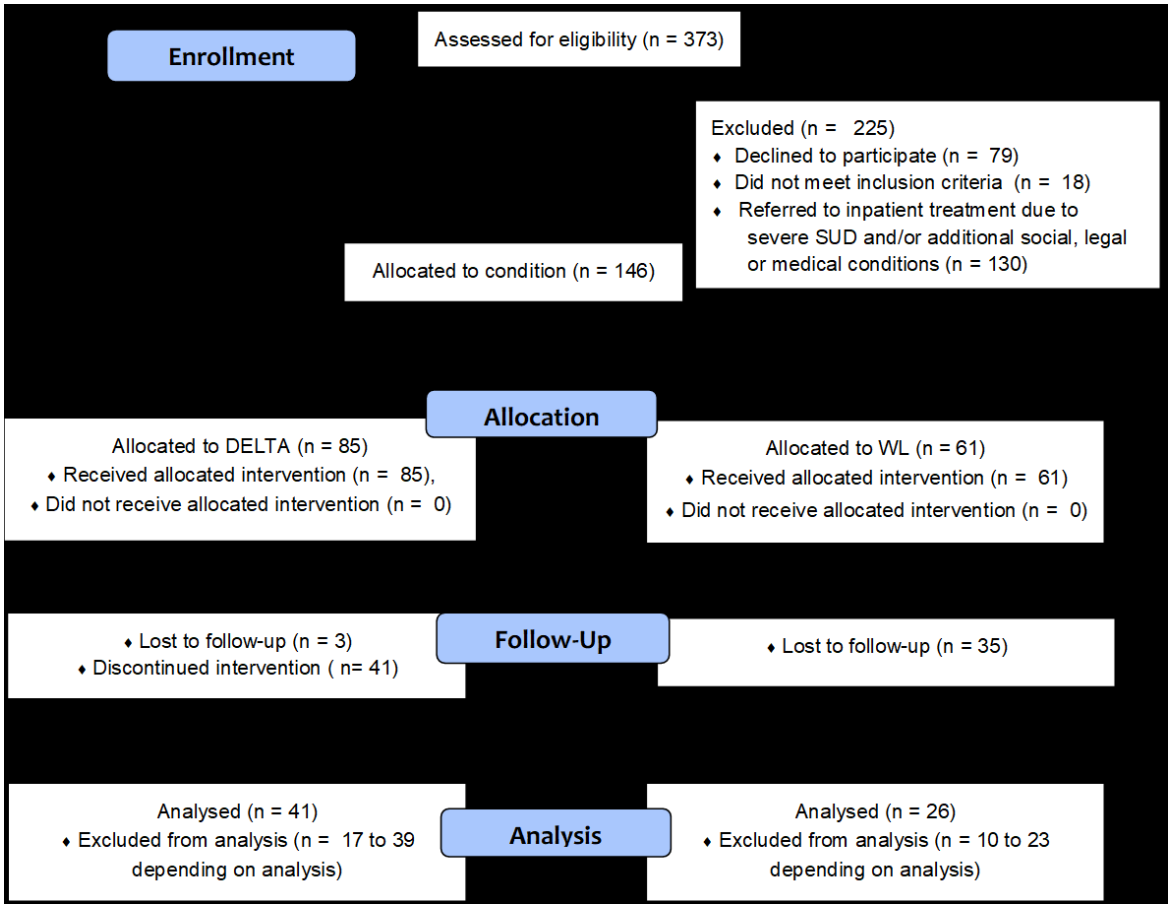

Figure 6-1. Flowchart of the DELTA evaluation trial.

6.2.2 Participants

N = 373 adolescents were recruited from one of the outpatient settings. N = 294 participants and their legal guardians agreed to participate. From these, n = 18 (6.1%) did not meet inclusion criteria and n = 130 (44.2%) were referred to inpatient treatment after screening. N = 9 WL participants in

youth welfare institutions received DELTA following a waiting period, which resulted in a sample comprised of n = 146 adolescent SUD patients for analysis. All participants who participated at least in one therapy session were included in the analysis.

6.2.3 Intervention

The manualized DELTA intervention (Golub et al., 2021) involved 16 weekly in-person sessions with 1-2 trained and experienced psychologists leading a group of 3-8 adolescent patients, lasting 60 minutes, accompanied by eight 1-on-1 sessions. The content for each session is predetermined and involves elements such as worksheets, group exercises, and homework. Additionally, each patient receives up to 8 individual session every two weeks (max. 60min) that may be used to address individual difficulties regarding psychosocial functioning, legal issues, educational career planning, etc. Before the first group session, all participants work out a therapy agreement with the therapist, detailing the rules of participation and the planned date of abstinence. A central feature of DELTA is the combination of different therapeutic modalities. Cognitive-behavioral methods are included to analyze use-related cognitions and behaviors in terms of their preceding stimuli (Ramo & Brown, 2008). Another behavioral method consists of applying regular positive reinforcement for active participation in the group. DELTA integrates principles of Motivational Interviewing (Millner & Rollnick, 2016), in a manner that accepts the continuous ambivalence of SUD patients towards abstinence. Additionally, contingency management is used to reward completed homework by free choice of emotion regulation skill (e.g. spicy sweets, smelling salts etc.). While creating DELTA we aimed to integrate the central mechanisms of psychological SUD treatment (Carey, 1996): therapeutic relationship, analysis of reasons for substance use, cooperative goal setting, and skills for dealing with emotional crises.

6.2.4 Waiting-list condition

Participants in the WL condition received treatment as usual, which could include measures such as referral to inpatient treatment in cases of severe SUD. In assisted living communities, n = 9 participants served as a WL by taking part in all assessments and then waiting 16 weeks before being included in the DELTA intervention.

6.2.5 Primary outcomes measures

6.2.5.1 Substance use problems

See chapter 1.5.4. The DVs from the DUDIT were the change between baseline and follow-up (FU) in DUDIT total and DUDIT-C score.

6.2.5.2 Substance use frequency

See chapter 1.5.6. Based on the two variables “frequency” and “quantity” from the substance use interview, a general substance use index ‘QF’ for the past month and past year was calculated by multiplying frequency and quantity estimates. The main DVs of the instrument were the differences between average monthly QF at baseline (referring to past-year use) and at FU (referring to past-month use).

6.2.6 Secondary outcome measures

6.2.6.1 Psychopathologies

Several instruments were used to assess common psychopathologies. See chapter 1.5.3 for the assessment of PTSD symptomatology, with this analysis focusing on the presence (present or absent) of hyperarousal, avoidance, and intrusion symptoms. Depressiveness was covered using the Beck Depression Inventory II (BDI-II) (Kühner et al., 2007), a self-report questionnaire with 21 items (Likert scale ranging from 0 to 3) resulting in a sum score where larger values equal stronger depressiveness. The Youth Self Report form (YSR), a multidimensional questionnaire with 118 items (Likert scale ranging from 0 to 2), measures different psychopathologies scales related to depression-related affective symptoms (‘YSR anxious/depressive’), depression-related social impairments (‘YSR social withdrawal’), attention-deficit disorder-related problems (‘YSR attention’), and conduct disorder-related problems (‘YSR aggressive’ as well as ‘YSR dissocial’) (Kuitunen-Paul, Eichler, et al., 2021). Psychopathologies related to prodromal symptoms of psychoticism are assessed via the Prodromal Questionnaire (PQ16) (Ising et al., 2012) with its 16 items (true vs. false) summed up to a score, with larger values indicating more symptoms of psychotic prodromal phases.

6.2.6.2 Life satisfaction

Adolescents rated their life satisfaction on the Satisfaction with Life Scale, German version (SWLS) (Glaesmer et al., 2011), a 5-item questionnaire. The SWLS covers global life satisfaction in contrast to related constructs such as positive affect or loneliness by asking for life conditions, achievements etc. to be rated on a seven-point Likert scale (1 strongly disagree to 7 strongly agree). Sum scores may range from 7 to 49, with higher scores indicating higher life satisfaction.

6.2.7 Descriptive measures

The number of sessions attended by each patient was used as an indicator for adherence to the therapy, ranging from 1 to 16 sessions. Further descriptive measures were the MINI-KID (see chapter 1.5.2) and our sociodemographic questionnaire (chapter 1.5.1) recording DSM-5 diagnoses and age and gender, respectively.

6.2.7.1 Therapy content evaluation

A self-designed questionnaire was applied to assess how helpful the participants perceive the group sessions to be. The questionnaire contains 20 items that are related to the contents of the different group sessions and refer to their usefulness in daily life. Each item is rated on a five-point scale (0 Never, 1 Rarely, 2 Sometimes, 3 Often, 4 Always) to indicate how helpful the specific content was for the participant's daily life.

6.2.8 Statistical analysis

Analyses were conducted with IBM SPSS Statistics 27.0. In most questionnaires (DUDIT, BDI-II, PQ16, SWLS), missing values were imputed if 80% or more of the items were answered. For YSR and UCLA PTSD scales, sum scores were used that ignored single item missings. To test the main hypotheses regarding SUD severity and substance use, group differences in DUDIT, DUDIT-C and QF change were calculated via multiple t-tests. To test for hypotheses regarding the secondary study aim (reducing symptoms of co-occurring disorders) multiple t-tests were calculated. A multivariate analysis would have severely limited the number of analyzed cases given that different cases had different missing patterns. In accordance with recommendations for clinical trials in small populations (Parmar et al., 2016), we moved to one-sided significance testing against a predefined

α = .05. In case of statistical significance, we corrected for the increased chance of false positives due to multiple testing by the Bonferroni correction. Effect sizes were classified according to Cohen (1988) into small effects (|d| ≥ 0.20), medium effects (|d| ≥ 0.50), and large effects (|d| ≥ 0.80).

6.3 Results

6.3.1 Baseline group composition

Analyzed participants aged 12.7-18.7 years (M = 16.1 years, SD = 1.2) included 38.4% females, see Table 6-1. The majority qualified for more than one SUD (57.0%) excluding nicotine use disorder. Both the DELTA intervention group and the WL group were comparable at baseline in terms of demographic and substance use characteristics, except for the proportion of participants recruited from youth welfare institutions being higher in the DELTA group (41% vs. 19%). From n = 146 baseline participants, n = 67 (45%) were retained for FU, of which n = 41 were part of the DELTA intervention group.

Table 6-1. Demographic and substance use characteristics of both groups at baseline.

	DELTA group	WL group	Group differences		
	n = 85	*n* = 61	Test statistic (*df*)	*p*	Effect size (*d*)
Females, *n* (%)	35 (41.2%)	21 (34.4%)	X^2 (1) = 0.68	.408	0.13
Age in years, *M* (*SD*)	16.1 (1.2)	16.2 (1.1)	*t* (144) = 0.08	.465	0.01
Living in youth welfare institutions, *n* (%)	35 (41%)	12 (19%)	X^2 (1) = 7.52	.006*	0.46
Substance Use Disorders, *n* (%) (*n* = 39 missings)					
Alcohol	30 (42%)	23 (62%)	X^2 (1) = 3.60	.057	0.37
Cannabis	49 (70%)	27 (72%)	X^2 (1) = 0.10	.747	0.06
Stimulants	35 (50%)	14 (37%)	X^2 (1) = 1.44	.230	0.23
Benzodiazepines	2 (2%)	0	---	---	---

Opiates	2 (2%)	1 (2%)	---	---	---
Hallucinogens	1 (1%)	0	---	---	---
Inhalants	1 (1%)	0	---	---	---
DUDIT score, *M* (*SD*)	18.2 (10.5)	17.2 (10.6)	*t* (109) = -0.48	.314	0.01

Note: *significant at the .05 level. DUDIT, Drug Use Disorders Identification Test. WL, waiting-list condition.

6.3.2 Non-responder analysis

Neither in DELTA nor WL, adolescents reached for FU differed from those lost to FU in terms of gender distribution, age, nor DUDIT score (see Appendix Table C-1). However, specifically in the DELTA group, those who were reached for FU had a higher baseline DUDIT score compared to those lost to FU.

6.3.3 Therapy adherence and content evaluation

In the DELTA group, adolescents participated in an average of 7.7 sessions (SD = 5.1), with 37% (n = 32) of them continuing up to the 10th session. Subjective ratings of how useful the therapy was perceived showed an average rating of M = 2.3 (SD = 0.38). That is, the therapy was typically rated as helping “sometimes” in all relevant aspects except for enhancing self-confidence, reducing fear, reducing feelings of helplessness, and increasing knowledge about substance use (see also Appendix Figure C-1). Best ratings were shown for reducing conflicts with important others, improving relationships with important others, and increasing control over one’s own substance use behavior.

6.3.4 Primary outcomes

In both groups, the DUDIT and DUDIT-C scores declined between the time points of baseline and FU, with the group differences not being significant (all p > .05) at both time points. However, we observed a larger reduction in DUDIT score in the DELTA group in comparison with the WL group with a small effect size, d = 0.23, see Table 6-2 and Figure 6-2. In the DELTA group, all QF values decreased between baseline and FU. In the WL group, all QF values except methamphetamine and alcohol reduced as well. The group difference in QF change was not significant for any comparison. However, the difference in methamphetamine change was equivalent to a large sized effect (d =

1.51), the difference in nicotine, cannabis, and MDMA use change was equivalent to a small effect (all d > 0.20), and the difference in alcohol use change was of a negligible size (d = 0.12). The number of attended sessions was strongly associated with amphetamine (r = -.69) and methamphetamine use (r = -.67), moderately associated with nicotine use (r = -.31), alcohol use (r = -.31), social withdrawal (r = -.33), dissocial symptoms (r = -.32) and attentional problems (r = -.36), with none of these associations reaching statistical significance, see Appendix Table C-2.

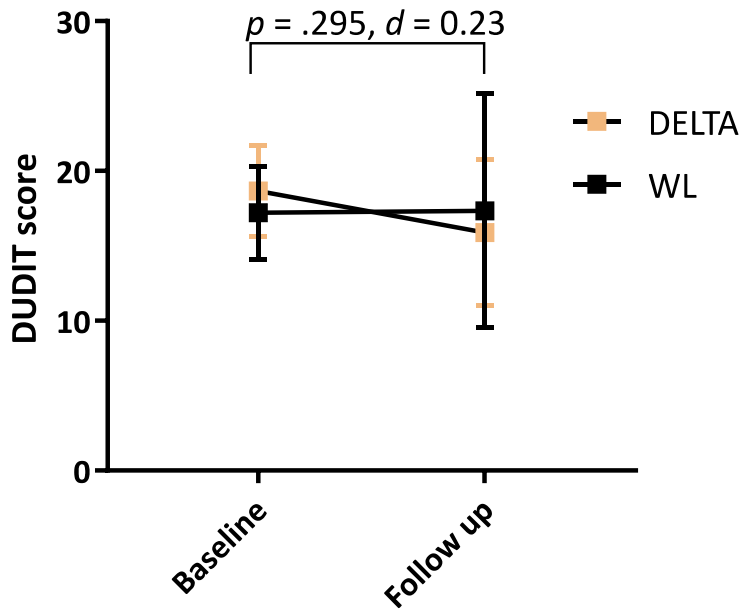

Figure 6-2. Changes in DUDIT score from baseline to FU, with statistics from t-test comparing the change score between the DELTA and WL condition.

Table 6-2. . Group differences in primary outcomes, with positive effect sizes indicating a bigger reduction in the DELTA group.

	DELTA group	WL group	Group differences		
Mean change from baseline to FU	Δ*M* (*SD*)	Δ*M* (*SD*)	Test statistic (*df*)	*p*-value (corrected)	Effect size(*d*)
Substance use					
Cigarettes per month	-224.5 (356.4), *n* = 26	-123.8 (286.4), *n* = 16	*t*(40) = 0.95	.173 (.865)	0.30
Standard drinks alcohol per month	-56.9 (223.3), *n* = 15	-80.3 (133.7), *n* = 11	*t*(24) = -0.30	.380 (.999)	-0.12
Grams of cannabis per month	-60.4 (98.2), *n* = 18	-34.0 (50.6), *n* = 10	*t*(26) = 0.78	.219 (.999)	0.31
Number of ecstasy pills per month	-6.4 (15.7), *n* = 8	-3.5 (6.5), *n* = 5	*t*(11) = 0.39	.351 (.999)	0.22

Grams of methamphetamine per month	-61.0 (68.1), *n* = 4	5.0 (12.2), *n* = 6	*t*(8) = 2.38	.022 (.110)	1.54
DUDIT-C score	-3.4 (6.3), *n* = 14	-3.1 (5.5), *n* = 7	*t*(19) = 0.10	.460	0.04
Substance use problems					
DUDIT score	-5.2 (13.4), *n* = 16	-2.4 (8.2), *n* = 8	*t*(22) = 0.54	.295	0.23

Note: Amphetamine not included because only *n* = 1 in waiting list. *P*-values were not corrected for multiple testing when differences were not statistically significant in the first place. Bonferroni correction was applied for substance use variables (5 comparisons). FU, follow-up; DUDIT, Drug Use Disorders Identification Test. MDMA, 3,4-Methylenedioxymethamphetamine. WL, waiting-list condition.

6.3.5 Secondary outcomes

As shown in Table 6-3, depressiveness decreased over time in both groups, with no differences between groups (d = -0.06). Psychopathologies broadly related to depression decreased in the DELTA group while these same psychopathologies increased in the WL group, representing a medium-sized yet insignificant group difference (d = 0.52 and 0.74). Psychopathologies related to conduct disorder decreased in both groups with a small to medium yet insignificant advantage for DELTA (d = 0.74 and 0.22). Psychopathologies related to PTSD did not change meaningfully over time nor did groups differ from each other as seen by insignificant and irrelevant or small effect sizes (d = 0.00 to -0.41). The same pattern was shown for psychopathologies related to psychoticism and schizophrenia (d = 0.12). Attention problems decreased in both groups with a small insignificant advantage for WL (d = -0.25). Satisfaction with life in general increased in both groups, without differences between DELTA and WL (d = -0.15). The number of attended sessions was moderately yet not significantly associated with decreased social withdrawal, decreased attention problems, and decreased dissocial behavior related to conduct disorder (all r = -.32 to -.36, all p = .163 to .223, see Appendix Table C-2).

Table 6-3. Group differences in secondary outcomes.

Secondary outcome	DELTA group	WL group	Group differences		
	Δ*M* (*SD*)	Δ*M* (*SD*)	Test statistic (*df*)	*p*-value	Effect size (*d*)
BDI-II sum	-2.4 (13.3), *n* = 17	-3.2 (14.4), *n* = 8	*t*(23) = -0.14	.445	-0.06
YSR anxious/depressive	-3.3 (8.2), *n* = 16	+1.5 (13.1), *n* = 4	*t*(18) = 0.94	.180	0.54

YSR social withdrawal	-4.1 (9.4), *n* = 16	+2.5 (5.1), *n* = 4	*t*(18) = 1.39	.100	0.78
YSR aggressive	-4.0 (5.2), *n* = 16	-0.3 (0.5), *n* = 3	*t*(17) = 1.18	.125	0.74
YSR dissocial	-6.3 (7.5), *n* = 16	-4.7 (3.2), *n* = 4	*t*(18) = 0.39	.348	0.22
UCLA symptoms intrusion	0.0 (1.1), *n* = 12	0.0 (0.5), *n* = 7	*t*(17) = ---	---	---
UCLA symptoms avoidance	+0.3 (1.6), *n* = 12	-0.2 (1.2), *n* = 7	*t*(17) = -0.87	.198	-0.41
UCLA symptoms hyperarousal	+0.2 (1.4), *n* = 12	+0.1 (0.3), *n* = 7	*t*(17) = -0.18	.428	-0.08
Exploratory					
YSR attention	-0.8 (10.4), *n* = 16	-3.5 (8.5), *n* = 4	*t*(18) = -0.45	.329	-0.25
PQ16 sum	-0.5 (1.3), *n* = 12	-0.4 (1.1), *n* = 7	*t*(17) = 0.26	.399	0.12
SWLS sum	+1.5 (7.3), *n* = 14	+0.6 (2.5), *n* = 9	*t*(21) = -0.35	.364	-0.15

Note: p-values were not corrected for multiple testing given since differences were not statistically significant in the first place. ADD/ADHD, attention-deficit disorder with/without hyperactivity. BDI-II, Beck Depression Inventory II. PQ16, Prodromal Questionnaire. PTSD, post-traumatic stress disorder. SWLS, Satisfaction With Life Scale. UCLA, UCLA PSTD questionnaire. WL, waiting-list condition. YSR, Youth Self Report questionnaire.

6.4 Discussion

We developed the DELTA intervention for adolescents with SUD. DELTA consists of 16 weekly sessions in a group setting plus eight 1-on-1 sessions. This evaluation of the DELTA intervention in outpatient and youth welfare settings showed evidence in favor of DELTA as compared to the WL controls. Despite a small sample size, we found clinically relevant changes in terms of substance use reduction, less SUD-related problems, and decreased psychopathologies.

In terms of our primary goal, we showed a small effect in the reduction of SUD severity in comparison to the WL group. Similar findings of small or inconsistent improvements were reported in studies for SUD in adults (Rawson et al., 2004). Furthermore, we observed a medium sized intervention effect in terms of reduced use of nicotine, cannabis and MDMA at FU, as well as a large effect for reduction of methamphetamine use. A similar study to ours in adolescents with CUD showed a 7-point decrease of CUD severity compared to our finding of a 5-point decrease across substances (Hoch et al., 2014). It should be noted that these differences might underestimate the efficacy of DELTA given that participants attended only half of the group sessions on average. This low attendance rate might be driven by the inclusion of patients who used amphetamine or methamphetamine, both of which were negatively associated with attendance. While this

suboptimal adherence rate is similar to rates observed in other group therapies for SUD (Goldberg et al., 2021; Petzold et al., 2021), an increased adherence might lead to even stronger intervention effects. Unfortunately, a small sample size precluded a sufficiently powered analysis. Clinical studies in adults with a 10-fold larger sample size revealed significant efficacy in promoting abstinence, reducing methamphetamine use or craving in participants of group interventions (AshaRani et al., 2020). In comparison, mindfulness based interventions in patients with SUD indicate uncertain effects in all primary outcomes (Goldberg et al., 2021). However, these larger studies (AshaRani et al., 2020) are limited to adult patients, often recruited from more structured inpatient settings.

In terms of co-occurring psychopathology, we did not find an indication that the reduction of SUD-specific variables is related to a reduction of PTSD-related symptoms. Our results indicate that for a proper treatment of co-occurring PTSD and SUD more specialized treatment forms are needed. However, we observed a clinical effect on the reduction of the depressive symptoms, understanding and influencing aversive emotions, and promoting prosocial behavior. Another study on manualized treatment of CUD showed an enduring relationship between decreasing cannabis use and decreasing depression among adolescents lasting for 9-months after receiving psychosocial interventions for CUD (Arias et al., 2020). These findings indicate that a treatment involving a reduction of substance use and SUD symptoms, such as DELTA, might also help to reduce secondary psychopathologies such as depressive symptoms (Hersh et al., 2014; Kaminer et al., 2007). Finally, results showed that antisocial behavior might be decreased by DELTA. Conduct disorder is prevalent in adolescents with SUD in general and specifically in methamphetamine users (Kuitunen-Paul, Roessner, et al., 2021), and was present in more than half of our participants compared to a population prevalence of 1.5-3.4% in children and adolescents (Steiner, 1997). Conduct disorder is furthermore known to have detrimental consequences on domains such as academic performance, interpersonal relationships, and adherence to the law, potentially leading to incarceration (Steiner, 1997). Reducing the underlying condition is a beneficial side effect, while it remains unclear if DELTA is the specific reason for this reduction, or if those whose conduct disorder problems already are in decline are more likely to engage in outpatient therapies such as DELTA.

6.4.1 Limitations

The small number of patients required strategies for analyzing small samples in clinical trials (Parmar et al., 2016). However, strategies such as one-sided testing, combination of FU assessments across a larger period of time, and re-allocating participants may reduce the internal validity of the study. The small sample may also limit the heterogeneity of the sample as well as decrease the possibility to find significant effects of additional factors. Additionally, the small sample size prohibited us from performing subgroup analysis, e.g., regarding outpatient settings or type of substance. Nevertheless, our study is one of the first ones to investigate a group-based manualized treatment for adolescents with heterogeneous SUDs. As in other multimodal interventions, it is difficult to distinguish which modules contribute to treatment effects. Furthermore, adolescent patients with SUDs often participate in treatment only reluctantly, as reflected in low session attendance, which decreases the possibility of detecting clinically meaningful effects.

6.4.2 Implications for program development

DELTA may be expanded towards smoking cessation as well, considering that neither DELTA nor other comparable programs specifically focus on nicotine use disorder or smoking behavior although the vast majority of adolescent SUD outpatients smoke (Wiedmann, Atzendorf, et al., 2022). Other relevant areas for improvement are indicated by the usability results. Lowest usability was reported for areas including strategies to reduce fear, to increase SUD-related knowledge, and to reignite self-confidence in patients. A revised manual should address these topics with adequate therapeutic methods.

Our study features several elements of pragmatic trials (e.g., diverse settings, simplified analysis design, non-randomization, uncontrolled environments) (Patsopoulos, 2011). It is therefore necessary to replicate our findings in multicenter randomized clinical trials controlling for variables relating to therapy setting, adjunct interventions or sample characteristics. For example, showing that DELTA is both feasible and effective when conducted in inpatient settings might extend existing detoxification treatments.

6.5 Conclusion

We presented first evidence that the DELTA intervention for adolescents with SUD is feasible, and preliminary evidence that DELTA might reduce SUD severity and substance use, especially methamphetamine. After replication, DELTA might be used a) in those adolescents who do not need to undergo inpatient detoxification treatment or b) as a supplement following detoxification, helping to stabilize patients in their abstinence once they finish detoxification. Until then, clinical effects should be cautiously interpreted.

6.6 Acknowledgements, Funding, Conflicts of Interest

LAB, SKP, VR and YG are authors of the DELTA treatment manual, thus they receive honoraria for the manual as published by Hogrefe Publishing. MFW reports no conflicting interests.

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7. General Discussion

7.1 Summary

In the following, a summary is presented of the main findings from the presented research projects in relation to the research aims and hypotheses. In short, we predicted that 1) SUD severity will differ between the three groups (noTE, TE, PTSD), 2) across substances, the PTSD group will show the highest frequency of substance use, and 3) the differences in hypothesis two are associated with a self-medication motive. Since chapter 2 contains a methodological introduction, the focus of this summary will be on the content related to chapters 3-6.

Chapter 2 contained the evaluation of a SUD assessment tool for adolescents. The evaluation of this tool was necessary in order to establish its use for the assessment of SUD severity and as a primary outcome for the clinical trial presented in chapter 6. More specifically, in the chapter the evaluation of the Drug Use Disorder Identification Test (DUDIT) for use in an adolescent clinical population when applying DSM-5 SUD criteria was presented. Our study was the first evaluation study of the DUDIT questionnaire in relation to the DSM-5 criteria of SUD. Furthermore, cut-off scores for the presence of a SUD in adolescent were established. The DUDIT showed an excellent discriminant validity and proved itself as a valid tool for the assessment of SUD severity in a clinical adolescent population. Based on this study, the DUDIT was applied as an instrument for measurement of the SUD severity in the context of adolescent SUD patients.

In **Chapter 3,** the DUDIT questionnaire was applied to assess whether clinically observed high co-occurrences of SUD and, TEs or PTSD are related to differences in SUD severity. In more detail, the chapter contained an evaluation of the differences in SUD severity between adolescents with a SUD ('noTE' group), adolescents with a SUD and a history of TE but not PTSD ('TE' group), and adolescents with SUD and co-occurring PTSD ('PTSD' group). Our results provided evidence that the prevalence of TEs and PTSD in adolescents with SUD is about three to five times higher than in the general population, with the majority of traumatized patients in the sample reporting a TE related to non-domestic violence. In line with the proposed hypothesis, the PTSD group showed a significantly more severe SUD than the other two groups. . In contrast to our expectation, the TE group did not differ significantly in SUD severity

from the noTE group; in fact, their respective mean SUD severity was nearly identical. Thus, our results indicate that PTSD as a disorder but not just TEs on their own are an important predictor of adolescent SUD severity. To further explore the relationship between SUD, PTSD and TEs an analysis of substance use patterns was subsequently performed.

The aim of the work presented in **Chapter 4** was to continue the exploration of group differences in more detail and evaluate the differences in patterns of tobacco, alcohol, cannabis, MDMA and amphetamine use. In this study, it was shown that past-month substance use frequency was nearly the same across groups and across substances, with only the use of MDMA being significantly more frequent and more prevalent in the PTSD group compared to the other two. Similar to the findings reported in chapter 3, the noTE and TE group did not differ in terms of their past-month substance use. The same pattern was also found for the age of first substance use. Participants in the PTSD group reported a significantly earlier age for their first substance use compared to the participants in the other two groups. Furthermore, the age of PTSD symptom onset was similar to the age of their first substance use, except for MDMA and amphetamines, the use of which started on average 2 years after PTSD symptom onset. Finally, this study demonstrated that the presence of the avoidance symptom cluster is related to a more frequent past-month MDMA use. Our second hypothesis was, due to these results, thus mostly rejected since past-month substance was mostly similar across groups. However, in line with the findings of the work presented in chapter 5 only the PTSD groups showed a significantly increased past-month substance use. This increase was only seen for the substance MDMA. Based on these results and, specifically the relationship between avoidance symptoms and increased MDMA use, it could be hypothesized that this pattern is likely to be the result of a self-medication motive.

In the work presented in **Chapter 5** this exploration of differences in substance use patterns between the groups of patients with/without a TE and PTSD was continued. The aim of the work was to investigate the relationship between a self-medication motive and MDMA use. Specifically, in this study past-year substance use was assessed, as well as the relationship between coping use motives and substance use frequency. The PTSD group showed a more frequent MDMA use over the past-year compared to the other two groups. Additionally, the PTSD group reported using substances more frequently for coping reasons, and the frequency of coping use motives was positively correlated with

the frequency of past-year MDMA use. Finally, we show that coping motives mediate the relationship between the group (noTE, TE, PTSD) and MDMA use frequency. In summary, the results presented in chapter 5 provide confirmatory evidence for the third hypothesis of this thesis, thereby strengthening the argument that the observed substance use patterns in adolescents with PTSD are related to a self-medication motive.

Chapter 6 contained the results of a pragmatic clinical trial assessing the efficacy of the DELTA multimodal therapy for the treatment of adolescent SUDs.

We report the effects of the DELTA intervention on SUD related outcomes as well as co-occurring psychopathologies. Specifically, the intervention group showed larger, albeit non-significant, reductions in SUD severity and substance use frequency 20 weeks after starting the DELTA program. However, no relationship could be detected between the intervention and changes in PTSD symptomatology. These results indicate the need for a standardized, more complex intervention for the treatment of a PTSD in adolescents with SUD. Indeed our results supporting the self-medication hypothesis emphasize a prominent need for targeting PTBS symptoms thus focusing on the precipitating psychopathology of which SUD seems to be a consequence.

7.2 Implications for the Self-Medication Hypothesis

The first aim of our work was to explore the relationship between SUD, TEs and PTSD, specifically with regard to their co-development. Moreover, we focused on an investigation of the three main theories about their co-occurrence (common risk factor, exposure and self-medication, see Figure 1-1). The findings presented in chapter 4 show that substance use (but not SUD) has the same age of onset as PTSD symptoms, while the results contained in chapter 5 support the notion that MDMA was used by participants out of a self-medication motive. Our data support the self-medication hypothesis, such that MDMA use might be a reaction to the development of PTSD symptoms, but not to the presence of a TE alone. However, the focus of the included studies was on substance use and not SUDs. The self-medication hypothesis predicts, that an increased substance use related to self-medication motives, would eventually develop into a related SUD. The participants with co-occurring SUD and PTSD did report more frequent, coping-related MDMDA use but did not show a higher rate of MDMA-related SUDs.

Instead, the distribution of SUDs was uniform across the three groups, with the PTSD group presenting more severe forms (as seen in chapter 3). Since our participants used a wide variety of substances, starting with PTSD symptom onset, the use of which mostly developed into a SUD, the self-medication drive should not so much be seen as a desire for specific subjective effects of specific substances, but rather more as a general desire for experiencing an altered state, that improves the PTSD symptomatology. This idea is in line with research showing that self-medication related substance use is often related to increased general substance use and that specific substances are often used to cope with a variety of psychopathological symptoms (Bizzarri et al., 2009; McKernan et al., 2015; Smith et al., 2017). MDMA might be particularly effective in alleviating PTSD symptoms, but the development of SUDs had already taken place at that point, as shown by our data in chapter 4. Furthermore, since MDMA is used mostly in specific social circles not every adolescent substance user with a PTSD is going to be exposed to this substance, which explains why other substances have been implicated in a similar fashion in previous studies (Hawn et al., 2020; Klee & Reid, 1998; Patel et al., 2021; Somohano et al., 2019). For example, in some studies have shown that PTSD is related specifically to alcohol or opiate use (Hawn et al., 2020; Klee & Reid, 1998; Somohano et al., 2019), with others suggesting a special relationship between cannabis use and PTSD symptomatology (Patel et al., 2021). However, to evaluate and update the self-medication hypothesis, complex longitudinal studies are needed, which will be used to assess how PTSD symptoms, SUD symptoms and substance use trajectories develop over time and in response to the occurrence of new TEs or the first use of new psychoactive substances.

These results imply that self-medication is not so much related to specific substances but to any form of consciousness alteration that can lead to symptom reduction. This more general relationship is supported by other studies in which it has been shown that trauma cues induce higher craving levels across substances (Farrelly et al., 2021; Romero-Sanchiz et al., 2022) and that the presence of PTSD is a predictor for the later development of a SUD regardless of substance (Borges et al., 2021; Wolitzky-Taylor et al., 2012). In summary, a self-medication motive is a strong motive for substance use in adolescents with PTSD and SUD, however, the development of a SUD is not necessarily dependent on a self-medication motive. Furthermore, MDMA use seems to be uniquely associated with co-occurring SUD and PTSD beyond the use of other recreationally used substances such as nicotine, alcohol,

cannabis, or amphetamine.

7.3 Relationship of MDMA and PTSD Symptoms

While at first glance, the increased MDMA use frequency in the PTSD group might seem arbitrary; this finding could well be reflective of the larger relationship between MDMA use and PTSD. MDMA has an extensive history as a therapeutic aid (Sessa et al., 2019). First synthesized in 1912 by Anton Köllisch (Benzenhöfer & Passie, 2006) and then brought to mainstream attention as a recreational drug by Alexander Shulgin in the 1960s, its unique psychoactive effects were soon applied in psychotherapeutic settings (Passie, 2018). The psychological effects led to MDMA, and similar substances like MDA, being called empathogens, as a number of therapists used these substances to support their clinical practice in couple therapy specifically and psychotherapy in general (Nichols, 2022). However, with the introduction of the misuse of drugs act, all legal application of MDMA for therapeutic purposes waned (Passie & Benzenhöfer, 2016). Despite this, illegal underground therapy is still conducted to this day, sometimes with fatal consequences (Sessa & Fischer, 2015). Nonetheless, research interest began to surge again in the early 2000s with Michael Mitthoefer leading a study in which the therapeutic effect of MDMA-supported psychotherapy was investigated for none other than PTSD (Mithoefer et al., 2011). This resurgence of research has been ongoing for the last 20 years, with similar projects now being conducted in Germany, the Netherlands, Norway, Portugal, Czech Republic & the UK (see clinicaltrials.gov NCT04030169), and MDMA-assisted psychotherapy for PTSD being on the cusp of approval in the United States (Nuwer, 2021). So far, a first phase-3 study has shown MDMA-assisted psychotherapy leading to significant reductions in PTSD symptomatology and showing larger treatment effects than a comparable therapeutic intervention with placebo (Mitchell et al., 2021). Interestingly, MDMA-assisted treatment for alcohol use disorder has also undergone a phase-1 study indicating therapeutic potential as well (Sessa et al., 2021). While these preliminary results seem promising, there are a variety of methodological issues that warrant skepticism with regard to the validity of these results (see Schenberg (2021), Aday et al. (2022), Muthukumaraswamy et al. (2021) for comprehensive overviews regarding the difficulties of studying clinical effects of strong psychoactive substances). The most important issues are the difficulty of providing proper blinding of participants and researchers in

clinical trials with psychoactive substances, the lack of comprehensive adverse event monitoring and the provision of appropriate therapies as comparators (Burke & Blumberger, 2021; Halvorsen et al., 2021). Furthermore, no clarity on the mechanisms responsible for these findings has been delivered so far. Some studies support biological theories that indicate how MDMA might induce neurogenesis in the hippocampal region and thus alter PTSD-related memories (Amoroso, 2015). Indeed, there are current research projects that aim to determine the specific biological underpinnings of MDMAs therapeutic effects in an effort to produce safer and more efficient pharmacological alternatives (Heifets et al., 2019). However, the majority of theories are related to the subjective effects of MDMA. In detail, the empathogenic response induced by MDMA is supposed to allow for a positive re-evaluation of fear and anxiety inducing thoughts and memories, thereby allowing patients to overcome PTSD-related avoidance behavior through memory reconsolidation (Feduccia & Mithoefer, 2018; Thal & Lommen, 2018). This idea is indeed in line with the findings presented in chapter 4, showing that the presence of avoidance symptoms is related to more frequent MDMA use. While this therapeutic history of MDMA might hint at an explanation for the reported results of the work described in this thesis, it is important to distinguish our findings from the literature on MDMA-assisted psychotherapy for PTSD. First, in this work the patients were adolescents with a co-occurring SUD, which differs from the population included in the clinical literature (most often adult military veterans). Second, our participants used MDMA in recreational contexts, meaning the substance was mostly used in the form of illegally sold ecstasy, which has a high chance of containing other substances like synthethic cathinones or amphetamine, in addition to MDMA (Oliver et al., 2019; Palamar & Salomone, 2021). Furthermore, recreational MDMA is mostly used in the context of raves or parties instead of a psychotherapeutic setting. Third, no assessment was made of potential reductions in PTSD symptomatology due to their MDMA use, which meant no indication was given of whether the MDMA use has any symptom-reducing effects at all. In previous research it has been suggested that recreational MDMA use might provide a coping mechanism mostly for a population that is not receiving other psychological treatment (Moonzwe et al., 2011). This opens up the question of the type of care that is appropriate for this population, which is explored in the next section.

7.4 Clinical Implications

Chapter 6 contained the results of a pragmatic clinical trial for adolescent SUD patients, including patients with co-occurring PTSD symptoms. In this trial it was shown, that PTSD symptoms were not reduced through the DELTA intervention. One reason for this result might be that explicit instructions in the manual are focused on SUD-related interventions. While the manual explicitly recommends the use of 1-on-1 sessions for the treatment for co-occurring disorders, the content of these sessions remains in the hands of the provider. Therefore, there was no possibility to evaluate the contents of the 1-on-1 sessions or analyze how much PTSD-related treatment was actually offered. Additionally, the 16-week DELTA program only provides space for eight 1-on-1 sessions between the provider and the patient. Since this frequency is below recommended levels for individual therapy a more comprehensive 1-on-1 component as part of the DELTA intervention might be more successful in reducing co-occurring symptoms. All in all, the DELTA intervention in its current form, while appropriate for the SUD context, seems to need additional elements to be a successful intervention for SUD and co-occurring PTSD.

The results of the pragmatic clinical trial are important in two ways: I) by showing that a reduction of MDMA use frequency is not related to changes in PTSD symptoms, it indicates that MDMA use for self-medication purposes might not be beneficial beyond the acute psychoactive effects. As outlined above, this finding is in line with the idea, that MDMA use might only reduce PTSD symptoms acutely and only when the PTSD symptoms are untreated (Moonzwe et al., 2011). II) The self-medication hypothesis implies that the development of a SUD is the consequence of PTSD-related substance use (see Figure 1-1). Based on this relationship, it can be expected that treating only the consequence, the SUD, will not change symptoms of the preceding cause, the PTSD symptomatology. Consequently, these findings indicate that SUD-focused programs need to be enhanced with specific evaluated PTSD treatment modules. For example, SUD-specific treatment could be offered in addition to cognitive processing therapy (Asmundson et al., 2019; Rosner et al., 2019), eye-movement desensitization and reprocessing (Beer, 2018; Karadag et al., 2020), trauma-focused CBT (Lindebø Knutsen et al., 2020; A. McGuire et al., 2021), or trauma-specific exposure therapy (Peltonen & Kangaslampi, 2019; Rossouw et al., 2018). Since pharmacological treatment options might not be ideal for patients with SUD or PTSD (Schäfer et al., 2019), non-pharmacological treatment involving altered states of consciousness, such as mindfulness-

based treatments (Boyd et al., 2018), also could be considered. However, the same might hold true for PTSD-focused treatment options, in the sense that the co-occurring SUD, which has already developed into an independent disorder, also needs specialized care. Therefore, the approach most appropriate would seem to be a combined treatment effort (see Figure 9-1). The most promising and best evaluated of such approaches is the 'Seeking Safety' program (Najavits, 2001), which is focused on adult patients although an adolescent version has been evaluated (Najavits et al., 2006). Additionally, a preliminary study evaluated an intervention specifically focused on adolescents with SUD and PTSD composed of mindfulness and CBT elements (Fortuna et al., 2018) and another adolescent-centric program is currently undergoing trial (Mills et al., 2020).

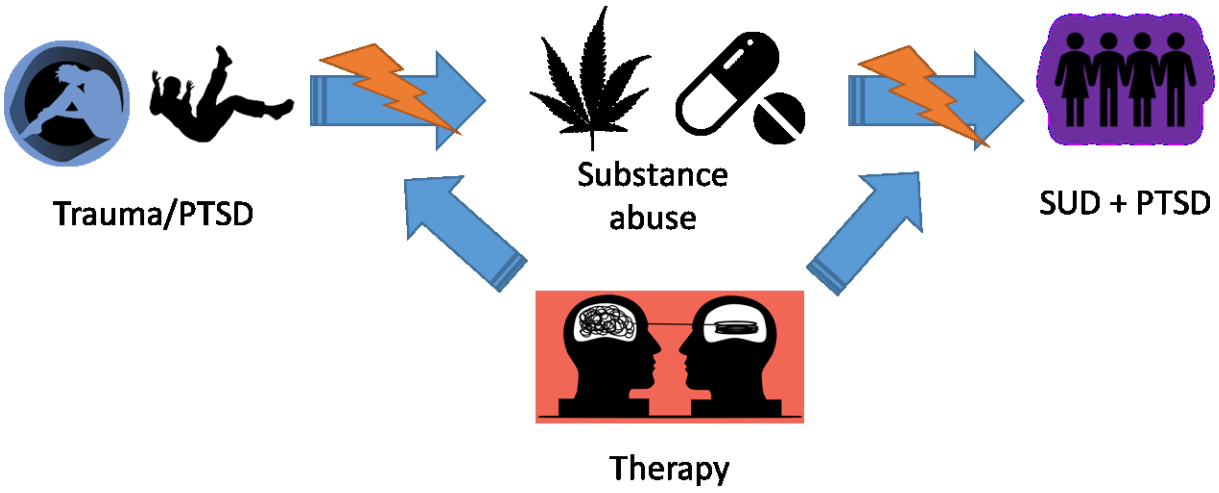

Figure 9-1. The need for therapeutic interventions to target both disorders, when SUD and PTSD co-occur in a single individual.

Apart from highlighting the need for specific clinical programs, the results presented in this thesis might sharpen a clinician's eye for the reasons their patients engage in substance use. Clinicians working in the field of adolescent SUD should be aware of the rampant issue of co-occurring disorders, especially PTSD, and should take care to investigate the function substance use plays in a patient's life. The findings presented in this thesis indicate that substance use might not be solely related to craving and SUD-related loss of control but rather a deliberate action undertaken to cope with stressful life events and debilitating symptoms. While working with this population, it is important to consider symptoms of other psychiatric disorders as factors that contribute to the maintenance of substance use patterns.

7.5 Limitations & Future Research

The conclusions presented so far are limited by a number of factors, which in turn could form the basis for future research projects. First, all of the presented studies sampled participants who were from a unique population: treatment-seeking adolescents with an existing SUD. This population already had existing problems with their substance use and in most cases showed additional co-occurring disorders (Wiedmann, Atzendorf, et al., 2022). Therefore, in a future study it could be investigated how substance use and traumatic symptoms are linked in a population of general substance-using adolescents.

Second, the conclusions presented above regarding coping motives in the sample depended on an imperfect self-designed measure. While care was taken to establish the validity of the instrument in some sense, it remains unconfirmed what the questionnaire actually measures. A more specific issue with this approach is that use motives across substances and across co-occurring disorders were assessed by asking for coping with negative emotional states in general. Future research would profit from asking participants about their use motives for specific substances and the relationship of their substance use with specific symptoms of PTSD.

Third, while it has been assumed that there is a self-medicating reason for the reported difference in MDMA use, all included studies are cross-sectional and include no measure of symptom relief. The cross-sectional design does not allow conclusions to be made about directionality, opening up the possibility that participants do not use MDMA because they have PTSD, but that they have PTSD because they use MDMA. While has been suggested that the evidence points to the former and not the latter, the side-effects of MDMA use might lead to pre-clinical symptoms of PTSD emerging to a greater degree (Morgan et al., 2002; Thomasius et al., 1997).

Additionally, no assessment was made of whether the reported MDMA use resulted in any form of symptom relief for participants, prohibiting the formation of any conclusions about recreational MDMA use in adolescents being symptom relieving. These issues could be resolved in a future project again by using a more detailed form of assessment. For example, forms of ecological momentary assessments (Votaw & Witkiewitz, 2021) could be used to assess PTSD symptoms at various times of day in relation to participants substance use.

Finally, all included DVs were based on subjective reports (DUDIT, UCLA PTSD scale, substance use assessment, use motive questionnaire). While allowing an assessment to be made of the situation from the participants' point of view, future studies could benefit from including a form of assessment that is more objective. In fact, one such project is currently underway at the Clinic for Child and Adolescent Psychiatry, with the aim of assessing differences in cognitive functioning between adolescents with only SUD, only PTSD, and co-occurring SUD and PTSD.

7.6 Conclusion

In this dissertation, research was presented in which the relationship between co-occurring SUD and PTSD in adolescents was assessed. The included studies showed that PTSD does occur at an increased rate in adolescents with SUD and that this co-occurrence is related to higher SUD severity, higher rates of MDMA use, an earlier initiation of substance use, and a more frequent substance use to cope with negative emotional states. The higher rates of MDMA use in the SUD and PTSD group was found to be partly mediated by the higher level of coping use motives reported in this population. This desire for self-medication might represent a lack of psychosocial support for adolescents with PTSD and SUD. Future research should investigate the detailed motives for adolescent substance use. Clinical work would benefit from taking into account the role substance use, specifically MDMA, might play for adolescents in their attempts to care for themselves and cope with the specific issues they have experienced.

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9. Appendices

9.1 Appendix A (chapter 4)

Table A-1. Shapiro-Wilk test for normality of the five outcome variables.

	Test statistic	p-value
#Days of tobacco use	W (120) = .540	<0.001
#Days of alcohol use	W (120) = .591	<0.001
#Days of cannabis use	W (120) = .738	<0.001
#Days of MDMA use	W (120) = .373	<0.001
#Days of amphetamine use	W (120) = .215	<0.001
Age of substance use	W (120) = .754	<0.001

Table A-2. Median and IQR values for the non-normally distributed continuous outcomes.

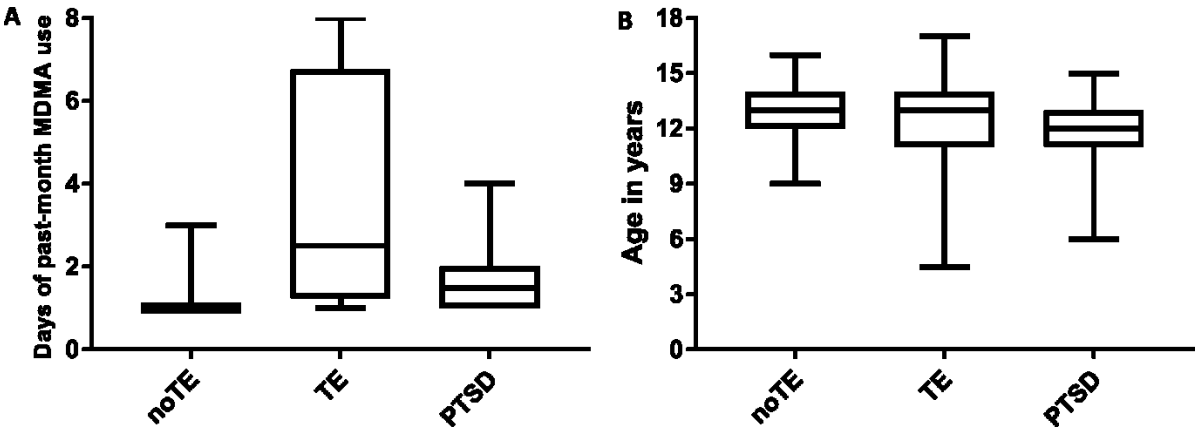
	Total sample (*n* = 121)	noTE (*n* = 35)	TE (*n* = 48)	PTSD (*n* = 38)
	Median days of substance use in the past month (IQR)			
Tobacco use across whole sample	30 (0)	30 (5)	30 (9)	30 (0)
Tobacco use across tobacco users	30 (0) (93%)	30 (0) (86%)	30 (0) (63%)	30 (0) (97%)
Alcohol use across whole sample	1 (3)	1 (8)	1 (3)	1 (4)
Alcohol use across alcohol users	3 (7) (55%)	6 (13) (54%)	2 (2) (58%)	3.5 (7) (52%)
Cannabis use across whole sample	1 (15)	2 (15)	0.5 (10)	1.5 (15)
Cannabis use across cannabis users	11 (18) (58%)	14.5 (18) (63%)	9 (13) (50%)	8 (22) (63%)
MDMA use across whole sample	0 (0)	0 (0)	0 (0)	0 (1)
MDMA use across MDMA users	1.5 (2) (16%)	1 (0) (9%)	2.5 (6) (8%)	1.25 (1) (32%)

Amphetamine use across whole sample	0 (0)	0 (0)	0 (0)	0 (0)
Amphetamine use across amphetamine users	4 (9) (7%)	0 (0) (3%)	12 (0) (6%)	3 (5) (13%)
Median age of first substance use (IQR)	12 (3.0)	13 (2.0)	13 (3.0)	12 (2.0)

Table A-3. Median and IQR values for the participants divided by the presence of PTSD symptom clusters.

PTSD symptom cluster		Total *N*	Median number of days of past month MDMA use (IQR)	Only MDMA users *N*	Median number of days of past month MDMA use (IQR)
Intrusion	present	62	0 (0)	14	1.25 (1)
	not present	24	0 (0)	2	5.5 (0)
Avoidance	present	43	0 (0)	13	1.5 (1)
	not present	43	0 (1)	3	3 (0)
Hyperarousal	present	67	0 (0)	13	1 (1)
	not present	19	0 (0)	3	3 (0)

Figure A-1. Boxplots of MDMA use frequency in the past month and age of first substance use.



Note: A, Median number of days of MDMA use in the past month across the three groups; B, median age of first substance use across the three groups.

9.2 Appendix B (chapter 5)

Table B-1. Shapiro-Wilk test for normality of the five outcome variables.

	Test statistic	*p*-value
#Days of tobacco use	W (23) = .54	<.001
#Days of alcohol use	W (23) = .75	<.001
#Days of cannabis use	W (23) = .83	.001
#Days of MDMA use	W (23) = .64	<.001
#Days of stimulant use	W (23) = .55	<.001
Coping score	W (23) = .89	.018

Note: *Days of substance use are the average number of days of substance use per month over the past year*

Table B-2. Results from the confirmatory factor analysis

Model	X^2(df)	X^2/*df*-ratio	*p*-value	CFI	SRMR	RMSEA [90% CI]
Theoretical model	64.09 (24)	2.67	<.001	.91	.09	.16 [.11 – .21]
Empirical model	45.79 (22)	2.08	.002	.95	.04	.13 [.07 – .18]
Combined model	49.33 (24)	2.05	.002	.94	.05	.13 [.08 – .18]

Notes. Good [acceptable] model fit is indicated by X2/df-ratio < 2 [<3], CFI ≥ .95 [.90 - .94], SRMR ≤ .05 [.05 - .10], and RMSEA ≤ .05 [.05-.10 acceptable]. CFI = Comparative Fit Index. RMSEA 90% CI = 90% confidence interval of the root mean square error of approximation. SRMR = Standardized Root Mean Square Residual.

9.3 Appendix C (chapter 6)

Table C-1. Comparison between participants reached at FU and Non-responders ('lost')

	Groups		**Group differences**		
	Total FU (*n* = 67)	**Total lost (*n* = 79)**	**Test statistic (*df*)**	***p***	**Effect size**
Females, *n* (%)	30 (44.7%)	26 (32.9%)	X^2 (1) = 2.16	.142	*d* = 0.25
Age in years, *M* (*SD*)	16.2 (1.1)	16.1 (1.3)	*t* (144) = - 0.20	.421	*d* = - 0.03
DUDIT, *M* (*SD*)	19.4 (11.4)	16.4 (9.7)	*t* (109) = - 1.50	.069	*d* = - 0.29
	DELTA FU (*n* = 41)	**DELTA lost (*n* = 44)**	**Test statistic (*df*)**	***p***	**Effect size**
Females, *n* (%)	20 (48.8%)	15 (34.1%)	X^2 (1) = 1.89	.169	*d* = 0.31

Age in years, *M* (*SD*)	16.3 (1.0)	16.0 (1.4)	*t* (83) = - 1.11	.136	*d* = - 0.24
DUDIT, *M* (*SD*)	21.0 (11.1)	15.7 (9.5)	*t* (62) = - 2.07	.021	*d* = - 0.52
	WL FU (*n* = 26)	**WL lost (*n* = 35)**	**Test statistic (*df*)**	***p***	**Effect size**
Females, *n* (%)	10 (38.5%)	11 (31.4%)	X^2 (1) = 0.33	.568	*d* = 0.15
Age in years, *M* (*SD*)	16.0 (1.2)	16.3 (1.1)	*t* (59) = 1.08	.142	*d* = 0.28
DUDIT, *M* (*SD*)	17.0 (11.5)	17.4 (10.0)	*t* (45) = 0.12	.453	*d* = 0.04

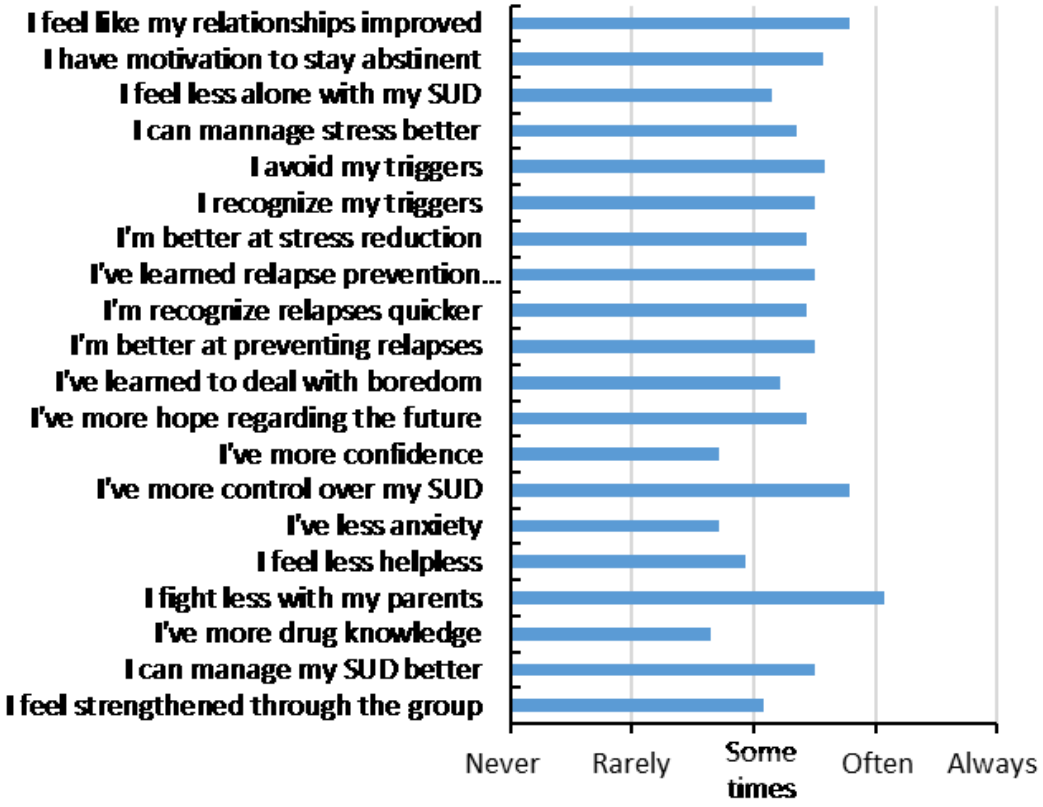
Note: DUDIT, Drug Use Disorder Identification Test; WL, waitlist condition

Table C-2. Associations between changes in primary/secondary outcomes and the number of DELTA sessions in the DELTA subsample, with medium or large associations considered relevant here.

	DELTA participants (*N* = 41)			
Mean change (from baseline to FU) regarding	***N***	$p_{\text{two-sided}}$	**Effect size** r_{Pearson}	**Interpretation according to Cohen (1988)**
Primary outcomes				
DUDIT score	16	.586	- .15	Small/irrelevant
DUDIT-C score	14	.752	- .09	Small/irrelevant
Nicotine QF	26	.128	- .31	Medium-sized association, n.s
Alcohol QF	15	.258	- .31	Medium-sized association, n.s
Cannabis QF	18	.291	- .26	Small/irrelevant
MDMA QF	8	.748	- .14	Small/irrelevant
Amphetamine QF	5	.198	- .69	Large association, n.s
Methamphetamine QF	4	.327	- .67	Large association, n.s
Secondary outcomes				
BDI-II sum	17	.659	+ .11	Small/irrelevant
YSR anxious/depressive	16	.394	- .22	Small/irrelevant
YSR social withdrawal	16	.208	- .33	Medium-sized association, n.s.
YSR aggressive	16	.523	+ .17	Small/irrelevant
YSR dissocial	16	.223	- .32	Medium-sized association, n.s.
UCLA symptoms intrusion	12	.510	- .01	Small/irrelevant
UCLA symptoms avoidance	12	.614	- .05	Small/irrelevant
UCLA symptoms hyperarousal	12	.592	- .17	Small/irrelevant
Exploratory analysis				
YSR attention	16	.163	- .36	Medium-sized association, n.s.
PQ16 sum	12	.922	- .03	Small/irrelevant
SWLS sum	14	.512	- .19	Small/irrelevant

Note: Amphetamine not included as it was not reported by DELTA participants. *P*-values were not corrected for multiple testing. Interpretation according to Cohen (1988): small ($r \geq .10$), medium ($r \geq .30$), large ($r >= .50$). ADD/ADHD, attention-deficit disorder with/without hyperativity. BDI-II, Beck Depression Inventory II. DUDIT, Drug Use Disorders Identification Test. MDMA, 3,4-Methylenedioxymethamphetamine. PQ16, Prodromal Questionnaire. n.s., not significant with $p_{\text{two-sided}}$ (uncorrected) ≥ .05. PTSD, post-traumatic stress disorder. SWLS, Satisfaction With Life Scale.UCLA,UCLA PSTD questionnaire. YSR, Youth Self Report questionnaire.

Figure C-1. Subjective ratings of how much the DELTA sessions helped to achieve certain goals in daily life. *N* = 12 to 14 per item.



10. Erklärung gemäß §5 der Promotionsordnung

Selbständigkeitserklärung

Hiermit versichere ich, dass ich die vorliegende Arbeit ohne unzulässige Hilfe Dritter und ohne Benutzung anderer als der angegebenen Hilfsmittel angefertigt habe. Die aus fremden Quellen direkt oder indirekt übernommenen Gedanken und Textteile sind als solche kenntlich gemacht. Die Arbeit wurde bisher weder im Inland noch im Ausland in gleicher oder ähnlicher Form einer anderen Prüfungsbehörde vorgelegt. Diese Dissertationsschrift wurde von September 2019 bis April 2022 am Institut für Kinder- und Jugendpsychiatrie und –psychotherapie unter der wissenschaftlichen Betreuung von Prof. Dr. Stefan Ehrlich und PD Dr. Dr. Yulia Golub angefertigt. Die Promotionsordnung des Bereichs Mathematik und Naturwissenschaften der Technischen Universität Dresden, in der Fassung vom 23.02.2011, letzte Änderung 23.05.2018, erkenne ich hiermit an. Die fünf grundlegenden Publikationen werden aktuell nicht in anderen Dissertationen verwendet und sind nach aktuellem Stand dafür auch zukünftig nicht vorgesehen. Alle oben gemachten Angaben zum Eigenanteil sind wahr.

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Dresden, den 05.05.2022
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