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Effectiveness of methamphetamine abuse treatment: Predictors of treatment completion and comparison of two residential treatment programs

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ABSTRACT

Background: There is an increasing demand of evidence-based treatment options for methamphetamine users, but research in this field is limited. This study therefore evaluates the efficacy of two residential treatment programs for methamphetamine users.

Method: A total of 108 patients with a history of methamphetamine abuse from two inpatient rehabilitation centers were studied for psychiatric symptoms, craving, psychosocial resources, and cognitive functioning at the start and end of therapy. Patients from one center ("amphetamine type stimulant group") received conventional group therapy plus an additional 10 h of group therapy focusing on stimulant use. Patients from the other center ("treatment as usual") received conventional group therapy only. Predictors of drop-out were estimated.

Results: A drop-out rate of 40.7% was observed without a significant difference between both centers. Patients remained significantly longer in treatment as usual compared to amphetamine type stimulant treatment. Irrespective of treatment program, craving and psychiatric symptoms significantly decreased while psychosocial resources, processing speed, and cognitive flexibility improved over time. Other cognitive measures yielded mixed results. History of injection drug use was a significant predictor for treatment drop-out.

Conclusions: Existing treatments are effective in reducing craving and psychiatric symptoms. Additional stimulant specific groups do not appear to influence treatment completion and secondary outcome measures. Institutions should therefore offer treatment for methamphetamine users, even if they do not provide a therapy content focusing on methamphetamine. History of injection drug use should receive attention in treatment to prevent drop-out. Changes in cognitive functioning need to be further explored.

1. Introduction

The use of synthetic stimulants, known as amphetamines, has been increasing globally during the last years showing a worldwide estimated annual prevalence of 0.7% in 2016, including both, the use of amphetamine and methamphetamine ("(Crystal)- Meth") (United Nations, 2018). Especially the methamphetamine market is expanding and increasing globally during the last years, showing a total quantity of 158 tons seized methamphetamine in 2016, while in 2013 this number was almost half as much with 88 tons (United Nations, 2018, 2015). In Europe, use of amphetamines differs a lot between countries, but the most recent European Drug report provides data showing that 1% of young adults (15–34 years) and 0.5% of all adults (15–64 years) used amphetamines during the last year (EMCDDA, 2018). Despite the lack of distinct data distinguishing between the prevalence of methamphetamine and amphetamine use, there is a visible trend of increasing methamphetamine availability in Europe when analyzing drug seizures and municipal wastewater (EMCDDA, 2018). In Germany, the geographical proximity to the Czech Republic, where methamphetamine production and use has been common for longtime, is seen as a major reason for an increased use in border regions during the last years, resulting in a lifetime prevalence for methamphetamine use of about 2% in eastern Germany (EMCDDA, 2014; Matos et al., 2018).

The numbers of methamphetamine users seeking treatment are rising accordingly, however evidence-based research on the efficacy of treatment programs for methamphetamine use is limited (ÄZQ, 2017).

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In an Australian study the authors found that cognitive behavioral therapy, as well as acceptance and commitment therapy reduced methamphetamine consumption and depressive symptoms (Smout et al., 2010). Two other studies originating from the USA (Rawson et al., 2004) and Thailand (Perngparn et al., 2011) investigated a manualized outpatient treatment program called "Matrix model". This highly structured manual was originally developed during the 1980s in California due to the high demand for treatment options for cocaine abuse. With increasing spread of methamphetamine in the United States, the Matrix model was also used to treat individuals abusing mainly methamphetamine (Center for Substance Abuse Treatment, 2006; Obert et al., 2000). In a multisite study, Rawson et al. (2004) compared the outpatient Matrix manual, composed of 36 sessions cognitive behavioral therapy groups, 12 sessions family education groups, each four session social support groups and individual counseling and weekly self-help groups with treatment as usual (TAU) at eight treatment centers. The authors found higher retention and completion rates in Matrix treatment compared to TAU. Additionally, Matrix participants were 31% more likely to have MA-free urine test results during treatment. However, there was no difference in urine free samples and functioning (measured with the addiction severity index) between Matrix and TAU neither at discharge nor at 6month follow up. Furthermore, Perngparn et al. (2011) found a similarly manualized but inpatient therapy to be superior to the outpatient Matrix therapy in the long run, which indicates that an inpatient approach in the treatment of methamphetamine dependence may be the method of choice.

On a national level in Germany rehabilitation programs for substance users generally consist of a six-month inpatient treatment, but there are no studies evaluating the efficacy of this treatment approach for methamphetamine users. In order to fill this unmet research need the study described herein, funded by the German Ministry of Health, aimed to compare existing treatment options for methamphetamine users. The prospective study used data from two different rehabilitation clinics with one offering an additional amphetamine type stimulant (ATS) group and the other one offering TAU (see also Soyka et al., 2017). The development of the ATS group was oriented on the free accessible matrix manuals and contains elements of psychoeducation, relapse prevention and cognitive techniques with a focus on the neurobiological effects of MA use. Therefore, this study gives insights on the efficacy of a stimulant specific treatment program (TAU plus ATS) and of a usual substance abuse treatment (TAU) in a German methamphetamine abusing cohort.

Since patients addicted to stimulants have been shown to exhibit high drop-out rates from psychosocial treatments (42.0% for cocaine users (Dutra et al., 2008), 31.7% for all stimulants (Minozzi et al., 2016), gaining an understanding of factors related to drop-out will improve treatment conditions for this group of patients. In order to identify these factors, this study examined not only drop-out and abstinence rates, but also sociodemographic variables, personality traits, craving, psychiatric comorbidities, as well as psychosocial resources. Previous publications have shown associations between sociodemographic factors and treatment outcome in stimulant users (Reske and Paulus, 2008), the big five personality traits and relapse (Fisher et al., 1998; McCormick et al., 1998), craving and relapse in MA users (Hartz et al., 2001), and cognitive impairments and relapse (Streeter et al., 2008) in cocaine dependent individuals. Due to evidence of neurocognitive impairment in methamphetamine users (Proebstl et al., 2018) the current study also analyzed cognitive functioning pre and post treatment and examined their impact on therapy outcomes. In order to evaluate the long-term effects of the two different treatment programs the study was designed as a longitudinal study with data acquisition at the beginning of treatment, after six months, and again one year after the second measurement. This paper compares intermediate results from beginning and end of treatment to gain insight into treatment completion rates and associated variables, and into treatment efficacy in terms of changes in psychiatric symptoms.

2. Methods

2.1. Institutions and participants

A total of 108 participants from two German rehabilitation hospitals (District Hospital Hochstadt and MEDIAN Clinic Mecklenburg) were recruited for the study. Both centers have several years of expertise in treating MA abusing patients and offer six month in-patient rehabilitation from illegal drugs, other addictions, and comorbid disorders.

The therapy concept for all MA abusing patients in Mecklenburg represented TAU made up of a multimodal therapy without any MA use specific content. Traditional elements as relapse prevention, self-reflection (e.g. function of substance use within the personal biography, consequences of substance use etc.), development of new behavioral strategies (e.g. coping with requirements of daily life, communication with significant others) and proving experiments (e.g. return journey, social interaction with former friends, emergency plans) were applied as group therapy. Participants from TAU received this conventional group therapy five times per week and all group members had been using stimulants, mainly MA. The therapy concept in Hochstadt for all MA users consisted of three weekly conventional group therapy sessions as well, plus the additional ATS group once per week. The content of the ATS group is displayed in Table 1. All ATS group members had been abusing MA.

All study subjects were patients in one of the two rehabilitation clinics and had chosen the respective institution without knowledge of the study. They were then invited to the study and recruited by psychologists and physicians of the respective institutions during the first two to four weeks after admission. Participation was voluntary and not required for receiving treatment. Accordingly, participating patients from Mecklenburg were assigned to TAU and participating patients from Hochstadt to ATS. Study inclusion criteria were a history of MA abuse or addiction (ICD-10 Diagnosis F15.2) and a minimum age of 18 years. The majority of subjects underwent the rehabilitation program because of problems related to MA use, but in some cases, patients came primarily because of addiction to other substances or polyvalent drug use. Since parallel use of or addiction to other substances is common, we included these patients as far as they also met the criteria for MA abuse or addiction. Subjects were excluded if they had acute psychotic symptoms, if they were intoxicated on test days, and if they were not able to read or comprehend the texts or study procedure. Informed written consent was obtained from all participants after a complete and extensive description of the study protocol by a health professional. The study protocol was approved by the Ethics Committee of the Ludwig-Maximilians-University of Munich in accordance with the principles laid down in the Helsinki Declaration (1964). All participants were financially reimbursed with 15 Euro after completion of the first two and 35 Euro by the completion of the third measurement. Routine urine samples and breath alcohol tests were collected in both centers to verify

Table 1
Amphetamine Type Stimulants group concept.

ATS Sessions
- Psychoeducation: Neurobiological effects of MA use - Effects of MA use on emotions: Analysis of emotional changes with and without MA use, Identification of and coping with emotions - Coping with avolition and lack of motivation after MA cessation - Effects of MA use and changes in sleep - Relapse prevention: Analysis of MA specific relapse situations and emotional triggers - Sexuality and MA use - Alcohol and MA use - Other compulsive or impulsive behaviors than substance use - Avoiding relapse traps: cognitive restructuring

ATS = amphetamine type stimulants, MA = methamphetamine.

use of any substance. These tests were part of the usual treatment center practice and were conducted on a sample basis and in case of suspected substance use.

2.2. Study design

The study design involves three measurements time points: 1. Baseline "T0″ at the beginning of treatment, 2. end of therapy "T1″ after approximately 24 weeks of treatment (in the last 3 weeks before discharge), and 3. follow-up "T2″ approximately one year after T1. The testing for T0 and T1 was conducted within the respective institutions. T0 and T1 Data were collected between November 2016 and June 2018 and T2 data acquisition is still running.

2.3. Outcome measures and instruments

The main outcome of interest was the completion of treatment, defined as fulfilling the treatment as scheduled. Individuals quitting the treatment prematurely (at own request or as a disciplinary decision) were defined as dropouts. The urine test results were used as a measure for a non-reported relapse, which led to a disciplinary dismissal.

Beside the treatment completion, measures of craving, health problems and psychosocial and cognitive functioning were assessed using the following instruments (see also Table 2): Sociodemographic factors and the patient addiction history were assessed using the structured interview "Documentation Standards for Addiction" (German Society for Addiction Research and Therapy, 2001). Psychiatric history and comorbidities were recorded using the Structured Clinical Interview for DSM-IV Axis I (German Version, Wittchen et al., 1997). Depressive symptoms were measured by the German Versions of Becks Depression Inventar-II (Hautzinger et al., 2006) and the 17–Items Hamilton Depressive Rating Scale (Hamilton, 1960). Further psychiatric and physical symptoms were acquired with the aid of the Symptom Checklist-90R (Franke, 1995). Craving was assessed using the Mannheimer Craving Scale (Nakovics et al., 2009) and symptoms of attention deficit hyperactivity disorder were assessed using German short version of the Wender Utah Rating Scale (Retz-Junginger et al., 2002). Personality traits were acquired by the German version of the NEO-Five-Factor-Inventory (Borkenau and Ostendorf, 2008) and psychosocial resources were documented by a German questionnaire named inventory of personal resources (Küfner et al., 2006). Cognitive abilities were measured by computer-based tests: Raven's Standard Progressive Matrices (Raven et al., 2016) for measuring the intelligence quotient, Cognitrone (Wagner and Karner, 2003) for measuring working accuracy and time, Trail-Making Test (Tischler and Petermann, 2010) for measuring cognitive processing speed and cognitive flexibility, Stroop Interference Test (Schuhfried, 2016) to assess the ability to control cognitive interference and N-back verbal test (Schellig and Schuri, 2016) to assess the verbal working memory.

Table 2
Study Instruments.

T0 (Beginning of Treatment)	T1 (End of Treatment)
• Documentation Standards for Addiction • Structured Clinical Interview for DSM-IV Axis I • Symptom Checklist 90-R • Becks Depression Inventar-II • Hamilton Depressive Rating Scale • Mannheimer Craving Scale • NEO-Five-Factor-Inventory • Raven's Standard Progressive Matrices • Inventory of personal psychosocial resources • Cognitrone • Trail-Making Test • Stroop Interference Test • N-back verbal test	• Symptom Checklist 90-R • Becks Depression Inventar-II • Hamilton Depressive Rating Scale • Mannheimer Craving Scale • Cognitrone • Inventory of personal psychosocial resources • Trail-Making Test • Stroop Interference Test • N-back verbal test

2.4. Statistical analyses

Scores from questionnaires were calculated according to the respective manuals and -where appropriate- standardized. Histograms were plotted to visually verify the normality assumption. Two normally distributed variables at one time point were compared using t-tests. Multiple mixed ANOVAs were calculated to compare mean differences between two groups taking into account both time points (T0 and T1). Since t-tests and ANOVAs are regarded as robust statistical procedures, both methods were also used for variables that deviated from the normality assumption. For the comparison of categorical variables chi^2 test, or in case of small cell counts, Fisher's exact test were performed. Logistic regression models were applied to investigate the effect of various factors on treatment drop-out. The significance level was set at $p = .05$. Due to the explorative character of this study factors regarding multiple testing were not considered. All statistical analyses were conducted in SPSS Version 24.

3. Results

3.1. Participants and treatment completion

A total of 108 participants took part in the first measurement (T0) of the study, with 53 subjects in the ATS and 55 in the TAU group. Out of this original sample, 57 participants remained for the second measurement T1 (30 in ATS, 27 in TAU) with a mean age of 32.33 years (SD = 8.01). A flow diagram of study participants is shown in Fig. 1. Table 3 lists the sociodemographic characteristics of T1 participants. T1 subjects from ATS treatment were significantly older than TAU subjects ($t(51.74) = 2.50$, $p = .016$), and ATS subjects were also older when they started to use MA $t(55) = 2.58$, $p = .013$).

Of the original 108 participants, 44 subjects (40.7%) stopped treatment prematurely. Comparing both clinics, in Hochstadt (ATS) 24 subjects (45.28%) left the treatment prematurely while in Mecklenburg (TAU) this was only the case for 20 participants (36.36%). The difference in drop-outs was not statistically significant ($\chi^2 = .89$, $p = .35$). The main reason for premature discontinuation of treatment was unreported relapse and subsequent disciplinary dismissal, followed by violation of other clinic rules (see Table 4). Gender was not associated with treatment completion ($\chi^2 = .00$, $p = .99$).

3.2. Quantity of group therapy and treatment retention

Participants at time point T1 had received a mean number of 87.37 unspecific group therapy sessions (SD = 23.27). Of these patients, those within the ATS condition had 10 additional sessions of ATS group treatment (SD = 0). Patients from TAU were subject to a mean of 101.07 group therapy hours (SD = 26.73), while patients from ATS received only a mean of 75.03 h of unspecific group therapy (SD = 8.51) ($t(30.73) = -4.86$, $p < .001$). The addition of the ATS group sessions in Hochstadt to the unspecific group therapy (m = 85.03 h, SD = 8.51) still showed significantly less total group therapy hours than TAU ($t(30.73) = -2.99$, $p = .006$).

The mean treatment duration of all 108 participants was 150.0 (SD = 70.26) days, with a significant difference between the centers, showing a longer retention in TAU with 171.82 (SD = 79.62) days than ATS with 128.0 (SD = 51.10) days ($t(106) = -3.33$, $p = .001$). A subset analysis of those completing the full treatment and those prematurely dropping-out showed that there was still a longer retention rate in TAU (m = 127.60 days, SD = 78.22) than in ATS (m = 82.71 days, SD = 40.44) within the group of drop-outs ($t(42) = -2.45$, $p = .019$) and within the group of completers ($t(27.45) = -2.07$, $p = .048$, TAU: m = 198.11, SD = 77.6; ATS: m = 166.83,

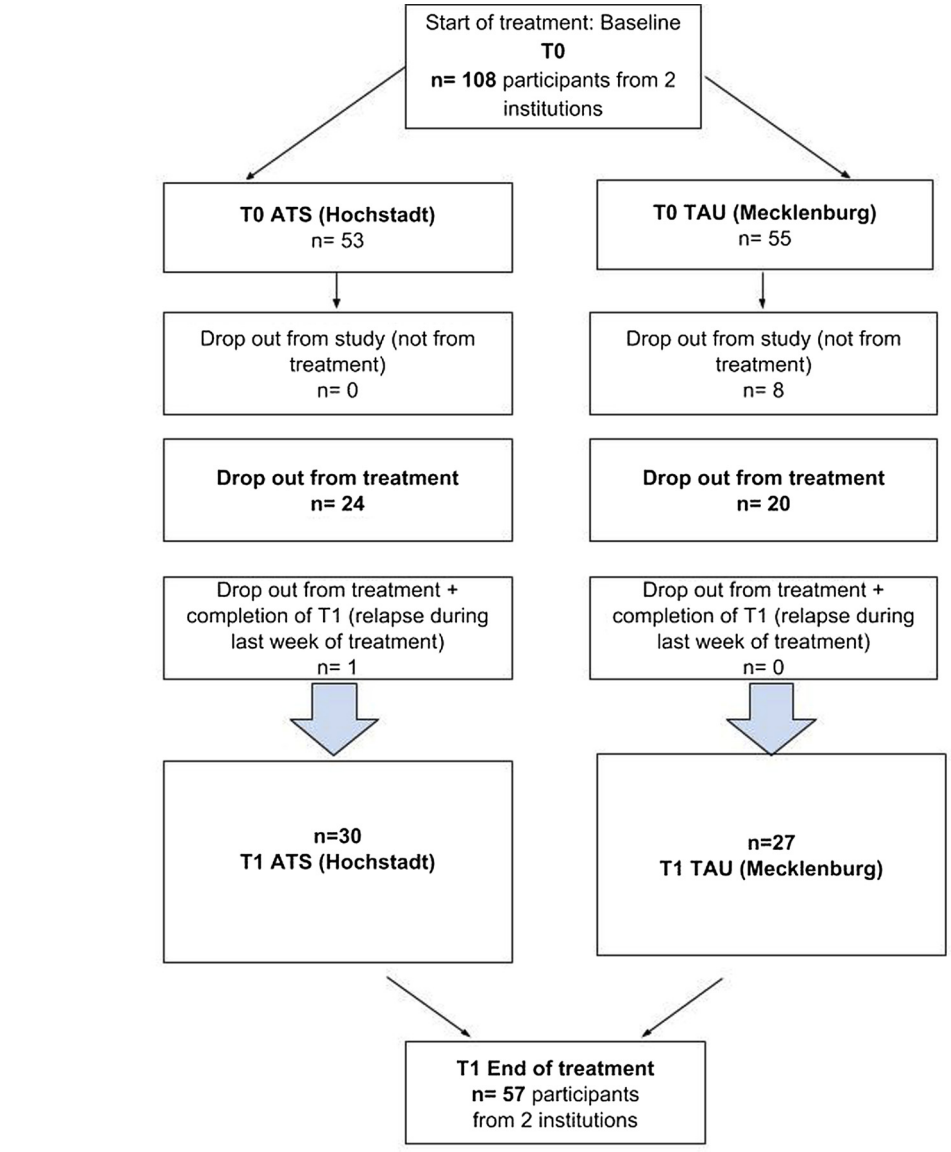


Fig. 1. Diagram of participants flow.

SD = 13.44).

3.3. Treatment effects

Mixed models ANOVAS were used to calculate the effects of time and treatment on variables of craving, psychiatric symptoms, and cognitive functioning (see Table 5 and Figs. 2 and 3).

3.3.1. Craving, psychiatric symptoms and psychosocial resources

Craving scores were significantly reduced over time ($F(1,45) = 16.78$, $p < .001$), but there was no effect of treatment ($F(1,45) = 0.18$, $p = .67$), and no interaction between time and treatment ($F(1,45) = 2.37$, $p = .13$).

Analyzing the BDI depression scores revealed significant effects of time ($F(1,51) = 29.27$, $p = < .001$), with decreased depression scores at T1 compared to T0. There was also a significant effect due to treatment ($F(1,51) = 4.81$, $p = .033$) with lower depression scores seen in ATS participants. The interaction between both factors was not significant ($F(1,51) = 2.24$, $p = .14$). The depression scores obtained by the Hamilton interview also displayed a significant reduction over time ($F(1,49) = 14.43$, $p < .001$). However, there was no significant influence of treatment ($F(1,49) = 1.47$, $p = .23$) and no interaction effect ($F(1,49) = .44$, $p = .84$).

A significant effect of time was likewise found when considering the global severity of psychiatric symptoms with an observed decrease in the GSI (global severity index) parameter of the symptom checklist 90R ($F(1,49) = 40.02$, $p < .001$). No further effects of treatment ($F(1,49) = 2.11$, $p = .15$) or interaction ($F(1,49) = .60$, $p = .44$) were found. Regarding changes in psychosocial resources a significant effect of time ($F(1,41) = 4.7$, $p = .036$) showed an increase of current resources from beginning to end of treatment, but no effect of treatment ($F(1,41) = 2.18$, $p = .15$) or interaction ($F(1,41) = .04$, $p = .84$).

3.3.2. Cognitive abilities

Further ANOVAs investigating the development of cognitive abilities revealed significant effects of time ($F(1,54) = 4.26$, $p = .044$), treatment ($F(1,54) = 8.79$, $p = .004$), as well as a significant interaction between time and treatment center ($F(1,54) = 6.43$, $p = .014$) on

Table 3
Sociodemographic characteristics of T1 study population.

	ATS	TAU	*p*
N	30	27	
Male	24 (80.0%)	21 (77.8%)	n.s.
Age	34.7 (± 8.84)	29.70 (± 6.12)	*
Age of onset of MA use	23.87 (± 6.73)	19.59 (± 5.67)	*
Lifetime use of MA	11.34 (± 6.35)	10.87 (± 5.75)	n.s.
Number of withdrawals	1.83 (± 2.23)	2.52 (± 3.32)	n.s.
IQ (n = 56)	92.47 (± 14.37)	93.19 (± 12.33)	n.s.
Years of education			n.s.
9 years	22 (73.3%)	18 (66.7%)	
10 years	8 (26.7%)	7 (25.9%)	
12 years	0	2 (7.4%)	
Employment			n.s.
Unemployed	25 (83.%)	22 (81.5%)	
Employed	4 (13.3%)	3 (11.1%)	
Other (e.g. retiree)	1 (3.3%)	2 (7.4%)	

Data displays means and standard deviations or total numbers and percentages; MA = methamphetamine; ATS: amphetamine type stimulant treatment, TAU = treatment as usual *$p < 0.05$.

Table 4
Reasons for early dismissal.

Reason for dismissal	n	Out of n = 44 drop-outs	Out of n = 108
Relapse	19	43.2%	17.6%
Violation of other rules	15	34.1%	13.9%
Transfer to another hospital or start of job	3	6.8%	2.8%
At own request	7	15.9%	6.5%
Total	44	100.0%	40.7%

working accuracy, showing a strong increase in accuracy in TAU subjects, while ATS subjects performance slightly decreased (see Fig. 3).

Analyzing cognitive processing speed assessed with Cognitrone showed again a significant effect of time ($F(1,55) = 34.03$, $p < .001$), but no further effects of treatment ($F(1,55) = .49$, $p = .49$), or interaction ($F(1,55) = .92$, $p = .34$). Results of processing speed with a smaller sample obtained by the trail making test (TMT-A) did not reveal any significant effects. However, when examining the results from the second part of the TMT, which indicates cognitive flexibility, an effect of time was found again ($F(1,21) = 10.33$, $p = .004$). This indicates that performance improved at T1, while treatment ($F(1,21) = .68$, $p = .42$) or interaction ($F(1,21) = 3.92$, $p = .061$) both had no effect.

Results from the Stroop test revealed no significant effects regarding the reading interference tendency. When looking at the naming interference tendency, there was a significant effect of treatment center ($F(1,20) = 5\ 0.07$, $p = .036$) showing a better performance in ATS than TAU participants and a significant interaction of treatment and time ($F(1,20) = 9.51$, $p = .006$), showing a decrease in performance over time in TAU participants and an increase in performance in ATS subjects. There was no main effect of time ($F(1,20) = .39$, $p = .54$).

We found no significant effects when investigating the verbal memory assessed by N back verbal.

3.4. Prediction of treatment completion

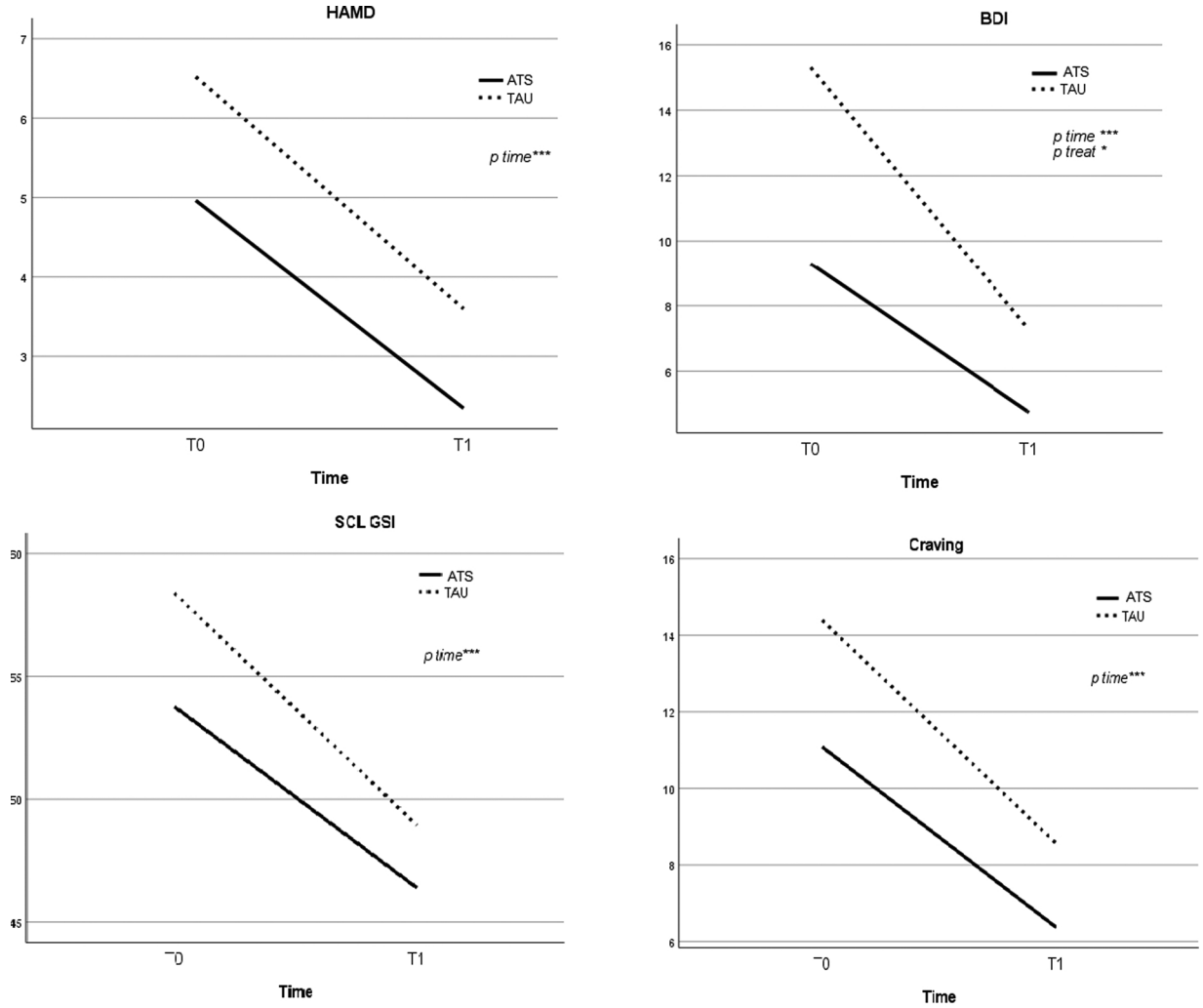
Univariate logistic regression analyses were performed to determine the impact of different psychological variables on treatment completion. Craving ($p = .78$) and cognitive functioning (Ravens' IQ: $p = .66$, Stroop naming interference $p = .28$) did not predict treatment completion as well as personality traits (openness $p = .91$, conscientiousness $p = .88$, extraversion $p = .34$, agreeableness $p = .22$, neuroticism $p = .99$) were also not found to have any effect. The number of suicide attempts ($p = .35$), the number of positive tested drug urine controls ($p = .65$), days of abstinence ($p = .54$), age at onset of MA use ($p = .19$), and years of MA use ($p = .55$) did neither predict a drop-out or completion.

In contrast, the influence of having ever injected any substance indicated a significant association between this type of drug use and treatment drop-out. Injection drug use of any substance lead to a 4.6 (95% CI: [1.6, 13.3], $p = .005$) fold increased odds for treatment drop-out when compared to non-injecting drug use. This translates to a probability of 0.70 to drop-out of treatment for a participant reporting

Table 5
Craving, psychiatric symptoms, resources and cognitive functions over time and treatment.

		TAU + ATS (Hochstadt)	n	TAU (Mecklenburg)	n	p
BDI	T0	9.30 (± 8.23)	27	15.31 (± 11.55)	26	p_{time} *** p_{treat} * $p_{time}x_{treat}$ n.s.
	T1	4.74 (± 4.62)		7.27 (± 7.2)		
MaCS	T0	11.08 (± 8.44)	24	14.39 (± 9.81)	23	p_{time} *** p_{treat} n.s. $p_{time}x_{treat}$ n.s.
	T1	6.38 (± 5.29)		8.57 (± 5.29)		
IPR	T0	219.91(± 41.71)	22	204.43(± 36.47)	21	p_{time} *** p_{treat} n.s. $p_{time}x_{treat}$ n.s
	T1	233.32(± 47.47)		215.48 (± 38.71)		
HAMD	T0	4.96 (± 5.98)	26	6.52 (± 5.36)	25	p_{time} *** p_{treat} n.s. $p_{time}x_{treat}$ n.s.
	T1	2.35 (± 2.95)		3.6 (± 4.77)		
SCL 90R GSI	T0	53.77 (± 9.73)	30	58.38 (± 9.48)	21	p_{time} *** p_{treat} n.s. $p_{time}x_{treat}$ n.s.
	T1	46.40 (± 9.80)		48.95 (± 10.45)		
Cognitrone accuracy	T0	53.27 (± 8.51)	30	43.62 (± 7.84)	26	p_{time} * p_{treat} ** $p_{time}x_{treat}$ *
	T1	52.57 (± 11.34)		50.46 (± 8.67)		
Cognitrone Speed	T0	49.71 (± 10.4)	31	48.81 (± 7.68)	26	p_{time} *** p_{treat} n.s. $p_{time}x_{treat}$ n.s.
	T1	56.52 (± 13.45)		53.69 (± 9.92)		
TMT – A speed	T0	46.25 (± 6.32)	8	48.13 (± 4.66)	15	p_{time} n.s. p_{treat} n.s. $p_{time}x_{treat}$ n.s.
	T1	46.25 (± 6.07)		50.27 (± 5.42)		
TMT- B flexibility	T0	47.50 (± 6.57)	8	48.00 (± 7.75)	15	p_{time} ** p_{treat} n.s. $p_{time}x_{treat}$ n.s.
	T1	48.75 (± 6.30)		53.27 (± 7.77)		
N back correct recalls	T0	50.50 (± 18.71)	8	57.56 (± 20.63)	16	p_{time} n.s. p_{treat} n.s. $p_{time}x_{treat}$ n.s.
	T1	48.00 (± 13.97)		57.50 (± 18.57)		
Stroop Reading interference	T0	50.29 (± 7.91)	7	46.47 (± 11.66)	15	p_{time} n.s. p_{treat} n.s. $p_{time}x_{treat}$ n.s.
	T1	45.57 (± 8.71)		46.60 (± 10.58)		
Stroop Naming interference	T0	54.00 (± 9.04)	7	48.73 (± 8.85)	15	p_{time} n.s. p_{treat} * $p_{time}x_{treat}$ **
	T1	57.00 (± 10.58)		44.20 (± 8.85)		

Data displays means and standard deviations; BDI = Becks Depression Inventory-II, MaCs = Mannheimer Craving Scale, IPR = Inventory of personal resources, HAMD = Hamilton Depression Rating Scale, SCL GSI: Symptom Checklist Global Severity Index, TMT = Trail Making Test, $p_{time=}$ effect of time, $p_{treat=}$ effect of treatment, $p_{time}^{x}{}_{treat=}$ interaction effect; *$p < 0.05$ **$p \leq 0.01$ ***$p \leq 0.001$.



HAMD= Hamilton Depressive Rating Scale, BDI= Becks Depression Inventory, SCL GSI= Symptom Checklist Global Severity Index; *p< 0.05 ***p ≤ 0.001

Fig. 2. Effects of time and treatment on craving and psychiatric symptoms.

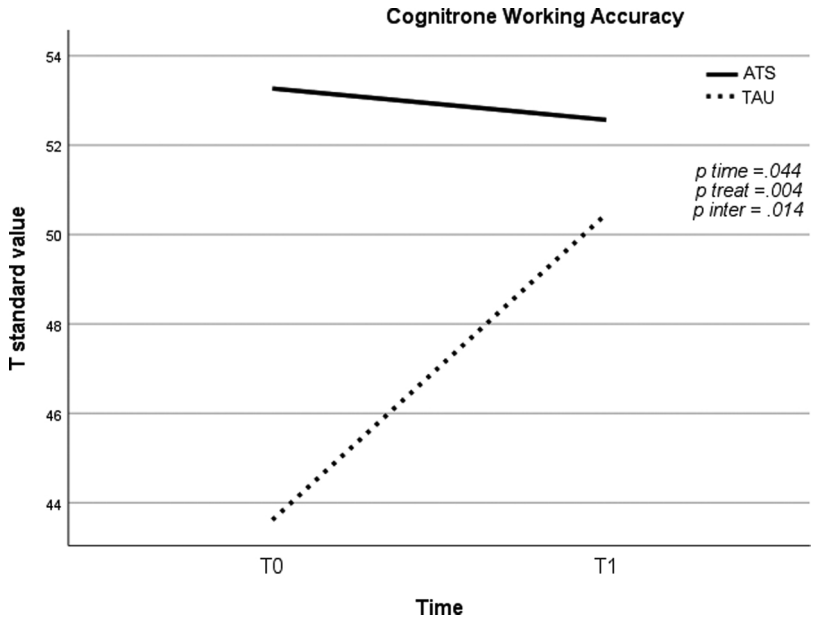


Fig. 3. Changes of working accuracy over time and treatment.

previous injection drug-use, and a probability of 0.34 for drop-out for someone not reporting this behavior. Further distinction for injection use of MA lead to a 10.2 (95% CI: [1.2, 88.7], p = .035) fold increase in the odds for treatment drop-out compared to non-injecting MA use. Here, the probability for drop-out for someone from the MA injecting group is 0.86 and the probability for drop-out for someone from the non-MA injecting group is 0.37.

The analysis of the motivational reasons for treatment (self-motivated or external, e.g. because of law requirements), did not reveal an association with treatment completion (($\chi 2$ (1) = 1.16, p = .28).

4. Discussion

The present study provides new data concerning the efficacy of methamphetamine abuse treatment. Our results show a significant reduction of depression, craving, and psychiatric symptom scores following six-month residential treatment in study participants. Additionally, subjects reported significantly more psychosocial resources after treatment. These effects were seen in both treatment centers, suggesting that methamphetamine dependent individuals benefit from already existing and standardly applied treatment methods with regard to secondary mental health outcomes. In terms of treatment completion rates, we found a total drop-out rate of 40.7%, which is similar to other studies in substance use disorders (Dutra et al., 2008; Minozzi et al., 2016) and which did not differ significantly between the treatments.

The observation that the more specialized ATS treatment was not superior to TAU regarding treatment completion and most secondary outcomes, suggests that success in these measures is not primarily based on a methamphetamine focusing therapy content. This implicates several further considerations as for example the question if treatment of methamphetamine abuse or addiction needs to have a stimulant specific content. Our results rather show that a less specific therapy is comparable to a treatment focused on methamphetamine. This knowledge is important in terms of facilitating treatment access for MA users, since institutions do not have to adopt new treatment strategies or elementary concept changes. This is especially important when looking at the rising numbers of MA treatment seeking individuals (EMCDDA, 2018)

Although the overall improvement after treatment raises optimism, the drop-out rate of about 40% still shows a need for a better understanding of other possible factors influencing treatment drop-out. In our analyses a higher risk for treatment drop-out was only associated with having previously injected substances, which has also been reported in a study on cocaine abuse (Greenwood et al., 2001). Here, the authors also found multiple sex partners to be a significant predictor for drop-out and suggested a common factor underlying both, injection drug use and sexual risk behavior. This illustrates the importance to prove if injection drug use is itself a risk factor for treatment drop-out, or if this is confounded by other variables associated with high-risk behavior. An explorative analysis of our study data revealed a significant association between MA injective use and additional abuse of opioids. However, use of opioids was not associated with treatment drop-out. Taken together the predictive power of “injecting MA” for treatment drop-out is ambiguous but paying more attention to the history of drug administration route may serve as a starting point to identify patients at higher risk of treatment drop-out.

Surprisingly craving scores did not predict treatment outcome. Since we initially did not differentiate between the reasons for treatment drop-out, individuals dropping out because of reasons other than relapse may have biased our results of craving and drop-out rate. However, a logistic regression analysis investigating the effect of craving only on those individuals who dropped out due to relapse did not find craving scores to predict treatment drop-out. Another factor which may have influenced these results is the time period between craving assessment and relapse. In this study craving was assessed at the beginning of treatment and was used to predict treatment completion, or drop-out, which means there was a delay of several weeks or months. In another study by Hartz et al. (2001) craving scores did significantly predict methamphetamine use in the week following the craving assessment, which represents a distinctly shorter time frame. Based on these results craving scores can potentially provide valuable information in identifying time periods with a high risk of relapse, but only when assessed regularly in short intervals. Furthermore, there is also evidence of neuronal correlates in methamphetamine relapsing patients (Gowin et al., 2015) and neuroimaging may therefore serve as additional instrument in estimating high-risk patients.

All other variables in our study failed to predict treatment completion, which is partly in line with already existing research on predictors of treatment outcome in substance users. For example, Brorson et al. (2013) reviewed a total of 122 studies investigating drop-outs from addiction treatment and found only few reliable risk factors. They found that younger age, comorbid personality disorder, low treatment alliance, and cognitive deficits were the most consistent predictors of treatment drop-out. However, we did not find cognitive functioning to predict treatment drop-out in our study and obtained ambiguous results concerning cognitive abilities in methamphetamine users: Overall patients performed within the standard ranges of the applied tests, but there are hints that cognitive abilities changes over treatment: Patients from ATS profited more from treatment in the performance of naming interference (Stroop test), but the reverse effect for function of working accuracy was found. Here patients from TAU showed a greater improvement over time and therefore profited more from treatment. Furthermore, an improved processing speed was observed over all participants from T0 to T1 when measured with Cognitrone. This was not found when measured with the Trail Making Test (TMT- A). A possible explanation for this difference may be the smaller sample size in the TMT tests, which resulted from technical problems at the ATS center with the computer tests TMT, Stroop, and N-back verbal. Therefore, only a reduced number of ATS patients took part in these cognitive tests, which may have biased these results. This may also account for a decrease of performance in Nback verbal and Stroop within the ATS patients. Results from the tests with larger samples indicate that rehabilitation treatment can improve cognitive functioning in methamphetamine users and that different treatment methods may influence the performance.

Taken together, the search of predictors for treatment success in methamphetamine using individuals is arduous and implicates further extensive analyses. For example, we did not investigate factors influencing treatment alliance. This can be seen as limitation, since previous research showed that the therapeutic alliance affects treatment engagement and retention (Meier et al., 2005) and that already the place of treatment can interact with the therapeutic alliance in substance abuse treatment (Bailly et al., 2018). In terms of our study, such factors may have also influenced the retention rate, as we found a longer retention rate in TAU patients compared to those in the ATS setting. Interestingly, the longer retention rates in TAU were seen in both groups, in drop-outs and those completing the full treatment. Therefore, the TAU center succeeded to interconnect with their patients longer, maybe because of a stronger therapeutic alliance or a different design of setting. One difference between the institutions, for example, was the ability to bring one’s children into TAU treatment, which was not possible at the ATS center. However, this dominance of TAU in retention rate was not enduring in terms of drop-outs, what underlines the need for long-term data which is still being collected. Long-term data can also help to evaluate the predictive power of drop-out rates, as a meta-analysis by Dutra et al. (2008) has also shown that high drop-out rates do not necessarily represent a lower treatment effect. They found the largest treatment effect sizes for interventions for cannabis and cocaine, but treatments for cocaine users also presented the highest drop-out rates.

Finally, future longitudinal studies with bigger samples at the

beginning are needed to verify the present results, since the rather small sample size after treatment -due to the high drop-out rate- might have limited the statistical power of our analyses.

5. Conclusions

The present study shows that six-month residential treatment programs for MA users lead to an improvement of psychiatric symptoms, craving, psychosocial resources, and some measures of cognitive functioning. TAU achieved similar treatment effects as the specialized ATS treatment, which indicates that existing, unspecialized treatment options are already an effective approach in treating methamphetamine dependence. Further data is necessary to evaluate the long-term effect, but in terms of intermediate treatment success, addiction treatment centers may not need to focus the therapy contents solely on methamphetamine. A subgroup which should be addressed specifically in treatment is the group of injecting MA users, since this was the only risk factor predicting treatment drop-out. Future studies evaluating treatment outcomes should also investigate further variables as therapeutic alliance or satisfaction with treatment.

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Contributors

FK wrote the first draft of the paper, calculated the first analyses and coordinated the study together with LP. LH was responsible for data extraction. AS, MR and SN conducted data assessments and interviews in the respective treatment centers. MS and MSJ were responsible for recruiting participants and for monitoring data assessment in the respective treatment centers. KM verified and completed all statistical analyses. GK and MS planned the study and its design and supervised the study as heads of the research team.

All authors read and approved the final manuscript.

Conflict of interest

None.

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