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Methamphetamine and cannabis abuse in adolescence: specific and long-term neurocognitive effects

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**Full manuscript title: Methamphetamine and cannabis abuse in adolescence:
specific and long-term neurocognitive effects**
Short title: Neurocognition in adolescent drug abuse

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Abstract

Objectives: Methamphetamine abuse affects brain structure and function. Although methamphetamine and cannabis are commonly abused together, few studies have investigated the differential neurocognitive consequences of methamphetamine abuse with or without cannabis. Furthermore, the effects of drug use on the developing adolescent brain remain poorly understood. We compared neurocognitive function between adolescents with ‘pure’ methamphetamine abuse, those with comorbid methamphetamine and cannabis abuse, and healthy controls at baseline and follow-up.

Methods: Individuals residing in the greater Cape Town region and between the ages of 13 and 18 years were recruited into either Meth-only ($n = 10$), Meth-cann ($n = 10$) or healthy control ($n = 20$) groups using a quasi-experimental design. All participants underwent a comprehensive neurocognitive assessment. Substance-use variables, psychiatric symptom counts and disinhibitory personality traits were also recorded. A portion of the Meth-only and control participants completed 12 month follow-up assessments.

Results: While the Meth-cann group demonstrated widespread neurocognitive deficits at baseline, these deficits were restricted to the self-monitoring domain in the Meth-only group at both baseline and follow-up.

Conclusions: Methamphetamine abuse with cannabis abuse is associated with significantly more neurocognitive impairment than methamphetamine abuse alone, and such deficits may be enduring.

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Strengths and limitations of this study

- Strength: Identification of neurocognitive sequelae in the early phase of drug abuse
- Strength: Identification of neurocognitive sequelae of relatively ‘pure’ drug abuse
- Potential limitation: limited size of follow-up group
- Potential limitation: findings specific to adolescent phase

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Introduction

Pre-clinical and human data suggest that various brain regions and neurocognitive functions may be differentially vulnerable to the effects of regular heavy methamphetamine use,[1, 2, 3, 4]. For instance, human studies have shown that methamphetamine abuse may lead to broad and long-term neurocognitive sequelae in memory, attention, task switching and response inhibition domains, and that such alternations in brain function may persist for years following abstinence,[5, 6, 7]. Furthermore, the offspring of methamphetamine abusing mothers suffer lasting damaging effects on cognitive development, for example,[8, 9, 10].

In addition to overall severe and persistent neurocognitive effects of heavy methamphetamine use, the adolescent brain may be particularly vulnerable to such effects given critical neuromaturation underway during this phase of development,[11, 12]. However, few data specifically address the question of neurocognitive sequelae of methamphetamine abuse in adolescents during the early stage of drug use trajectory. Over the 1990s and into the present, substance abuse statistics have revealed alarming increases in methamphetamine abuse rates to the extent that methamphetamine abuse may be considered an “epidemic” in the United States,[13]. Increases in methamphetamine abuse have been noted elsewhere too: methamphetamine has recently attained the status of primary drug of abuse among adolescents in developing countries such as South Africa,[14]. This represents a dramatic shift in drug use patterns in this age group in recent years, and raises issues about the impact of methamphetamine on the developing brain during this critical time of brain development.

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Despite overall increased rates of methamphetamine abuse, several fundamental questions about the consequences of such abuse remain incompletely unanswered, thus calling for more empirical work in the area. First, although drug co-administration is a common trend in worldwide patterns of drug abuse,[15], the differential consequences of methamphetamine abuse with or without cannabis use on adolescent brain function and structure are not yet clearly delineated. Second, while externalizing psychopathology commonly co-occurs with heavy methamphetamine use, the functional impact of such comorbidity remains unclear,[16,17]. Lastly, the long-term neurocognitive outcome of adolescent methamphetamine abuse with minimal externalizing psychopathology remains an open question.

Given the worldwide pattern of drug co-administration, it is particularly challenging to examine the impact of single or specific drug use combinations in most settings. However, in the Cape Town region of South Africa, we are presented with a population of adolescent drug users who name methamphetamine as their sole drug of abuse. In this region, crystal methamphetamine is referred to as “Tik”, an onomatopoeic term in the local lingua franca, Afrikaans, for the sound made by heated crystals in glass receptacles used by the local community to heat and inhale methamphetamine vapors.

Our focus in this report is a neurocognitive comparison between adolescents abusing methamphetamine alone, those abusing both methamphetamine and cannabis, and healthy controls with no history of past or current substance misuse. We also examine drug-related changes in these measures over time by presenting follow-up data for a portion of the original sample. We supplement the primary neurocognitive investigation with clinical data on

subthreshold (including externalizing) psychopathology and disinhibitory personality traits in this cohort.

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Methods

PARTICIPANTS

We recruited 13-18 year old English- and Afrikaans-speaking adolescents of low socioeconomic status and mixed ancestry from the Cape Town region in South Africa. Participants in the initial cohort (N = 40) were recruited into either the (1) Methamphetamine only group (“Meth-only group”; n = 10); (2) Methamphetamine and cannabis group (“Meth-cann group”; n = 10); or (3) control group (n = 20), matched for age, level of education and socio-economic status.

Participants were divided into groups based on information elicited during a clinical interview including administration of the Schedule for Affective Disorders and Schizophrenia for School Aged Children (6-18 years) Lifetime Version (K-SADS-PL;[18]) and DSM-IV-TR,[19] criteria for substance dependence. Participants in the Meth-only group endorsed diagnoses of methamphetamine abuse or dependence with current and regular methamphetamine use (more than 3 doses per week for the last 6 months) alongside minimal (i.e., sub-diagnostic threshold and low lifetime consumption) alcohol, cannabis and other substance use; participants in the Meth-cann group endorsed diagnoses of both methamphetamine and cannabis abuse or dependence, with current and regular methamphetamine and cannabis use (more than 3 doses per week for the last 6 months), alongside minimal alcohol and other substance use; the control group comprised mostly non-users (individuals with no exposure to methamphetamine, cannabis or alcohol) and a smaller number of light users (lifetime history of less than 10 doses of any illicit substances), all without past or current history of substance use disorders.

Exclusionary criteria for study participation included first language other than English or Afrikaans; current or past DSM-IV Axis I disorder including major depression, psychosis,

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3 anxiety, eating, conduct, childhood and pervasive developmental, and attention
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5 deficit/hyperactivity disorders; current or past use of psychotropic medication; alcohol use in
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7 excess of 8 units per month for any period of 2 month or more; a positive breathalyser result at
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9 assessment visits; evidence or report of significant medical, physical, neurological or infectious
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11 conditions that may affect assessments of brain function (e.g., diabetes, developmental delays,
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13 fetal alcohol spectrum disorders, hepatitis B or C, HIV+); history of head injury with loss of
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15 consciousness for greater than 5 minutes; history of ECT treatment; history of placement in
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17 special needs classes or academic streaming as a result of poor school performance (estimated IQ
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19 < 75); left-handedness; poor vision, claustrophobia or metal implant in the body (included for the
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21 purposes of the imaging portion of the larger study). Additional exclusionary criteria for
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23 participant groups included a negative urinary drug screen result for methamphetamine (Meth-
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25 only group) or methamphetamine/cannabis (Meth-cann group); a positive urinary drug screen
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27 result for any illicit substance (control group); a positive urinary drug screen for any other illicit
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29 substance aside from methamphetamine or cannabis where relevant (all groups). Aside from
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31 these criteria, individuals who had experimented with other drugs were not excluded, provided
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33 that they did not endorse diagnostic criteria for current or past SUD, and had not consumed more
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35 than 10 doses of the drug in their lifetime or used the drug in the previous 6 months.
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46 A portion of participants in the original control group (n = 10) as well as all but one participant
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48 in the Meth-only group (n = 9) were followed-up 12 months after initial recruitment to examine
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50 substance use trajectory, as well as changes in relevant personality and neurocognitive measures
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MEASURES

Psychopathology

In order to minimize the possible confounding effects of psychopathological comorbidity on neurocognitive measures, our primary outcome measures of interest, we recruited only individuals with relatively modest behavioral problems (i.e., not meeting diagnostic criteria for non-substance-related disorders). In order to characterize subtle psychopathology, however, we chose to sum total sub-diagnostic threshold symptom counts from the K-SADS-PL for post-traumatic stress disorder (PTSD), attention deficit/hyperactivity disorder (ADHD), conduct disorder (CD), and oppositional-defiant disorder (ODD). Symptom counts for CD and ODD were tallied to form a composite variable representing sub-diagnostic externalizing pathology (range = 0 to 20). Previous studies have demonstrated the benefit of adopting similar means of assessing psychopathology in drug-using samples,[20, 21]. ADHD symptoms were assessed separately, and were not included in the composite externalizing score, based on evidence suggesting that ADHD is inconsistently related to SUD severity, for example,[22] and that the diagnosis falls outside the classification of disruptive behavioral disorders categorized by social deviance [23]. In addition, self-reported indices of anxiety were recorded using the Multidimensional Anxiety Scale for Children (MASC;[24]).

Disinhibitory personality traits

Disinhibitory personality traits were measured using self-rated subscales from three major self-report inventories. Specifically, impulsivity and venturesomeness were measured using the relevant subscales from the Impulsivity-Venturesomeness Scales,[25]. Alpha reliability

coefficients for males on the Impulsivity and Venturesomeness subscales are 0.78 and 0.71 respectively, and 0.75 and 0.73 for females respectively, and the construct validity of both subscales are acceptable. Novelty seeking was measured using the relevant subscale from Cloninger's [26] Tridimensional Character Inventory. The Novelty Seeking subscale has been reported as reliable (0.79) and valid,[27, 28]. In addition, we included the Thrill and Adventure Seeking, Excitement Seeking, Disinhibition and Boredom Susceptibility subscales from Zuckerman and colleagues's [29] Sensation Seeking Scale (SSS) at the follow-up assessment. Items referring directly to alcohol and drug use were excluded from the subscale scores in order to avoid contamination of these measures with measures of substance use central to group classification. Alpha coefficients measuring the internal consistency of the SSS subscales lie between 0.56 and 0.76, and the construct validity of the subscales was reported as good.

Neurocognitive battery and composite scores

A general-purpose neurocognitive test battery was selected. Due to the unavailability of current, culturally appropriate, unbiased South African tests,[30, 31], age-appropriate international tests with established utility in cross-cultural and multilingual contexts and in SUD studies were selected. In consultation with an Afrikaans linguistics specialist, appropriate cultural and language adaptations were made to the tests. Examples of these adaptations included replacement of items/terminology unfamiliar to South Africans, simplifications of test instructions, and substitution of items to ensure equivalent difficulty levels in both Afrikaans and English. Test instructions, stimuli, and response booklets were translated into Afrikaans and back-translated into English by independent translators. Nine composite domain scores were derived from the individual neurocognitive tests as follows:

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6 (1) Attention: Children’s Color Trails Test (CCTT;[32]) times for trails 1 and 2; Children’s
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8 Memory Scale (CMS;[33]) numbers forward and backward subtests; Auditory Verbal
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10 Learning Test (AVLT;[34]) trial 1 score.
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13 (2) Coordination: Dominant and non-dominant peg insertion time, peg removal time, and
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15 number of drops on the Grooved Pegboard Test (GPT;[35]).
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18 (3) Verbal reasoning: Vocabulary and Similarities subtests from the WASI.
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21 (4) Non-verbal reasoning: Block Design and Matrix Reasoning subtests from the Wechsler
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23 Abbreviated Scale of Intelligence (WASI;[36])
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25 (5) Verbal memory: AVLT immediate and delayed recall scores, and long-term percent
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27 retention.
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30 (6) Visual memory: Rey-Osterrieth Complex Figure (ROCF;[37]) immediate and delayed
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32 recall scores; scores on trials 1-3, immediate and delayed recall of the CMS Dots subtest.
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34 (7) Verbal generativity: phonemic fluency total score for letters L, B and S; semantic fluency
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36 total score for animal category.
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39 (8) Planning: ROCF copy; Tower of London,[38] total correct score and total moves score.
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42 (9) Self-monitoring: error total on the CCTT (i.e., near-misses, prompts, color sequence
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44 errors and number sequence errors); error total on phonemic and semantic fluency tasks
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46 (i.e., rule violations, set-loss errors and repetitions); error total on the Tower of London
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48 (i.e, rule and time violations).
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PROCEDURE

Participants were recruited from local schools of similar sociodemographic profiles within a 10 mile radius of the testing site at Tygerberg teaching hospital. Recruiting social workers gave educational talks regarding substance misuse in the classrooms; children were then invited to speak face-to-face and one-on-one with social workers. This first contact was used to screen for basic eligibility criteria, following which interested participants were provided with study information and consent forms to take home. Thereafter, recruiting social workers made telephonic or face-to-face contact with children's parents/guardians, finalizing written informed consent from parents/guardians and written assent from participants. Assenting participants were then invited to our testing site for the research visit, commencing with a semi-structured clinical evaluation conducted by a qualified psychiatrist. Participants also underwent physical and neurological examinations, venous blood sampling, and urine drug screening. Of the participants at initial recruitment, exclusions were made on the basis of co-morbid other drug use (3), current severe mood disorder (1), and repeatedly failing urine drug screens on the days of proposed testing (1), resulting in a final sample of 40 participants.

Participants visited the testing site on separate occasions to complete neurocognitive testing and self-report personality measures. All testing was administered by trained professionals, and completed in participants' home language (English or Afrikaans). As per the exclusion criteria, participants underwent urine drug screening on each testing occasion. The Western Cape Education Department and Stellenbosch University's Ethics Committee granted written approval for the study, which was conducted in adherence to the guidelines contained in the Declaration of Helsinki,[39].

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STATISTICAL ANALYSIS

Neurocognitive composite scores

Where appropriate, neurocognitive test measures were reverse scored so that higher scores reflected better functioning. Thereafter, composite neurocognitive scores were computed to reduce the number of variables initially examined. A hybrid method (described by Medina et al.,[40]) grouped measures into domains based on theoretical assumptions,[41], then average domain z-scores were computed. Goodness-of-fit was assessed by calculating Cronbach’s alpha coefficients for each domain. We derived 10 composite neurocognitive domains, with Cronbach’s alphas ranging from 0.59 to 0.86. The tests in each composite are listed above, and in Table 5 along with descriptive statistics for each measure.

After appropriate cross-checking and cleaning of data, statistical analysis was performed using SPSS version 17.0. Kolmogorov-Smirnov and Levene’s tests were conducted to test for normality of data and homogeneity of variance, respectively. We examined group differences in demographic variables, as well as differences on outcome measures (within the same group over time, as well as across groups) using a series of ANOVAs. Although we explored a range of outcome measures in this analysis, the analysis was primarily of an explorative nature and so the threshold for statistical significance was set at 0.05.

Results

SOCIO-DEMOGRAPHIC CHARACTERISTICS

The groups were well-matched on key socio-demographic variables. While there were no significant between-group differences in age, years of successfully completed education, number of school grades repeated, or socio-economic status (measured using a proxy measure of annual income) at either initial recruitment or follow-up, females and Afrikaans-speakers outnumbered males and English speakers, respectively (see Table 1).

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Table 1
Socio-demographic Characteristics at Baseline Testing and 12-month Follow-up

	Baseline testing				12-month follow-up		
Outcome variable	Overall (<i>n</i> = 40)	Meth group (<i>n</i> = 10)	Meth-cann group (<i>n</i> = 10)	Control group (<i>n</i> = 20)	Overall (<i>n</i> = 19)	Meth group (<i>n</i> = 9)	Control group (<i>n</i> = 10)
Test age (in months)	188.10 (15.89)	187.90 (16.35)	189.80 (15.75)	187.35 (16.48)	198.53 (16.83)	198.22 (17.92)	198.80 (16.77)
Sex							
Female: Male	25: 15	7: 3	7: 3	11: 9	13: 6	6: 3	7: 3
First language							
English: Afrikaans	7: 33	1: 9	1: 9	5: 15	2: 17	1: 8	1: 9
Education (in years)	8.10 (1.32)	7.90 (1.45)	8.00 (1.56)	8.25 (1.16)	8.74 (1.28)	8.44 (1.33)	9.00 (1.25)
Repeated grades	0.38 (0.59)	0.40 (0.52)	0.70 (0.82)	0.20 (0.41)	0.63 (0.76)	0.78 (0.67)	0.50 (0.85)
Annual income (ZAR) ^a	56 370 (13 604)	59 389 (14 384)	54 451 (18 906)	55 819 (10 272)	56 987 (15 225)	59 095 (15 225)	55 090 (11 479)

Note. Means are presented with standard deviations in parentheses

^aPresented as a proxy measure for socio-economic status

SUBSTANCE USE

Substance use data for both test occasions (baseline testing, and 12-month follow-up) appear in Table 2. The participant groups were well differentiated with regard to substance use. With regard to baseline, and as expected, the Meth-cann group demonstrated significantly greater cannabis lifetime exposure than both the Meth-only ($p < .001$) and control ($p < .001$) groups, whose lifetime cannabis exposure was very low. Participants in the Meth-only and Meth-cann groups had consumed a significantly greater amount of both methamphetamine ($p = .025$ and $p = .002$, respectively) and nicotine ($p = .005$ and $p = .014$, respectively) than participants in the control group; however, there was no difference in methamphetamine or nicotine exposure between the Meth-only and Meth-cann groups ($p = .546$ and $p = .725$). The three groups did not differ with regard to alcohol exposure ($F(2, 37) = 2.158$, $p = .130$, $\eta^2 = .104$).

At follow-up, there was no difference between the control and Meth-only groups with regard to alcohol or cannabis lifetime exposure ($p = .020$ and $p = .14$, respectively). Similar to baseline, participants in the Meth-only group had consumed more nicotine and methamphetamine than those in the control group at follow-up ($p = .004$ and $p < .001$, respectively).

With regard to substance use trajectory, neither alcohol nor nicotine exposure changed significantly over time for either the control ($p = .069$ and $p = .423$, respectively) or Meth-only ($p = .135$ and $p = .929$, respectively) group. Although cannabis use increased numerically in the Meth-only group over the test-retest interval, it was not significantly increased ($p = .159$). Cannabis exposure was also unchanged for the control group between baseline and follow-up ($p = .465$). Methamphetamine exposure remained zero at both testing occasions for the control

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group, and did not increase significantly in the Meth-only group over the same period ($F(17, 19) = 0.001, p = .978, \eta^2 = .000$). The absence of an increase in methamphetamine use in the Meth-only group over this period was due to the fact that most (6 out of 9) participants had abstained from methamphetamine use for at least six months (i.e., no longer endorsed current methamphetamine use disorders) between the two testing occasions.

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Table 2

Substance Lifetime Exposure Across Groups at Baseline Testing and 12-month Follow-up

Outcome variable	Baseline testing			12-month follow-up	
	Meth group (n = 10)	Meth-cann group (n = 10)	Control group (n = 20)	Meth group (n = 9)	Control group (n = 10)
Alcohol (standard units)	19.00 (26.45)	23.60 (28.45)	7.55 (13.84)	51.00 (58.30)	22.90 (30.95)
Nicotine (cigarettes)	5088.10 (7250.28)	4431.40 (4012.89)	286.90 (922.97)	4843.49 (3714.54)	638.60 (1443.24)
Cannabis ('joints')	5.70 (5.40)	917.70 (854.19)	0.10 (0.31)	151.67 (331.94)	0.20 (0.42)
Methamphetamine ('hits' smoked)	534.20 (531.20)	736.80 (514.53)	0 (0)	527.56 (522.82)	0 (0)

Note. Means are presented with standard deviations in parentheses

PSYCHOPATHOLOGY

No participants endorsed diagnostically significant levels of psychopathology (aside from the relevant SUDs) at initial recruitment. Looking at sub-diagnostic threshold symptom counts, the Meth-only group demonstrated significantly greater externalizing symptoms (conduct disorder and oppositional disorder symptom counts) than the control group at both baseline ($p = .024$) and follow-up ($p = .043$). In contrast, externalizing symptom counts were not elevated in the Meth-cann group at baseline. There were no other significant between-group differences in non-substance-related symptom counts. There were also no significant differences between baseline and follow-up in either the Meth-only or control groups. These clinical data are presented in Table 3.

Table 3

Sub-diagnostic Psychopathology and Self-reported Anxiety Across Groups at Baseline Testing and 12-month Follow-up

Outcome variable	Baseline testing			12-month follow-up	
	Meth group (<i>n</i> = 10)	Meth-cann group (<i>n</i> = 10)	Control group (<i>n</i> = 20)	Meth group (<i>n</i> = 9)	Control group (<i>n</i> = 10)
Sub-diagnostic symptom counts					
ADHD	3.50 (6.19)	4.30 (5.33)	0.80 (1.64)	3.56 (7.07)	3.60 (8.33)
PTSD	2.40 (4.53)	1.70 (1.83)	2.35 (4.39)	1.67 (4.27)	1.50 (2.76)
Externalizing composite ^a	4.80 (6.41)	3.30 (4.08)	0.60 (1.70)	7.44 (5.70)	1.90 (5.32)
MASC subtotals					
Physical symptoms	12.60 (5.87)	14.50 (7.28)	11.73 (7.89)	10.44 (10.25)	10.20 (6.83)
Harm avoidance	17.50 (5.38)	18.70 (3.71)	17.40 (5.10)	19.44 (4.98)	19.50 (3.27)
Social anxiety	12.60 (4.55)	14.00 (5.83)	12.00 (7.51)	8.11 (6.83)	9.40 (2.22)
Separation/panic	9.30 (5.23)	10.90 (5.90)	8.80 (5.57)	9.00 (7.23)	8.60 (4.03)
Total score	50.80 (13.55)	57.00 (19.77)	48.80 (21.20)	46.11 (24.64)	46.40 (9.11)

Note. Means are presented with standard deviations in parentheses. ^aTotal symptoms of conduct disorder and oppositional defiant disorder

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DISINHIBITORY PERSONALITY TRAITS

Of all the disinhibitory personality traits measured, group differences emerged only on the Novelty Seeking Scale: the Meth-cann and Meth-only groups scored significantly higher than the control group at baseline ($p = .024$). There were no other between-group differences on measures of disinhibitory personality traits at either baseline or follow-up. There were also no significant differences between baseline and follow-up for any disinhibitory personality traits in either the Meth-only or control groups. Descriptive statistics for disinhibitory personality trait measures appear in Table 4.

Table 4

Disinhibitory Personality Traits Across Groups at Baseline Testing and 12-month Follow-up

Outcome variable	Baseline testing			12-month follow-up	
	Meth group (n = 10)	Meth-cann group (n = 10)	Control group (n = 20)	Meth group (n = 9)	Control group (n = 10)
IVS ^a Impulsivity	9.30 (2.79)	10.30 (3.02)	9.89 (3.59)	8.89 (3.82)	7.50 (4.33)
IVS ^a Venturesomeness	8.60 (3.10)	8.70 (2.83)	8.79 (2.46)	7.22 (2.64)	7.20 (2.57)
Novelty seeking scale total	61.70 (8.90)	64.60 (7.31)	57.26 (6.68)	61.11 (9.84)	52.50 (11.52)
SSS ^b Disinhibition	-	-	-	3.44 (1.42)	2.60 (1.17)
SSS ^b Boredom susceptibility	-	-	-	3.78 (1.86)	3.70 (2.21)
SSS ^b Thrill and adventure seeking	-	-	-	4.22 (2.82)	5.90 (1.79)
SSS ^b Experience seeking	-	-	-	4.00 (1.41)	3.60 (1.71)

Note. Means are presented with standard deviations in parentheses. ^aIVS: Impulsivity-Venturesomeness Scale. ^bSSS: Sensation Seeking Scale.

NEUROCOGNITIVE PERFORMANCE

At baseline, there were significant group differences in neurocognitive test performance in the non-verbal reasoning, verbal memory, planning, and self-monitoring domains. For each of these domains, the Meth-cann group had impaired performance relative to the control group (non-verbal reasoning: $p = .012$; verbal memory: $p = .024$, planning: $p = .013$, and self-monitoring: $p < .001$). Additional group differences at baseline were observed in the verbal memory domain where the Meth-cann group performed worse than the Meth-only group ($p = .023$); and in the self-monitoring domain where the Meth-only group performed worse than the control group ($p < .001$). Impaired self-monitoring in the Meth-only group relative to the control group was maintained at follow-up ($p = .003$). There were no other significant differences either between groups at baseline or follow-up, or within groups between baseline and follow-up. Descriptive statistics for individual neurocognitive tests as well as neurocognitive composite domains appear in Table 5.

Table 5

Neurocognitive Performance Within Composite Domains at Baseline Testing and 12-month Follow-up

	Baseline testing			12-month follow-up	
	Meth group (<i>n</i> = 10)	Meth-cann group (<i>n</i> = 10)	Control group (<i>n</i> = 20)	Meth group (<i>n</i> = 9)	Control group (<i>n</i> = 10)
Attention ($\alpha = 0.74$)	-0.25 (0.63)	-0.43 (0.61)	0.19 (0.75)	0.02 (0.22)	0.25 (0.20)
CCTT					
Trial 1 time	25.50 (10.63)	25.10 (10.38)	19.55 (6.59)	19.11 (6.92)	18.90 (7.53)
Trial 2 time	48.40 (13.12)	53.10 (16.46)	43.65 (12.21)	42.44 (8.97)	40.60 (13.25)
CMS					
Numbers forward	6.90 (1.52)	8.00 (1.05)	7.85 (1.57)	7.11 (1.54)	7.90 (1.52)
Numbers backward	3.60 (0.70)	3.10 (0.99)	4.50 (1.54)	3.56 (1.59)	4.30 (0.82)
AVLT Trial 1	7.40 (1.96)	6.00 (1.41)	6.95 (1.96)	8.00 (2.24)	7.10 (1.66)
Coordination ($\alpha = 0.79$)	-0.22 (0.62)	-0.27 (0.50)	0.14 (0.57)	-0.08 (0.21)	0.36 (0.18)
GPT					
Dominant hand peg insertion time	72.00 (8.77)	75.80 (8.54)	69.65 (11.13)	71.56 (5.57)	67.20 (11.61)
Non-dominant hand peg insertion time	87.40 (14.73)	81.10 (13.40)	77.00 (13.12)	77.22 (9.72)	69.00 (8.71)
Dominant hand peg removal time	24.70 (6.57)	25.30 (2.75)	22.75 (3.46)	23.33 (3.16)	22.90 (4.65)
Non-dominant hand peg removal time	25.20 (4.52)	26.30 (3.27)	23.20 (3.59)	25.11 (7.36)	22.80 (4.19)
Dominant hand drops	2.60 (1.71)	3.00 (1.33)	2.95 (2.16)	2.89 (2.15)	2.60 (1.35)
Non-dominant hand drops	3.10 (1.10)	3.40 (1.96)	3.05 (2.26)	3.11 (1.76)	2.60 (1.90)
Verbal reasoning ($\alpha = 0.84$)	-0.46 (1.01)	-0.28 (0.78)	0.30 (0.90)	-0.00 (0.31)	0.34 (0.24)
WASI Vocabulary subtest	25.20 (10.30)	26.60 (6.85)	33.15 (8.45)	29.33 (12.34)	29.50 (4.88)
WASI Similarities subtest	18.20 (6.46)	19.60 (6.87)	22.60 (7.18)	22.11 (8.43)	22.30 (4.64)
Non-verbal reasoning ($\alpha = 0.78$)	-0.26 (0.92)	-0.47 (0.61)	0.34 (0.80)	0.05 (0.30)	0.07 (0.25)
WASI Block Design subtest	22.80 (10.29)	22.40 (10.76)	31.00 (11.74)	28.00 (14.93)	26.30 (12.13)
WASI Matrix Reasoning subtest	15.80 (6.63)	13.40 (4.38)	19.05 (5.05)	17.67 (8.00)	16.80 (6.78)

Verbal memory ($\alpha = 0.86$)	0.20 (0.99)	-0.60 (0.88)	0.08 (0.52)	-0.25 (0.26)	0.49 (0.24)
AVLT					
Immediate recall	10.00 (1.33)	8.30 (2.58)	10.45 (1.93)	9.11 (2.57)	10.90 (1.85)
Delayed recall	9.80 (2.04)	7.90 (3.04)	10.30 (1.90)	9.44 (3.50)	11.50 (1.96)
Long-term percent retention	94.91 (31.34)	76.61 (18.12)	87.19 (11.11)	84.01 (24.48)	100.95 (23.70)
Visual memory ($\alpha = 0.79$)	-0.14 (0.72)	-0.13 (0.62)	-0.02 (0.81)	0.29 (0.25)	0.09 (0.23)
ROCF					
Immediate recall	19.25 (6.51)	18.00 (8.01)	17.28 (7.29)	19.33 (6.51)	19.60 (4.20)
Delayed recall	18.45 (5.90)	17.55 (7.58)	17.68 (7.73)	19.22 (6.18)	19.00 (4.73)
CMS Dots					
Trials 1-3	17.30 (3.13)	16.90 (1.97)	18.10 (3.82)	20.22 (3.63)	18.50 (3.57)
Immediate recall	5.50 (1.78)	6.00 (1.63)	6.10 (1.68)	6.33 (1.94)	6.00 (2.06)
Delayed recall	5.40 (1.58)	5.80 (1.69)	6.20 (1.64)	6.56 (1.88)	5.80 (1.99)
Verbal generativity ($\alpha = 0.59$)	-0.38 (1.04)	-0.06 (0.57)	0.23 (0.72)	0.17 (0.29)	0.03 (0.25)
Phonemic fluency: total words	24.40 (9.68)	29.00 (4.76)	28.55 (6.58)	29.56 (12.47)	24.10 (10.73)
Semantic fluency: total words	13.30 (4.24)	13.70 (2.58)	15.75 (3.04)	14.56 (3.05)	15.10 (3.11)
Planning ($\alpha = 0.73$)	-0.13 (0.66)	-0.47 (0.76)	0.22 (0.66)	0.05 (0.21)	0.13 (0.20)
ROCF copy	30.40 (4.19)	29.15 (5.19)	31.48 (2.77)	30.17 (4.57)	30.55 (3.02)
Tower of London					
Total correct score	3.40 (1.51)	2.80 (1.40)	3.30 (1.38)	3.89 (1.45)	3.50 (1.35)
Total moves score	33.90 (16.29)	39.50 (13.82)	26.65 (12.36)	29.00 (11.74)	25.20 (8.27)
Self-monitoring	-0.71 (0.84)	-0.56 (0.99)	0.63 (0.40)	-0.72 (0.23)	0.68 (0.21)
CCTT total errors	0.60 (0.97)	1.10 (0.99)	0.65 (0.81)	0.89 (1.05)	0.80 (1.03)
Phonemic fluency errors	3.60 (4.86)	1.60 (0.97)	0.80 (1.06)	2.78 (3.49)	0.90 (1.10)
Semantic fluency errors	0.40 (0.70)	0.10 (0.32)	0.25 (0.55)	0.33 (0.50)	0.20 (0.42)
Tower of London total errors	2.20 (3.10)	3.20 (3.16)	0.50 (1.10)	2.22 (5.89)	0.30 (0.48)

Note. Means are presented with standard deviations in parentheses.

Discussion

The main finding of this study was two-fold. First, combined abuse of methamphetamine and cannabis was associated with relatively more widespread neurocognitive impairment than methamphetamine abuse alone. Second, increased externalizing psychopathology and poorer self-monitoring associated with methamphetamine abuse appear to persist into abstinence.

Adolescents who abused methamphetamine alone showed some limited neurocognitive dysfunction in the self-monitoring domain; however, adolescents who abused both cannabis and methamphetamine were susceptible to additional and more widespread cognitive dysfunction across several domains including verbal memory, planning, and non-verbal reasoning. Although cannabis is currently the most common secondary illicit substance for methamphetamine users,[15] few studies have examined the outcomes of concurrent methamphetamine and cannabis consumption. Our finding appears to stand in contrast to earlier pre-clinical work suggesting that methamphetamine neurotoxicity in fact attenuates the impact of certain cannabis-related behavioral and cognitive sequelae in rats,[42]. Similarly, an earlier clinical study showed no significant differences on neurocognitive outcomes in 'pure' methamphetamine abusers compared to those abusing both methamphetamine and cannabis,[43]. Future research should aim to scrutinize the mechanisms of apparent differential effects of single versus concomitant drug use in order to clarify under which circumstances polysubstance use may provide a protective neurocognitive effect,[16, 44].

The incidental finding that the Meth-only group largely abstained from methamphetamine use between baseline and follow-up assessments, teamed with overall consistency in the profiles of

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relative individual substance consumption between the control and Meth-only groups from baseline to follow-up (i.e., the group differences in methamphetamine and nicotine exposure at baseline were maintained at follow-up, but not increased) provides an interesting perspective on the differential effects of current versus abstinent drug use. Since neither the control nor Meth-only groups showed significant increases in lifetime exposure to any individual substance between baseline and follow-up, it seems probable that the clinical group differences that remained relevant from baseline to follow-up (increased externalizing psychopathology and poorer self-monitoring) represent the enduring correlates of substance exposure established at baseline. Indeed, this proposition is supported by other studies showing that elevated sub-diagnostic externalizing psychopathology as well as deficits in executive functions such as self-monitoring may persist long after substance use has ceased,[20, 45].

A potential limitation of this study is that follow-up assessments were limited to Meth-only and control participants, and therefore comment on the long-term neurocognitive effects of concomitant methamphetamine and cannabis abuse is beyond the scope of this paper. Both a strength and potential limitation of this study is that we focus here on the correlates of substance abuse during adolescence, a critical phase of neuromaturation. Our findings are therefore valuable for application within this important developmental group; however, the applicability of these findings to adult drug-using populations with longer drug use histories remains to be seen. Furthermore, relatively longer-term follow-up studies of similar adolescent samples would be useful in order to examine the longevity of substance-related effects on neurocognition.

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3 In summary, our findings demonstrate 1) the differential consequences on adolescent brain
4 function and behavior of methamphetamine abuse with or without cannabis, and 2) the
5 differential acute and long-term effects of methamphetamine abuse in adolescence. These
6 observations contribute to accumulating literature describing clinically relevant correlates of
7 adolescent substance abuse. Given these findings, future studies should aim to clarify the
8 specificity and longevity of clinical and neurocognitive effects of 'pure' methamphetamine abuse
9 versus concurrent methamphetamine and cannabis use by examining current users with longer
10 substance abuse histories, as well as abstinent users at relatively longer follow-up intervals.
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Natalie Cuzen, Helen Ferrett, Dan Stein and Deborah Yurgelun-Todd each fulfilled all three of the ICMJE guidelines for authorship as follows: 1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; 2) drafting the article and/or revising it critically for important intellectual content; and 3) final approval of the version to be published.

Competing interests

The authors report no conflicts of interest.

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Data sharing statement

Extra data are available by emailing ncuzen@gmail.com

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Methamphetamine and cannabis abuse in adolescence: a quasi-experimental study on specific and long-term neurocognitive effects

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Abstract

Objectives: Methamphetamine abuse affects brain structure and function. Although methamphetamine and cannabis are commonly abused together, few studies have investigated the differential neurocognitive consequences of methamphetamine abuse with or without cannabis. Furthermore, the effects of drug use on the developing adolescent brain remain poorly understood. We compared neurocognitive function between adolescents with ‘pure’ methamphetamine abuse, those with comorbid methamphetamine and cannabis abuse, and healthy controls at baseline and follow-up.

Methods: Individuals residing in the greater Cape Town region and between the ages of 13 and 18 years were recruited into either Meth-only ($n = 10$), Meth-cann ($n = 10$) or healthy control ($n = 20$) groups using a quasi-experimental design. All participants underwent a comprehensive neurocognitive assessment. Substance-use variables and psychiatric symptom counts were also recorded. A portion of the Meth-only and control participants completed 12 month follow-up assessments.

Results: While the Meth-cann group demonstrated widespread neurocognitive deficits at baseline, these deficits were restricted to the self-monitoring domain in the Meth-only group at both baseline and follow-up.

Conclusions: Methamphetamine abuse with cannabis abuse is associated with significantly more neurocognitive impairment than methamphetamine abuse alone, and such deficits may be enduring.

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Strengths and limitations of this study

- Strength: Identification of neurocognitive sequelae in the early phase of drug abuse
- Strength: Identification of neurocognitive sequelae of relatively ‘pure’ drug abuse
- Strength: Findings specific to adolescent phase
- Potential limitation: Limited sample size of all three groups

For peer review only

Introduction

Pre-clinical and human data suggest that various brain regions and neurocognitive functions may be differentially vulnerable to the effects of regular heavy methamphetamine use,[1, 2, 3, 4]. For instance, human studies have shown that methamphetamine abuse may lead to broad and long-term neurocognitive sequelae in memory, attention, task switching and response inhibition domains, and that such alternations in brain function may persist for years following abstinence,[5, 6, 7]. Furthermore, the offspring of methamphetamine abusing mothers suffer lasting damaging effects on cognitive development, for example,[8, 9, 10]. There are a number of reviews that explore the neurocognitive effects of drug use (particularly methamphetamine or cannabis) in adolescents, for example [11, 12, 13]. Marijuana-using adolescents have displayed neurocognitive deficits in the memory and executive functioning domains, [13]. Furthermore, in a recent study, it was found that the primary deficit amongst methamphetamine-using adolescents is executive functioning [14]. However, these studies and many reviews focus on single drug-using adolescents. Many studies do not explore the combination of cannabis and methamphetamine use in adolescents, and the neurocognitive effects this combination has on the developing brain.

In addition to overall severe and persistent neurocognitive effects of heavy methamphetamine use, the adolescent brain may be particularly vulnerable to such effects given critical neuromaturation underway during this phase of development,[15, 16]. However, few data specifically address the question of neurocognitive sequelae of methamphetamine abuse in adolescents during the early stage of drug use trajectory. Over the 1990s and into the present, substance abuse statistics have revealed alarming increases in methamphetamine abuse rates to

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the extent that methamphetamine abuse may be considered an “epidemic” in the United States,[17]. Increases in methamphetamine abuse have been noted elsewhere too: methamphetamine has recently attained the status of primary drug of abuse among adolescents in developing countries such as South Africa,[18]. This represents a dramatic shift in drug use patterns in this age group in recent years, and raises issues about the impact of methamphetamine on the developing brain during this critical time of brain development.

Despite overall increased rates of methamphetamine abuse, several fundamental questions about the consequences of such abuse remain incompletely unanswered, thus calling for more empirical work in the area. First, although drug co-administration is a common trend in worldwide patterns of drug abuse,[18], the differential consequences of methamphetamine abuse with or without cannabis use on adolescent brain function and structure are not yet clearly delineated. Second, while externalizing psychopathology commonly co-occurs with heavy methamphetamine use, the functional impact of such comorbidity remains unclear,[19,20]. Lastly, the long-term neurocognitive outcome of adolescent methamphetamine abuse with minimal externalizing psychopathology remains an open question.

Given the worldwide pattern of drug co-administration, it is particularly challenging to examine the impact of single or specific drug use combinations in most settings. However, in the Cape Town region of South Africa, we are presented with a population of adolescent drug users who name methamphetamine as their sole drug of abuse. In this region, crystal methamphetamine is referred to as “Tik”, an onomatopoeic term in the local lingua franca, Afrikaans, for the sound

made by heated crystals in glass receptacles used by the local community to heat and inhale methamphetamine vapors.

Our focus in this report is a neurocognitive comparison between adolescents abusing methamphetamine alone, those abusing both methamphetamine and cannabis, and healthy controls with no history of past or current substance misuse. We also examine drug-related changes in these measures over time by presenting follow-up data for a portion of the original sample. We supplement the primary neurocognitive investigation with clinical data on subthreshold (including externalizing) psychopathology. We hypothesized that cognitive impairment would be worse in the combined group ('meth-cann' group) when compared to the other groups.

Methods

PARTICIPANTS

We recruited 13-18 year old English- and Afrikaans-speaking adolescents of low socioeconomic status and mixed ancestry from the Cape Town region in South Africa. Participants in the initial cohort (N = 40) were recruited into either the (1) Methamphetamine only group (“Meth-only group”; n = 10); (2) Methamphetamine and cannabis group (“Meth-cann group”; n = 10); or (3) control group (n = 20), matched for age, level of education and socio-economic status.

Participants were divided into groups based on information elicited during a clinical interview including administration of the Schedule for Affective Disorders and Schizophrenia for School Aged Children (6-18 years) Lifetime Version (K-SADS-PL;[21]) and DSM-IV-TR,[22] criteria for substance dependence. Participants in the Meth-only group endorsed diagnoses of methamphetamine abuse or dependence with current and regular methamphetamine use (more than 3 doses per week for the last 6 months) alongside minimal (i.e., sub-diagnostic threshold and low lifetime consumption) alcohol, cannabis and other substance use; participants in the Meth-cann group endorsed diagnoses of both methamphetamine and cannabis abuse or dependence, with current and regular methamphetamine and cannabis use (more than 3 doses per week for the last 6 months), alongside minimal alcohol and other substance use; the control group comprised mostly non-users (individuals with no exposure to methamphetamine, cannabis or alcohol) and a smaller number of light users (lifetime history of less than 10 doses of any illicit substances), all without past or current history of substance use disorders.

Exclusionary criteria for study participation included first language other than English or Afrikaans; current or past DSM-IV Axis I disorder including major depression, psychosis,

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3 anxiety, eating, conduct, childhood and pervasive developmental, and attention
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5 deficit/hyperactivity disorders; current or past use of psychotropic medication; alcohol use in
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7 excess of 8 units per month for any period of 2 months or more; a positive breathalyser result at
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9 assessment visits; evidence or report of significant medical, physical, neurological or infectious
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11 conditions that may affect assessments of brain function (e.g., diabetes, developmental delays,
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13 fetal alcohol spectrum disorders, hepatitis B or C, HIV+); history of head injury with loss of
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15 consciousness for greater than 5 minutes; history of ECT treatment; history of placement in
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17 special needs classes or academic streaming as a result of poor school performance (estimated IQ
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19 < 75); left-handedness; poor vision, claustrophobia or metal implant in the body (included for the
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21 purposes of the imaging portion of the larger study). Additional exclusionary criteria for
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23 participant groups included a negative urinary drug screen result for methamphetamine (Meth-
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25 only group) or methamphetamine/cannabis (Meth-cann group); a positive urinary drug screen
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27 result for any illicit substance (control group); a positive urinary drug screen for any other illicit
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29 substance aside from methamphetamine or cannabis where relevant (all groups). Aside from
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31 these criteria, individuals who had experimented with other drugs were not excluded, provided
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33 that they did not endorse diagnostic criteria for current or past SUD, and had not consumed more
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35 than 10 doses of the drug in their lifetime or used the drug in the previous 6 months.
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46 A portion of participants in the original control group (n = 10) as well as all but one participant
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48 in the Meth-only group (n = 9) were followed-up 12 months after initial recruitment to examine
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50 substance use trajectory, as well as changes in neurocognitive measures over time.
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55 MEASURES

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Psychopathology

In order to minimize the possible confounding effects of psychopathological comorbidity on neurocognitive measures, our primary outcome measures of interest, we recruited only individuals with relatively modest behavioral problems (i.e., not meeting diagnostic criteria for non-substance-related disorders). In order to characterize subtle psychopathology, however, we chose to sum total sub-diagnostic threshold symptom counts from the K-SADS-PL for post-traumatic stress disorder (PTSD), attention deficit/hyperactivity disorder (ADHD), conduct disorder (CD), and oppositional-defiant disorder (ODD). Symptom counts for CD and ODD were tallied to form a composite variable representing sub-diagnostic externalizing pathology (range = 0 to 20). Previous studies have demonstrated the benefit of adopting similar means of assessing psychopathology in drug-using samples,[25, 25]. ADHD symptoms were assessed separately, and were not included in the composite externalizing score, based on evidence suggesting that ADHD is inconsistently related to SUD severity, for example,[26] and that the diagnosis falls outside the classification of disruptive behavioral disorders categorized by social deviance [27]. In addition, self-reported indices of anxiety were recorded using the Multidimensional Anxiety Scale for Children (MASC;[28]).

Neurocognitive battery and composite scores

A general-purpose neurocognitive test battery was selected. Due to the unavailability of current, culturally appropriate, unbiased South African tests,[29, 30], age-appropriate international tests with established utility in cross-cultural and multilingual contexts and in SUD studies were selected. In consultation with an Afrikaans linguistics specialist, appropriate cultural and language adaptations were made to the tests. Examples of these adaptations included

replacement of items/terminology unfamiliar to South Africans, simplifications of test instructions, and substitution of items to ensure equivalent difficulty levels in both Afrikaans and English. Test instructions, stimuli, and response booklets were translated into Afrikaans and back-translated into English by independent translators. Nine composite domain scores were derived from the individual neurocognitive tests as follows:

- (1) Attention: Children's Color Trails Test (CCTT;[31]) times for trails 1 and 2; Children's Memory Scale (CMS;[32]) numbers forward and backward subtests; Auditory Verbal Learning Test (AVLT;[33]) trial 1 score.
- (2) Coordination: Dominant and non-dominant peg insertion time, peg removal time, and number of drops on the Grooved Pegboard Test (GPT;[34]).
- (3) Verbal reasoning: Vocabulary and Similarities subtests from the WASI.
- (4) Non-verbal reasoning: Block Design and Matrix Reasoning subtests from the Wechsler Abbreviated Scale of Intelligence (WASI;[35])
- (5) Verbal memory: AVLT immediate and delayed recall scores, and long-term percent retention.
- (6) Visual memory: Rey-Osterrieth Complex Figure (ROCF;[36]) immediate and delayed recall scores; scores on trials 1-3, immediate and delayed recall of the CMS Dots subtest.
- (7) Verbal generativity: phonemic fluency total score for letters L, B and S; semantic fluency total score for animal category.
- (8) Planning: ROCF copy; Tower of London,[37] total correct score and total moves score.
- (9) Self-monitoring: error total on the CCTT (i.e., near-misses, prompts, color sequence errors and number sequence errors); error total on phonemic and semantic fluency tasks

(i.e., rule violations, set-loss errors and repetitions); error total on the Tower of London (i.e., rule and time violations).

PROCEDURE

Participants were recruited from local schools of similar sociodemographic profiles within a 10 mile radius of the testing site at Tygerberg teaching hospital. Recruiting social workers gave educational talks regarding substance misuse in the classrooms; children were then invited to speak face-to-face and one-on-one with social workers. This first contact was used to screen for basic eligibility criteria, following which interested participants were provided with study information and consent forms to take home. Thereafter, recruiting social workers made telephonic or face-to-face contact with children’s parents/guardians, finalizing written informed consent from parents/guardians and written assent from participants. Assenting participants were then invited to our testing site for the research visit, commencing with a semi-structured clinical evaluation conducted by a qualified psychiatrist. Participants also underwent physical and neurological examinations, venous blood sampling, and urine drug screening. Of the participants at initial recruitment, exclusions were made on the basis of co-morbid other drug use (n = 3), current severe mood disorder (n = 1), and repeatedly failing urine drug screens on the days of proposed testing (n = 1), resulting in a final sample of 40 participants.

Participants visited the testing site on two separate occasions to complete neurocognitive testing, at the baseline and at the follow-up visit. All testing was administered by trained professionals,

and completed in participants' home language (English or Afrikaans). As per the exclusion criteria, participants underwent urine drug screening on each testing occasion. The Western Cape Education Department and Stellenbosch University's Ethics Committee granted written approval for the study, which was conducted in adherence to the guidelines contained in the Declaration of Helsinki,[38].

STATISTICAL ANALYSIS

Neurocognitive composite scores

Where appropriate, neurocognitive test measures were reverse scored so that higher scores reflected better functioning. Thereafter, composite neurocognitive scores were computed to reduce the number of variables initially examined. A hybrid method (described by Medina et al.,[39]) grouped measures into domains based on theoretical assumptions,[40], then average domain z-scores were computed. Goodness-of-fit was assessed by calculating Cronbach's alpha coefficients for each domain. We derived 10 composite neurocognitive domains, with Cronbach's alphas ranging from 0.59 to 0.86. The tests in each composite are listed above, and in Table 4 along with descriptive statistics for each measure.

After appropriate cross-checking and cleaning of data, statistical analysis was performed using SPSS version 17.0. Kolmogorov-Smirnov and Levene's tests were conducted to test for normality of data and homogeneity of variance, respectively. We examined group differences in demographic variables, as well as differences on outcome measures (within the same group over time, as well as across groups) using a series of ANOVAs. Although we explored a range of outcome measures in this analysis, the analysis was primarily of an explorative nature and so the threshold for statistical significance was set at 0.05.

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Results

SOCIO-DEMOGRAPHIC CHARACTERISTICS

The groups were well-matched on key socio-demographic variables. While there were no significant between-group differences in age, years of successfully completed education, number of school grades repeated, or socio-economic status (measured using a proxy measure of annual income) at either initial recruitment or follow-up, females and Afrikaans-speakers outnumbered males and English speakers, respectively (see Table 1).

Table 1

Socio-demographic Characteristics at Baseline Testing and 12-month Follow-up

	Baseline testing				12-month follow-up		
Outcome variable	Overall (<i>n</i> = 40)	Meth group (<i>n</i> = 10)	Meth-cann group (<i>n</i> = 10)	Control group (<i>n</i> = 20)	Overall (<i>n</i> = 19)	Meth group (<i>n</i> = 9)	Control group (<i>n</i> = 10)
Test age (in months)	188.10 (15.89)	187.90 (16.35)	189.80 (15.75)	187.35 (16.48)	198.53 (16.83)	198.22 (17.92)	198.80 (16.77)
Sex							
Female: Male	25: 15	7: 3	7: 3	11: 9	13: 6	6: 3	7: 3
First language							
English: Afrikaans	7: 33	1: 9	1: 9	5: 15	2: 17	1: 8	1: 9
Education (in years)	8.10 (1.32)	7.90 (1.45)	8.00 (1.56)	8.25 (1.16)	8.74 (1.28)	8.44 (1.33)	9.00 (1.25)
Repeated grades	0.38 (0.59)	0.40 (0.52)	0.70 (0.82)	0.20 (0.41)	0.63 (0.76)	0.78 (0.67)	0.50 (0.85)
Annual income (ZAR) ^a	56 370 (13 604)	59 389 (14 384)	54 451 (18 906)	55 819 (10 272)	56 987 (15 225)	59 095 (15 225)	55 090 (11 479)

Note. Means are presented with standard deviations in parentheses

^aPresented as a proxy measure for socio-economic status

SUBSTANCE USE

Substance use data for both test occasions (baseline testing, and 12-month follow-up) appear in Table 2. The participant groups were well differentiated with regard to substance use. With regard to baseline, and as expected, the Meth-cann group demonstrated significantly greater cannabis lifetime exposure than both the Meth-only ($p < .001$) and control ($p < .001$) groups, whose lifetime cannabis exposure was very low. Participants in the Meth-only and Meth-cann groups had consumed a significantly greater amount of both methamphetamine ($p = .025$ and $p = .002$, respectively) and nicotine ($p = .005$ and $p = .014$, respectively) than participants in the control group; however, there was no difference in methamphetamine or nicotine exposure between the Meth-only and Meth-cann groups ($p = .546$ and $p = .725$). The three groups did not differ with regard to alcohol exposure ($F(2, 37) = 2.158$, $p = .130$, $\eta^2 = .104$).

At follow-up, there was no difference between the control and Meth-only groups with regard to alcohol or cannabis lifetime exposure ($p = .020$ and $p = .14$, respectively). Similar to baseline, participants in the Meth-only group had consumed more nicotine and methamphetamine than those in the control group at follow-up ($p = .004$ and $p < .001$, respectively).

With regard to substance use trajectory, neither alcohol nor nicotine exposure changed significantly over time for either the control ($p = .069$ and $p = .423$, respectively) or Meth-only ($p = .135$ and $p = .929$, respectively) group. Although cannabis use increased numerically in the Meth-only group over the test-retest interval, it was not significantly increased ($p = .159$). Cannabis exposure was also unchanged for the control group between baseline and follow-up ($p = .465$). Methamphetamine exposure remained zero at both testing occasions for the control

group, and did not increase significantly in the Meth-only group over the same period ($F(17, 19) = 0.001, p = .978, \eta^2 = .000$). The absence of an increase in methamphetamine use in the Meth-only group over this period was due to the fact that most (6 out of 9) participants had abstained from methamphetamine use for at least six months (i.e., no longer endorsed current methamphetamine use disorders) between the two testing occasions.

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Table 2
Substance Lifetime Exposure Across Groups at Baseline Testing and 12-month Follow-up

Outcome variable	Baseline testing			12-month follow-up	
	Meth group (<i>n</i> = 10)	Meth-cann group (<i>n</i> = 10)	Control group (<i>n</i> = 20)	Meth group (<i>n</i> = 9)	Control group (<i>n</i> = 10)
Alcohol (standard units)	19.00 (26.45)	23.60 (28.45)	7.55 (13.84)	51.00 (58.30)	22.90 (30.95)
Nicotine (cigarettes)	5088.10 (7250.28)	4431.40 (4012.89)	286.90 (922.97)	4843.49 (3714.54)	638.60 (1443.24)
Cannabis ('joints')	5.70 (5.40)	917.70 (854.19)	0.10 (0.31)	151.67 (331.94)	0.20 (0.42)
Methamphetamine ('hits' smoked)	534.20 (531.20)	736.80 (514.53)	0 (0)	527.56 (522.82)	0 (0)

Note. Means are presented with standard deviations in parentheses

PSYCHOPATHOLOGY

No participants endorsed diagnostically significant levels of psychopathology (aside from the relevant SUDs) at initial recruitment. Looking at sub-diagnostic threshold symptom counts, the Meth-only group demonstrated significantly greater externalizing symptoms (conduct disorder and oppositional disorder symptom counts) than the control group at both baseline ($p = .024$) and follow-up ($p = .043$). In contrast, externalizing symptom counts were not elevated in the Meth-cann group at baseline. There were no other significant between-group differences in non-substance-related symptom counts. There were also no significant differences between baseline and follow-up in either the Meth-only or control groups. These clinical data are presented in Table 3.

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Table 3
Sub-diagnostic Psychopathology and Self-reported Anxiety Across Groups at Baseline Testing and 12-month Follow-up

Outcome variable	Baseline testing			12-month follow-up	
	Meth group (n = 10)	Meth-cann group (n = 10)	Control group (n = 20)	Meth group (n = 9)	Control group (n = 10)
Sub-diagnostic symptom counts					
ADHD	3.50 (6.19)	4.30 (5.33)	0.80 (1.64)	3.56 (7.07)	3.60 (8.33)
PTSD	2.40 (4.53)	1.70 (1.83)	2.35 (4.39)	1.67 (4.27)	1.50 (2.76)
Externalizing composite ^a	4.80 (6.41)	3.30 (4.08)	0.60 (1.70)	7.44 (5.70)	1.90 (5.32)
MASC subtotals					
Physical symptoms	12.60 (5.87)	14.50 (7.28)	11.73 (7.89)	10.44 (10.25)	10.20 (6.83)
Harm avoidance	17.50 (5.38)	18.70 (3.71)	17.40 (5.10)	19.44 (4.98)	19.50 (3.27)
Social anxiety	12.60 (4.55)	14.00 (5.83)	12.00 (7.51)	8.11 (6.83)	9.40 (2.22)
Separation/panic	9.30 (5.23)	10.90 (5.90)	8.80 (5.57)	9.00 (7.23)	8.60 (4.03)
Total score	50.80 (13.55)	57.00 (19.77)	48.80 (21.20)	46.11 (24.64)	46.40 (9.11)

Note. Means are presented with standard deviations in parentheses. ^aTotal symptoms of conduct disorder and oppositional defiant disorder

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NEUROCOGNITIVE PERFORMANCE

At baseline, there were significant group differences in neurocognitive test performance in the non-verbal reasoning, verbal memory, planning, and self-monitoring domains. For each of these domains, the Meth-cann group had impaired performance relative to the control group (non-verbal reasoning: $p = .012$; verbal memory: $p = .024$, planning: $p = .013$, and self-monitoring: $p < .001$). Additional group differences at baseline were observed in the verbal memory domain where the Meth-cann group performed worse than the Meth-only group ($p = .023$); and in the self-monitoring domain where the Meth-only group performed worse than the control group ($p < .001$). Impaired self-monitoring in the Meth-only group relative to the control group was maintained at follow-up ($p = .003$). There were no other significant differences either between groups at baseline or follow-up, or within groups between baseline and follow-up. Descriptive statistics for individual neurocognitive tests as well as neurocognitive composite domains appear in Table 4.

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Table 4
Neurocognitive Performance Within Composite Domains at Baseline Testing and 12-month Follow-up

	Baseline testing			12-month follow-up	
	Meth group (n = 10)	Meth-cann group (n = 10)	Control group (n = 20)	Meth group (n = 9)	Control group (n = 10)
Attention ($\alpha = 0.74$)	-0.25 (0.63)	-0.43 (0.61)	0.19 (0.75)	0.02 (0.22)	0.25 (0.20)
CCTT					
Trial 1 time	25.50 (10.63)	25.10 (10.38)	19.55 (6.59)	19.11 (6.92)	18.90 (7.53)
Trial 2 time	48.40 (13.12)	53.10 (16.46)	43.65 (12.21)	42.44 (8.97)	40.60 (13.25)
CMS					
Numbers forward	6.90 (1.52)	8.00 (1.05)	7.85 (1.57)	7.11 (1.54)	7.90 (1.52)
Numbers backward	3.60 (0.70)	3.10 (0.99)	4.50 (1.54)	3.56 (1.59)	4.30 (0.82)
AVLT Trial 1	7.40 (1.96)	6.00 (1.41)	6.95 (1.96)	8.00 (2.24)	7.10 (1.66)
WASI Vocabulary subtest	25.20 (10.30)	26.60 (6.85)	33.15 (8.45)	29.33 (12.34)	29.50 (4.88)
WASI Similarities subtest	18.20 (6.46)	19.60 (6.87)	22.60 (7.18)	22.11 (8.43)	22.30 (4.64)
Non-verbal reasoning ($\alpha = 0.78$)	-0.26 (0.92)	-0.47 (0.61)	0.34 (0.80)	0.05 (0.30)	0.07 (0.25)
WASI Block Design subtest	22.80 (10.29)	22.40 (10.76)	31.00 (11.74)	28.00 (14.93)	26.30 (12.13)
WASI Matrix Reasoning subtest	15.80 (6.63)	13.40 (4.38)	19.05 (5.05)	17.67 (8.00)	16.80 (6.78)

Verbal memory ($\alpha = 0.86$)	0.20 (0.99)	-0.60 (0.88)	0.08 (0.52)	-0.25 (0.26)	0.49 (0.24)
AVLT					
Immediate recall	10.00 (1.33)	8.30 (2.58)	10.45 (1.93)	9.11 (2.57)	10.90 (1.85)
Delayed recall	9.80 (2.04)	7.90 (3.04)	10.30 (1.90)	9.44 (3.50)	11.50 (1.96)
Long-term percent retention	94.91 (31.34)	76.61 (18.12)	87.19 (11.11)	84.01 (24.48)	100.95 (23.70)
Visual memory ($\alpha = 0.79$)	-0.14 (0.72)	-0.13 (0.62)	-0.02 (0.81)	0.29 (0.25)	0.09 (0.23)
ROCF					
Immediate recall	19.25 (6.51)	18.00 (8.01)	17.28 (7.29)	19.33 (6.51)	19.60 (4.20)
Delayed recall	18.45 (5.90)	17.55 (7.58)	17.68 (7.73)	19.22 (6.18)	19.00 (4.73)
CMS Dots					
Trials 1-3	17.30 (3.13)	16.90 (1.97)	18.10 (3.82)	20.22 (3.63)	18.50 (3.57)
Immediate recall	5.50 (1.78)	6.00 (1.63)	6.10 (1.68)	6.33 (1.94)	6.00 (2.06)
Delayed recall	5.40 (1.58)	5.80 (1.69)	6.20 (1.64)	6.56 (1.88)	5.80 (1.99)
Verbal generativity ($\alpha = 0.59$)	-0.38 (1.04)	-0.06 (0.57)	0.23 (0.72)	0.17 (0.29)	0.03 (0.25)
Phonemic fluency: total words	24.40 (9.68)	29.00 (4.76)	28.55 (6.58)	29.56 (12.47)	24.10 (10.73)
Semantic fluency: total words	13.30 (4.24)	13.70 (2.58)	15.75 (3.04)	14.56 (3.05)	15.10 (3.11)
Planning ($\alpha = 0.73$)	-0.13 (0.66)	-0.47 (0.76)	0.22 (0.66)	0.05 (0.21)	0.13 (0.20)
ROCF copy	30.40 (4.19)	29.15 (5.19)	31.48 (2.77)	30.17 (4.57)	30.55 (3.02)
Tower of London					
Total correct score	3.40 (1.51)	2.80 (1.40)	3.30 (1.38)	3.89 (1.45)	3.50 (1.35)
Total moves score	33.90 (16.29)	39.50 (13.82)	26.65 (12.36)	29.00 (11.74)	25.20 (8.27)
Self-monitoring	-0.71 (0.84)	-0.56 (0.99)	0.63 (0.40)	-0.72 (0.23)	0.68 (0.21)
CCTT total errors	0.60 (0.97)	1.10 (0.99)	0.65 (0.81)	0.89 (1.05)	0.80 (1.03)
Phonemic fluency errors	3.60 (4.86)	1.60 (0.97)	0.80 (1.06)	2.78 (3.49)	0.90 (1.10)
Semantic fluency errors	0.40 (0.70)	0.10 (0.32)	0.25 (0.55)	0.33 (0.50)	0.20 (0.42)
Tower of London total errors	2.20 (3.10)	3.20 (3.16)	0.50 (1.10)	2.22 (5.89)	0.30 (0.48)

Note. Means are presented with standard deviations in parentheses.

Discussion

The main finding of this study was two-fold. First, combined abuse of methamphetamine and cannabis was associated with relatively more widespread neurocognitive impairment than methamphetamine abuse alone. Second, increased externalizing psychopathology and poorer self-monitoring associated with methamphetamine abuse appear to persist into abstinence.

Adolescents who abused methamphetamine alone showed some limited neurocognitive dysfunction in the self-monitoring domain; however, adolescents who abused both cannabis and methamphetamine were susceptible to additional and more widespread cognitive dysfunction across several domains including verbal memory, planning, and non-verbal reasoning. Although cannabis is currently the most common secondary illicit substance for methamphetamine users,[19] few studies have examined the outcomes of concurrent methamphetamine and cannabis consumption. Our finding appears to stand in contrast to earlier pre-clinical work suggesting that methamphetamine neurotoxicity in fact attenuates the impact of certain cannabis-related behavioral and cognitive sequelae in rats,[41]. Similarly, an earlier clinical study showed no significant differences on neurocognitive outcomes in ‘pure’ methamphetamine abusers compared to those abusing both methamphetamine and cannabis,[42]. Future research should aim to scrutinize the mechanisms of apparent differential effects of single versus concomitant drug use in order to clarify under which circumstances polysubstance use may provide a protective neurocognitive effect,[21, 43].

The incidental finding that the Meth-only group largely abstained from methamphetamine use between baseline and follow-up assessments, teamed with overall consistency in the profiles of

relative individual substance consumption between the control and Meth-only groups from baseline to follow-up (i.e., the group differences in methamphetamine and nicotine exposure at baseline were maintained at follow-up, but not increased) provides an interesting perspective on the differential effects of current versus abstinent drug use. Since neither the control nor the Meth-only groups showed significant increases in lifetime exposure to any individual substance between baseline and follow-up, it seems probable that the clinical group differences that remained relevant from baseline to follow-up (increased externalizing psychopathology and poorer self-monitoring) represent the enduring correlates of substance exposure established at baseline. Indeed, this proposition is supported by other studies showing that elevated sub-diagnostic externalizing psychopathology as well as deficits in executive functions such as self-monitoring may persist long after substance use has ceased,[23,44].

A potential limitation of this study is that follow-up assessments were limited to Meth-only and control participants, and therefore comment on the long-term neurocognitive effects of concomitant methamphetamine and cannabis abuse is beyond the scope of this paper. Both a strength and potential limitation of this study is that we focus here on the correlates of substance abuse during adolescence, a critical phase of neuromaturation. It must be noted that, although the sample size was small, the findings are valuable for application within this important developmental group. However, the applicability of these findings to adult drug-using populations with longer drug use histories remains to be seen. Furthermore, relatively longer-term follow-up studies of similar adolescent samples would be useful in order to examine the longevity of substance-related effects on neurocognition.

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In summary, our findings demonstrate 1) the differential consequences on adolescent brain function and behavior of methamphetamine abuse with or without cannabis, and 2) the differential acute and long-term effects of methamphetamine abuse in adolescence. These observations contribute to accumulating literature describing clinically relevant correlates of adolescent substance abuse. Given these findings, future studies should aim to clarify the specificity and longevity of clinical and neurocognitive effects of ‘pure’ methamphetamine abuse versus concurrent methamphetamine and cannabis use by examining current users with longer substance abuse histories, as well as abstinent users at relatively longer follow-up intervals.

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Objectives: Methamphetamine abuse affects brain structure and function. Although methamphetamine and cannabis are commonly abused together, few studies have investigated the differential neurocognitive consequences of methamphetamine abuse with or without cannabis. Furthermore, the effects of drug use on the developing adolescent brain remain poorly understood. We compared neurocognitive function between adolescents with ‘pure’ methamphetamine abuse, those with comorbid methamphetamine and cannabis abuse, and healthy controls at baseline and follow-up.

Methods: Individuals residing in the greater Cape Town region and between the ages of 13 and 18 years were recruited into either Meth-only ($n = 10$), Meth-cann ($n = 10$) or healthy control ($n = 20$) groups using a quasi-experimental design. All participants underwent a comprehensive neurocognitive assessment. Substance-use variables, and psychiatric symptom counts and disinhibitory personality traits were also recorded. A portion of the Meth-only and control participants completed 12 month follow-up assessments.

Results: While the Meth-cann group demonstrated widespread neurocognitive deficits at baseline, these deficits were restricted to the self-monitoring domain in the Meth-only group at both baseline and follow-up.

Conclusions: Methamphetamine abuse with cannabis abuse is associated with significantly more neurocognitive impairment than methamphetamine abuse alone, and such deficits may be enduring.

Strengths and limitations of this study

- Strength: Identification of neurocognitive sequelae in the early phase of drug abuse
- Strength: Identification of neurocognitive sequelae of relatively 'pure' drug abuse
- Strength: Findings specific to adolescent phase
- Potential limitation: Limited sample size of all three follow-up groups
- ~~Potential limitation: findings specific to adolescent phase~~

Introduction

Pre-clinical and human data suggest that various brain regions and neurocognitive functions may be differentially vulnerable to the effects of regular heavy methamphetamine use,[1, 2, 3, 4]. For instance, human studies have shown that methamphetamine abuse may lead to broad and long-term neurocognitive sequelae in memory, attention, task switching and response inhibition domains, and that such alternations in brain function may persist for years following abstinence,[5, 6, 7]. Furthermore, the offspring of methamphetamine abusing mothers suffer lasting damaging effects on cognitive development, for example,[8, 9, 10]. There are a number of reviews that explore the neurocognitive effects of drug use (particularly methamphetamine or cannabis) in adolescents, for example [11, 12, 13]. Marijuana-using adolescents have displayed neurocognitive deficits in the memory and executive functioning domains, [13]. Furthermore, in a recent study, it was found that the primary deficit amongst methamphetamine-using adolescents is executive functioning [14]. However, these studies and many reviews focus on single drug-using adolescents. Many studies do not explore the combination of cannabis and methamphetamine use in adolescents, and the neurocognitive effects this combination has on the developing brain.

In addition to overall severe and persistent neurocognitive effects of heavy methamphetamine use, the adolescent brain may be particularly vulnerable to such effects given critical neuromaturation underway during this phase of development,[15, 16]. However, few data specifically address the question of neurocognitive sequelae of methamphetamine abuse in adolescents during the early stage of drug use trajectory. Over the 1990s and into the present, substance abuse statistics have revealed alarming increases in methamphetamine abuse rates to

the extent that methamphetamine abuse may be considered an “epidemic” in the United States,[173]. Increases in methamphetamine abuse have been noted elsewhere too: methamphetamine has recently attained the status of primary drug of abuse among adolescents in developing countries such as South Africa,[184]. This represents a dramatic shift in drug use patterns in this age group in recent years, and raises issues about the impact of methamphetamine on the developing brain during this critical time of brain development.

Despite overall increased rates of methamphetamine abuse, several fundamental questions about the consequences of such abuse remain incompletely unanswered, thus calling for more empirical work in the area. First, although drug co-administration is a common trend in worldwide patterns of drug abuse,[185], the differential consequences of methamphetamine abuse with or without cannabis use on adolescent brain function and structure are not yet clearly delineated. Second, while externalizing psychopathology commonly co-occurs with heavy methamphetamine use, the functional impact of such comorbidity remains unclear,[196,4720]. Lastly, the long-term neurocognitive outcome of adolescent methamphetamine abuse with minimal externalizing psychopathology remains an open question.

Given the worldwide pattern of drug co-administration, it is particularly challenging to examine the impact of single or specific drug use combinations in most settings. However, in the Cape Town region of South Africa, we are presented with a population of adolescent drug users who name methamphetamine as their sole drug of abuse. In this region, crystal methamphetamine is referred to as “Tik”, an onomatopoeic term in the local lingua franca, Afrikaans, for the sound

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made by heated crystals in glass receptacles used by the local community to heat and inhale methamphetamine vapors.

Our focus in this report is a neurocognitive comparison between adolescents abusing methamphetamine alone, those abusing both methamphetamine and cannabis, and healthy controls with no history of past or current substance misuse. We also examine drug-related changes in these measures over time by presenting follow-up data for a portion of the original sample. We supplement the primary neurocognitive investigation with clinical data on subthreshold (including externalizing) psychopathology, ~~and disinhibitory personality traits in this cohort.~~ We hypothesized that cognitive impairment would be worse in the combined group ('meth-cann' group) when compared to the other groups.

Methods

PARTICIPANTS

We recruited 13-18 year old English- and Afrikaans-speaking adolescents of low socioeconomic status and mixed ancestry from the Cape Town region in South Africa. Participants in the initial cohort (N = 40) were recruited into either the (1) Methamphetamine only group ("Meth-only group"; n = 10); (2) Methamphetamine and cannabis group ("Meth-cann group"; n = 10); or (3) control group (n = 20), matched for age, level of education and socio-economic status.

Participants were divided into groups based on information elicited during a clinical interview including administration of the Schedule for Affective Disorders and Schizophrenia for School Aged Children (6-18 years) Lifetime Version (K-SADS-PL;^[2148]) and DSM-IV-TR,^[4922] criteria for substance dependence. Participants in the Meth-only group endorsed diagnoses of methamphetamine abuse or dependence with current and regular methamphetamine use (more than 3 doses per week for the last 6 months) alongside minimal (i.e., sub-diagnostic threshold and low lifetime consumption) alcohol, cannabis and other substance use; participants in the Meth-cann group endorsed diagnoses of both methamphetamine and cannabis abuse or dependence, with current and regular methamphetamine and cannabis use (more than 3 doses per week for the last 6 months), alongside minimal alcohol and other substance use; the control group comprised mostly non-users (individuals with no exposure to methamphetamine, cannabis or alcohol) and a smaller number of light users (lifetime history of less than 10 doses of any illicit substances), all without past or current history of substance use disorders.

Exclusionary criteria for study participation included first language other than English or Afrikaans; current or past DSM-IV Axis I disorder including major depression, psychosis,

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anxiety, eating, conduct, childhood and pervasive developmental, and attention deficit/hyperactivity disorders; current or past use of psychotropic medication; alcohol use in excess of 8 units per month for any period of 2 months or more; a positive breathalyser result at assessment visits; evidence or report of significant medical, physical, neurological or infectious conditions that may affect assessments of brain function (e.g., diabetes, developmental delays, fetal alcohol spectrum disorders, hepatitis B or C, HIV+); history of head injury with loss of consciousness for greater than 5 minutes; history of ECT treatment; history of placement in special needs classes or academic streaming as a result of poor school performance (estimated IQ < 75); left-handedness; poor vision, claustrophobia or metal implant in the body (included for the purposes of the imaging portion of the larger study). Additional exclusionary criteria for participant groups included a negative urinary drug screen result for methamphetamine (Meth-only group) or methamphetamine/cannabis (Meth-cann group); a positive urinary drug screen result for any illicit substance (control group); a positive urinary drug screen for any other illicit substance aside from methamphetamine or cannabis where relevant (all groups). Aside from these criteria, individuals who had experimented with other drugs were not excluded, provided that they did not endorse diagnostic criteria for current or past SUD, and had not consumed more than 10 doses of the drug in their lifetime or used the drug in the ~~pervious~~previous 6 months.

A portion of participants in the original control group (n = 10) as well as all but one participant in the Meth-only group (n = 9) were followed-up 12 months after initial recruitment to examine substance use trajectory, as well as changes in ~~relevant personality and~~ neurocognitive measures over time.

MEASURES

Psychopathology

In order to minimize the possible confounding effects of psychopathological comorbidity on neurocognitive measures, our primary outcome measures of interest, we recruited only individuals with relatively modest behavioral problems (i.e., not meeting diagnostic criteria for non-substance-related disorders). In order to characterize subtle psychopathology, however, we chose to sum total sub-diagnostic threshold symptom counts from the K-SADS-PL for post-traumatic stress disorder (PTSD), attention deficit/hyperactivity disorder (ADHD), conduct disorder (CD), and oppositional-defiant disorder (ODD). Symptom counts for CD and ODD were tallied to form a composite variable representing sub-diagnostic externalizing pathology (range = 0 to 20). Previous studies have demonstrated the benefit of adopting similar means of assessing psychopathology in drug-using samples,^[2025, 2425]. ADHD symptoms were assessed separately, and were not included in the composite externalizing score, based on evidence suggesting that ADHD is inconsistently related to SUD severity, for example,^[2622] and that the diagnosis falls outside the classification of disruptive behavioral disorders categorized by social deviance ^[2723]. In addition, self-reported indices of anxiety were recorded using the Multidimensional Anxiety Scale for Children (MASC;^[2824]).

Disinhibitory personality traits

~~Disinhibitory personality traits were measured using self-rated subscales from three major self-report inventories. Specifically, impulsivity and venturesomeness were measured using the relevant subscales from the Impulsivity-Venturesomeness Scales,^[25]. Alpha reliability~~

Comment [SK1]: Removed due to Reviewer 2's feedback suggesting that this section doesn't add to the article and detracts from the findings

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coefficients for males on the Impulsivity and Venturesomeness subscales are 0.78 and 0.71 respectively, and 0.75 and 0.73 for females respectively, and the construct validity of both subscales are acceptable. Novelty seeking was measured using the relevant subscale from Cloninger's [26] Tridimensional Character Inventory. The Novelty Seeking subscale has been reported as reliable (0.79) and valid,[27, 28]. In addition, we included the Thrill and Adventure Seeking, Excitement Seeking, Disinhibition and Boredom Susceptibility subscales from Zuckerman and colleagues's [29] Sensation Seeking Scale (SSS) at the follow up assessment. Items referring directly to alcohol and drug use were excluded from the subscale scores in order to avoid contamination of these measures with measures of substance use central to group classification. Alpha coefficients measuring the internal consistency of the SSS subscales lie between 0.56 and 0.76, and the construct validity of the subscales was reported as good.

Neurocognitive battery and composite scores

A general-purpose neurocognitive test battery was selected. Due to the unavailability of current, culturally appropriate, unbiased South African tests,[3029, 3130], age-appropriate international tests with established utility in cross-cultural and multilingual contexts and in SUD studies were selected. In consultation with an Afrikaans linguistics specialist, appropriate cultural and language adaptations were made to the tests. Examples of these adaptations included replacement of items/terminology unfamiliar to South Africans, simplifications of test instructions, and substitution of items to ensure equivalent difficulty levels in both Afrikaans and English. Test instructions, stimuli, and response booklets were translated into Afrikaans and back-translated into English by independent translators. Nine composite domain scores were derived from the individual neurocognitive tests as follows:

- (1) Attention: Children's Color Trails Test (CCTT;^[3231]) times for trails 1 and 2;
Children's Memory Scale (CMS;^[3332]) numbers forward and backward subtests;
Auditory Verbal Learning Test (AVLT;^[3433]) trial 1 score.
- (2) Coordination: Dominant and non-dominant peg insertion time, peg removal time, and
number of drops on the Grooved Pegboard Test (GPT;^[3534]).
- (3) Verbal reasoning: Vocabulary and Similarities subtests from the WASI.
- (4) Non-verbal reasoning: Block Design and Matrix Reasoning subtests from the Wechsler
Abbreviated Scale of Intelligence (WASI;^[3635]).
- (5) Verbal memory: AVLT immediate and delayed recall scores, and long-term percent
retention.
- (6) Visual memory: Rey-Osterrieth Complex Figure (ROCF;^[3736]) immediate and delayed
recall scores; scores on trials 1-3, immediate and delayed recall of the CMS Dots subtest.
- (7) Verbal generativity: phonemic fluency total score for letters L, B and S; semantic fluency
total score for animal category.
- (8) Planning: ROCF copy; Tower of London;^[3837] total correct score and total moves score.
- (9) Self-monitoring: error total on the CCTT (i.e., near-misses, prompts, color sequence
errors and number sequence errors); error total on phonemic and semantic fluency tasks
(i.e., rule violations, set-loss errors and repetitions); error total on the Tower of London
(i.e., rule and time violations).

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PROCEDURE

Participants were recruited from local schools of similar sociodemographic profiles within a 10 mile radius of the testing site at Tygerberg teaching hospital. Recruiting social workers gave educational talks regarding substance misuse in the classrooms; children were then invited to speak face-to-face and one-on-one with social workers. This first contact was used to screen for basic eligibility criteria, following which interested participants were provided with study information and consent forms to take home. Thereafter, recruiting social workers made telephonic or face-to-face contact with children’s parents/guardians, finalizing written informed consent from parents/guardians and written assent from participants. Assenting participants were then invited to our testing site for the research visit, commencing with a semi-structured clinical evaluation conducted by a qualified psychiatrist. Participants also underwent physical and neurological examinations, venous blood sampling, and urine drug screening. Of the participants at initial recruitment, exclusions were made on the basis of co-morbid other drug use (n = 3), current severe mood disorder (n = 1), and repeatedly failing urine drug screens on the days of proposed testing (n = 1), resulting in a final sample of 40 participants.

Participants visited the testing site on two separate occasions to complete neurocognitive testing, at the baseline and at the follow-up visit and self-report personality measures. All testing was administered by trained professionals, and completed in participants’ home language (English or Afrikaans). As per the exclusion criteria, participants underwent urine drug screening on each testing occasion. The Western Cape Education Department and Stellenbosch University’s Ethics Committee granted written approval for the study, which was conducted in adherence to the guidelines contained in the Declaration of Helsinki,^[3938].

STATISTICAL ANALYSIS

Neurocognitive composite scores

Where appropriate, neurocognitive test measures were reverse scored so that higher scores reflected better functioning. Thereafter, composite neurocognitive scores were computed to reduce the number of variables initially examined. A hybrid method (described by Medina et al.,^[4039]) grouped measures into domains based on theoretical assumptions,^[4140] then average domain z-scores were computed. Goodness-of-fit was assessed by calculating Cronbach's alpha coefficients for each domain. We derived 10 composite neurocognitive domains, with Cronbach's alphas ranging from 0.59 to 0.86. The tests in each composite are listed above, and in Table [5-4](#) along with descriptive statistics for each measure.

After appropriate cross-checking and cleaning of data, statistical analysis was performed using SPSS version 17.0. Kolmogorov-Smirnov and Levene's tests were conducted to test for normality of data and homogeneity of variance, respectively. We examined group differences in demographic variables, as well as differences on outcome measures (within the same group over time, as well as across groups) using a series of ANOVAs. Although we explored a range of outcome measures in this analysis, the analysis was primarily of an explorative nature and so the threshold for statistical significance was set at 0.05.

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Results

SOCIO-DEMOGRAPHIC CHARACTERISTICS

The groups were well-matched on key socio-demographic variables. While there were no significant between-group differences in age, years of successfully completed education, number of school grades repeated, or socio-economic status (measured using a proxy measure of annual income) at either initial recruitment or follow-up, females and Afrikaans-speakers outnumbered males and English speakers, respectively (see Table 1).

Table 1

Socio-demographic Characteristics at Baseline Testing and 12-month Follow-up

Outcome variable	Baseline testing				12-month follow-up		
	Overall (<i>n</i> = 40)	Meth group (<i>n</i> = 10)	Meth-cann group (<i>n</i> = 10)	Control group (<i>n</i> = 20)	Overall (<i>n</i> = 19)	Meth group (<i>n</i> = 9)	Control group (<i>n</i> = 10)
Test age (in months)	188.10 (15.89)	187.90 (16.35)	189.80 (15.75)	187.35 (16.48)	198.53 (16.83)	198.22 (17.92)	198.80 (16.77)
Sex							
Female: Male	25: 15	7: 3	7: 3	11: 9	13: 6	6: 3	7: 3
First language							
English: Afrikaans	7: 33	1: 9	1: 9	5: 15	2: 17	1: 8	1: 9
Education (in years)	8.10 (1.32)	7.90 (1.45)	8.00 (1.56)	8.25 (1.16)	8.74 (1.28)	8.44 (1.33)	9.00 (1.25)
Repeated grades	0.38 (0.59)	0.40 (0.52)	0.70 (0.82)	0.20 (0.41)	0.63 (0.76)	0.78 (0.67)	0.50 (0.85)
Annual income (ZAR) ^a	56 370 (13 604)	59 389 (14 384)	54 451 (18 906)	55 819 (10 272)	56 987 (15 225)	59 095 (15 225)	55 090 (11 479)

Note. Means are presented with standard deviations in parentheses

^aPresented as a proxy measure for socio-economic status

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SUBSTANCE USE

Substance use data for both test occasions (baseline testing, and 12-month follow-up) appear in Table 2. The participant groups were well differentiated with regard to substance use. With regard to baseline, and as expected, the Meth-cann group demonstrated significantly greater cannabis lifetime exposure than both the Meth-only ($p < .001$) and control ($p < .001$) groups, whose lifetime cannabis exposure was very low. Participants in the Meth-only and Meth-cann groups had consumed a significantly greater amount of both methamphetamine ($p = .025$ and $p = .002$, respectively) and nicotine ($p = .005$ and $p = .014$, respectively) than participants in the control group; however, there was no difference in methamphetamine or nicotine exposure between the Meth-only and Meth-cann groups ($p = .546$ and $p = .725$). The three groups did not differ with regard to alcohol exposure ($F(2, 37) = 2.158$, $p = .130$, $\eta^2 = .104$).

At follow-up, there was no difference between the control and Meth-only groups with regard to alcohol or cannabis lifetime exposure ($p = .020$ and $p = .14$, respectively). Similar to baseline, participants in the Meth-only group had consumed more nicotine and methamphetamine than those in the control group at follow-up ($p = .004$ and $p < .001$, respectively).

With regard to substance use trajectory, neither alcohol nor nicotine exposure changed significantly over time for either the control ($p = .069$ and $p = .423$, respectively) or Meth-only ($p = .135$ and $p = .929$, respectively) group. Although cannabis use increased numerically in the Meth-only group over the test-retest interval, it was not significantly increased ($p = .159$). Cannabis exposure was also unchanged for the control group between baseline and follow-up ($p = .465$). Methamphetamine exposure remained zero at both testing occasions for the control

group, and did not increase significantly in the Meth-only group over the same period ($F(17, 19) = 0.001, p = .978, \eta^2 = .000$). The absence of an increase in methamphetamine use in the Meth-only group over this period was due to the fact that most (6 out of 9) participants had abstained from methamphetamine use for at least six months (i.e., no longer endorsed current methamphetamine use disorders) between the two testing occasions.

Table 2
Substance Lifetime Exposure Across Groups at Baseline Testing and 12-month Follow-up

Outcome variable	Baseline testing			12-month follow-up	
	Meth group (n = 10)	Meth-cann group (n = 10)	Control group (n = 20)	Meth group (n = 9)	Control group (n = 10)
Alcohol (standard units)	19.00 (26.45)	23.60 (28.45)	7.55 (13.84)	51.00 (58.30)	22.90 (30.95)
Nicotine (cigarettes)	5088.10 (7250.28)	4431.40 (4012.89)	286.90 (922.97)	4843.49 (3714.54)	638.60 (1443.24)
Cannabis ('joints')	5.70 (5.40)	917.70 (854.19)	0.10 (0.31)	151.67 (331.94)	0.20 (0.42)
Methamphetamine ('hits' smoked)	534.20 (531.20)	736.80 (514.53)	0 (0)	527.56 (522.82)	0 (0)

Note. Means are presented with standard deviations in parentheses

PSYCHOPATHOLOGY

No participants endorsed diagnostically significant levels of psychopathology (aside from the relevant SUDs) at initial recruitment. Looking at sub-diagnostic threshold symptom counts, the Meth-only group demonstrated significantly greater externalizing symptoms (conduct disorder and oppositional disorder symptom counts) than the control group at both baseline ($p = .024$) and follow-up ($p = .043$). In contrast, externalizing symptom counts were not elevated in the Meth-cann group at baseline. There were no other significant between-group differences in non-substance-related symptom counts. There were also no significant differences between baseline and follow-up in either the Meth-only or control groups. These clinical data are presented in Table 3.

Table 3
Sub-diagnostic Psychopathology and Self-reported Anxiety Across Groups at Baseline Testing and 12-month Follow-up

Outcome variable	Baseline testing			12-month follow-up	
	Meth group (n = 10)	Meth-cann group (n = 10)	Control group (n = 20)	Meth group (n = 9)	Control group (n = 10)
Sub-diagnostic symptom counts					
ADHD	3.50 (6.19)	4.30 (5.33)	0.80 (1.64)	3.56 (7.07)	3.60 (8.33)
PTSD	2.40 (4.53)	1.70 (1.83)	2.35 (4.39)	1.67 (4.27)	1.50 (2.76)
Externalizing composite ^a	4.80 (6.41)	3.30 (4.08)	0.60 (1.70)	7.44 (5.70)	1.90 (5.32)
MASC subtotals					
Physical symptoms	12.60 (5.87)	14.50 (7.28)	11.73 (7.89)	10.44 (10.25)	10.20 (6.83)
Harm avoidance	17.50 (5.38)	18.70 (3.71)	17.40 (5.10)	19.44 (4.98)	19.50 (3.27)
Social anxiety	12.60 (4.55)	14.00 (5.83)	12.00 (7.51)	8.11 (6.83)	9.40 (2.22)
Separation/panic	9.30 (5.23)	10.90 (5.90)	8.80 (5.57)	9.00 (7.23)	8.60 (4.03)
Total score	50.80 (13.55)	57.00 (19.77)	48.80 (21.20)	46.11 (24.64)	46.40 (9.11)

Note. Means are presented with standard deviations in parentheses. ^aTotal symptoms of conduct disorder and oppositional defiant disorder

DISINHIBITORY PERSONALITY TRAITS

Comment [SK2]: Removed due to Reviewer 2's comment

Of all the disinhibitory personality traits measured, group differences emerged only on the Novelty Seeking Scale: the Meth-cann and Meth-only groups scored significantly higher than the control group at baseline ($p = .024$). There were no other between-group differences on measures of disinhibitory personality traits at either baseline or follow-up. There were also no significant differences between baseline and follow-up for any disinhibitory personality traits in either the Meth-only or control groups. Descriptive statistics for disinhibitory personality trait measures appear in Table 4.

Comment [SK3]: Removed to simplify the article

Table 4
Disinhibitory Personality Traits Across Groups at Baseline Testing and 12-month Follow-up

Outcome variable	Baseline testing			12-month follow up	
	Meth-group (n=10)	Meth-cann group (n=10)	Control-group (n=20)	Meth-group (n=9)	Control-group (n=10)
IVS ^a Impulsivity	9.30 (2.79)	10.30 (3.02)	9.89 (3.59)	8.89 (3.82)	7.50 (4.33)
IVS ^a Venturesomeness	8.60 (3.10)	8.70 (2.83)	8.79 (2.46)	7.22 (2.64)	7.20 (2.57)
Novelty seeking scale total	61.70 (8.90)	64.60 (7.31)	57.26 (6.68)	61.11 (9.84)	52.50 (11.52)
SSS ^b Disinhibition	-	-	-	3.44 (1.42)	2.60 (1.17)
SSS ^b Boredom susceptibility	-	-	-	3.78 (1.86)	3.70 (2.21)
SSS ^b Thrill and adventure seeking	-	-	-	4.22 (2.82)	5.90 (1.79)
SSS ^b Experience seeking	-	-	-	4.00 (1.41)	3.60 (1.71)

Note. Means are presented with standard deviations in parentheses. ^aIVS: Impulsivity-Venturesomeness Scale. ^bSSS: Sensation Seeking Scale.

NEUROCOGNITIVE PERFORMANCE

At baseline, there were significant group differences in neurocognitive test performance in the non-verbal reasoning, verbal memory, planning, and self-monitoring domains. For each of these domains, the Meth-cann group had impaired performance relative to the control group (non-verbal reasoning: $p = .012$; verbal memory: $p = .024$, planning: $p = .013$, and self-monitoring: $p < .001$). Additional group differences at baseline were observed in the verbal memory domain where the Meth-cann group performed worse than the Meth-only group ($p = .023$); and in the self-monitoring domain where the Meth-only group performed worse than the control group ($p < .001$). Impaired self-monitoring in the Meth-only group relative to the control group was maintained at follow-up ($p = .003$). There were no other significant differences either between groups at baseline or follow-up, or within groups between baseline and follow-up. Descriptive statistics for individual neurocognitive tests as well as neurocognitive composite domains appear in Table 45.

Table 45

Neurocognitive Performance Within Composite Domains at Baseline Testing and 12-month Follow-up

	Baseline testing			12-month follow-up	
	Meth group (n = 10)	Meth-cann group (n = 10)	Control group (n = 20)	Meth group (n = 9)	Control group (n = 10)
Attention ($\alpha = 0.74$)	-0.25 (0.63)	-0.43 (0.61)	0.19 (0.75)	0.02 (0.22)	0.25 (0.20)
CCTT					
Trial 1 time	25.50 (10.63)	25.10 (10.38)	19.55 (6.59)	19.11 (6.92)	18.90 (7.53)
Trial 2 time	48.40 (13.12)	53.10 (16.46)	43.65 (12.21)	42.44 (8.97)	40.60 (13.25)
CMS					
Numbers forward	6.90 (1.52)	8.00 (1.05)	7.85 (1.57)	7.11 (1.54)	7.90 (1.52)
Numbers backward	3.60 (0.70)	3.10 (0.99)	4.50 (1.54)	3.56 (1.59)	4.30 (0.82)
AVLT Trial 1	7.40 (1.96)	6.00 (1.41)	6.95 (1.96)	8.00 (2.24)	7.10 (1.66)
Coordination ($\alpha = 0.79$)	-0.22 (0.62)	-0.27 (0.50)	0.14 (0.57)	-0.08 (0.21)	0.36 (0.18)
—GPT					
—Dominant hand peg insertion time	72.00 (8.77)	75.80 (8.54)	69.65 (11.13)	71.56 (5.57)	67.20 (11.61)
—Non dominant hand peg insertion time	87.40 (14.73)	81.10 (13.40)	77.00 (13.12)	77.22 (9.72)	69.00 (8.71)
—Dominant hand peg removal time	24.70 (6.57)	25.30 (2.75)	22.75 (3.46)	23.33 (3.16)	22.90 (4.65)
—Non dominant hand peg removal time	25.20 (4.52)	26.30 (3.27)	23.20 (3.59)	25.11 (7.36)	22.80 (4.19)
—Dominant hand drops	2.60 (1.71)	3.00 (1.33)	2.95 (2.16)	2.89 (2.15)	2.60 (1.35)
—Non dominant hand drops	3.10 (1.10)	3.40 (1.96)	3.05 (2.26)	3.11 (1.76)	2.60 (1.90)
Verbal reasoning ($\alpha = 0.84$)	-0.46 (1.01)	-0.28 (0.78)	0.30 (0.90)	-0.00 (0.31)	0.34 (0.24)
WASI Vocabulary subtest	25.20 (10.30)	26.60 (6.85)	33.15 (8.45)	29.33 (12.34)	29.50 (4.88)
WASI Similarities subtest	18.20 (6.46)	19.60 (6.87)	22.60 (7.18)	22.11 (8.43)	22.30 (4.64)
Non-verbal reasoning ($\alpha = 0.78$)	-0.26 (0.92)	-0.47 (0.61)	0.34 (0.80)	0.05 (0.30)	0.07 (0.25)
WASI Block Design subtest	22.80 (10.29)	22.40 (10.76)	31.00 (11.74)	28.00 (14.93)	26.30 (12.13)
WASI Matrix Reasoning subtest	15.80 (6.63)	13.40 (4.38)	19.05 (5.05)	17.67 (8.00)	16.80 (6.78)

Verbal memory ($\alpha = 0.86$)	0.20 (0.99)	-0.60 (0.88)	0.08 (0.52)	-0.25 (0.26)	0.49 (0.24)
AVLT					
Immediate recall	10.00 (1.33)	8.30 (2.58)	10.45 (1.93)	9.11 (2.57)	10.90 (1.85)
Delayed recall	9.80 (2.04)	7.90 (3.04)	10.30 (1.90)	9.44 (3.50)	11.50 (1.96)
Long-term percent retention	94.91 (31.34)	76.61 (18.12)	87.19 (11.11)	84.01 (24.48)	100.95 (23.70)
Visual memory ($\alpha = 0.79$)	-0.14 (0.72)	-0.13 (0.62)	-0.02 (0.81)	0.29 (0.25)	0.09 (0.23)
ROCF					
Immediate recall	19.25 (6.51)	18.00 (8.01)	17.28 (7.29)	19.33 (6.51)	19.60 (4.20)
Delayed recall	18.45 (5.90)	17.55 (7.58)	17.68 (7.73)	19.22 (6.18)	19.00 (4.73)
CMS Dots					
Trials 1-3	17.30 (3.13)	16.90 (1.97)	18.10 (3.82)	20.22 (3.63)	18.50 (3.57)
Immediate recall	5.50 (1.78)	6.00 (1.63)	6.10 (1.68)	6.33 (1.94)	6.00 (2.06)
Delayed recall	5.40 (1.58)	5.80 (1.69)	6.20 (1.64)	6.56 (1.88)	5.80 (1.99)
Verbal generativity ($\alpha = 0.59$)	-0.38 (1.04)	-0.06 (0.57)	0.23 (0.72)	0.17 (0.29)	0.03 (0.25)
Phonemic fluency: total words	24.40 (9.68)	29.00 (4.76)	28.55 (6.58)	29.56 (12.47)	24.10 (10.73)
Semantic fluency: total words	13.30 (4.24)	13.70 (2.58)	15.75 (3.04)	14.56 (3.05)	15.10 (3.11)
Planning ($\alpha = 0.73$)	-0.13 (0.66)	-0.47 (0.76)	0.22 (0.66)	0.05 (0.21)	0.13 (0.20)
ROCF copy	30.40 (4.19)	29.15 (5.19)	31.48 (2.77)	30.17 (4.57)	30.55 (3.02)
Tower of London					
Total correct score	3.40 (1.51)	2.80 (1.40)	3.30 (1.38)	3.89 (1.45)	3.50 (1.35)
Total moves score	33.90 (16.29)	39.50 (13.82)	26.65 (12.36)	29.00 (11.74)	25.20 (8.27)
Self-monitoring	-0.71 (0.84)	-0.56 (0.99)	0.63 (0.40)	-0.72 (0.23)	0.68 (0.21)
CCTT total errors	0.60 (0.97)	1.10 (0.99)	0.65 (0.81)	0.89 (1.05)	0.80 (1.03)
Phonemic fluency errors	3.60 (4.86)	1.60 (0.97)	0.80 (1.06)	2.78 (3.49)	0.90 (1.10)
Semantic fluency errors	0.40 (0.70)	0.10 (0.32)	0.25 (0.55)	0.33 (0.50)	0.20 (0.42)
Tower of London total errors	2.20 (3.10)	3.20 (3.16)	0.50 (1.10)	2.22 (5.89)	0.30 (0.48)

Note. Means are presented with standard deviations in parentheses.

Discussion

The main finding of this study was two-fold. First, combined abuse of methamphetamine and cannabis was associated with relatively more widespread neurocognitive impairment than methamphetamine abuse alone. Second, increased externalizing psychopathology and poorer self-monitoring associated with methamphetamine abuse appear to persist into abstinence.

Adolescents who abused methamphetamine alone showed some limited neurocognitive dysfunction in the self-monitoring domain; however, adolescents who abused both cannabis and methamphetamine were susceptible to additional and more widespread cognitive dysfunction across several domains including verbal memory, planning, and non-verbal reasoning. Although cannabis is currently the most common secondary illicit substance for methamphetamine users,^[4519] few studies have examined the outcomes of concurrent methamphetamine and cannabis consumption. Our finding appears to stand in contrast to earlier pre-clinical work suggesting that methamphetamine neurotoxicity in fact attenuates the impact of certain cannabis-related behavioral and cognitive sequelae in rats,^[4241]. Similarly, an earlier clinical study showed no significant differences on neurocognitive outcomes in ‘pure’ methamphetamine abusers compared to those abusing both methamphetamine and cannabis,^[4342]. Future research should aim to scrutinize the mechanisms of apparent differential effects of single versus concomitant drug use in order to clarify under which circumstances polysubstance use may provide a protective neurocognitive effect,^[4621, 4443].

The incidental finding that the Meth-only group largely abstained from methamphetamine use between baseline and follow-up assessments, teamed with overall consistency in the profiles of

relative individual substance consumption between the control and Meth-only groups from baseline to follow-up (i.e., the group differences in methamphetamine and nicotine exposure at baseline were maintained at follow-up, but not increased) provides an interesting perspective on the differential effects of current versus abstinent drug use. Since neither the control nor the Meth-only groups showed significant increases in lifetime exposure to any individual substance between baseline and follow-up, it seems probable that the clinical group differences that remained relevant from baseline to follow-up (increased externalizing psychopathology and poorer self-monitoring) represent the enduring correlates of substance exposure established at baseline. Indeed, this proposition is supported by other studies showing that elevated sub-diagnostic externalizing psychopathology as well as deficits in executive function ns such as self-monitoring may persistent long after substance use has ceased,[[2023](#),[4544](#)].

A potential limitation of this study is that follow-up assessments were limited to Meth-only and control participants, and therefore comment on the long-term neurocognitive effects of concomitant methamphetamine and cannabis abuse is beyond the scope of this paper. Both a strength and potential limitation of this study is that we focus here on the correlates of substance abuse during adolescence, a critical phase of neuromaturation. It must be noted that, although the sample size was small, the findings Our findings are ~~therefore~~ valuable for application within this important developmental group. However, the applicability of these findings to adult drug-using populations with longer drug use histories remains to be seen. Furthermore, relatively longer-term follow-up studies of similar adolescent samples would be useful in order to examine the longevity of substance-related effects on neurocognition.

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In summary, our findings demonstrate 1) the differential consequences on adolescent brain function and behavior of methamphetamine abuse with or without cannabis, and 2) the differential acute and long-term effects of methamphetamine abuse in adolescence. These observations contribute to accumulating literature describing clinically relevant correlates of adolescent substance abuse. Given these findings, future studies should aim to clarify the specificity and longevity of clinical and neurocognitive effects of ‘pure’ methamphetamine abuse versus concurrent methamphetamine and cannabis use by examining current users with longer substance abuse histories, as well as abstinent users at relatively longer follow-up intervals.

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