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Neuropsychological deficits in adolescent methamphetamine abusers

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Abstract

Background—Methamphetamine (METH) is a widely abused psychostimulant that is associated with neurotoxicity and neurocognitive impairments in adults. However, the effects of METH use on neurocognitive performance of adolescents are unclear.

Methods—Fifty-four adolescent METH users and 74 age-matched comparison subjects (ages 12 to 23 years) were evaluated with a battery of neuropsychological tests. The cognitive domains evaluated include psychomotor (Symbol Digit, Trail Making), executive function (Stroop Interference task, Wisconsin Card Sort task), fine-motor speed (Grooved Pegboard), memory (Digit span and Auditory Verbal Learning Task), as well as attention and working memory (California Computerized Assessment package).

Results—METH users were slower on the Stroop Interference task than the comparison subjects ($F(1,114)=4.33, p=0.03$). METH subjects also performed worse than controls on the Wechsler Adult Intelligence Scale III/Wechsler Intelligence Scale for Children IV (WAIS/WISC) Matrices task ($F(1,114)=4.37, p=0.04$) and performed significantly worse on the Peg Board task than the comparison subjects for both the dominant ($F(1,114)=7.56, p=0.01$) and non-dominant ($F(1,114)=6.75, p=0.01$). Lastly, length of abstinence was associated with improved performance on the Peg Board test with the dominant hand ($r=-0.34$), as well as the WAIS/WISC Forward Digit Span task ($r=0.38$).

Conclusions—METH use is associated with impaired executive functions in adolescent users.

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Keywords

Amphetamine; Cognition; Human

Introduction

Methamphetamine (METH) is a psychostimulant that has an extensive history of widespread abuse (King and Ellinwood 2004). For example, the 2007 National Survey on Drug Use (NSDUH) and Health report from Substance Abuse and Mental Health Services Administration (SAMHSA) indicated that roughly 157,000 Americans 12 years or older initiated methamphetamine use in the past year, with the highest rates found in the western half of the USA. Methamphetamine use thus represents a major public health concern in part because of the neurotoxic effects of chronic consumption.

Chronic METH exposure is clearly neurotoxic in non-human subjects (Davidson et al. 2001; Woolverton et al. 1989), especially to striatal dopaminergic neurons (Kieburz et al. 1996). METH neurotoxicity was confirmed in humans using post-mortem tissue obtained from verified METH users (Mirecki et al. 2004). Additionally, neuroimaging studies consistently present evidence of decreased neuronal markers, particularly in striatal regions (Sekine et al. 2008; Johanson et al. 2006; Ernst et al. 2000; McCann et al. 2008a; McCann et al. 1998; Sekine et al. 2001; Volkow et al. 2001a; Volkow et al. 2001b). Lastly, several structural MRI studies reported alterations in cortical and subcortical volumes in adult METH users (Thompson et al. 2004; Chang et al. 2005; Jernigan et al. 2005)

Although the above morphometric differences may be the result of premorbid differences, it is also possible that these neurotoxic effects may contribute to the development of both psychiatric disorders (Cadet et al. 2003; Cadet et al. 1998) and cognitive deficits, including deficits on verbal memory, processing speed, executive function, and attention tasks (Meredith et al. 2005; Scott et al. 2007). For example, recently abstinent METH users exhibited lower dopamine transporter (DAT) binding to [^{11}C]-methylphenidate in the striatum, which was associated with motor slowing and memory impairments (Volkow et al. 2001b). Another study reported short-term memory deficits that were associated with reductions in DAT binding of [^{11}C]WIN 35428 (McCann et al. 2008b). Intravenous METH users also showed deficits in visual memory (Moon et al. 2007). Lastly, amphetamine users, more than ecstasy users, demonstrated impaired associative memory processing on functional MRI (Jager et al. 2008). However, both reduction in DAT binding and cognitive impairment may improve with prolonged abstinence, but that improvement likely depends on the interaction of drug use history and premorbid factors (Johanson et al. 2006).

While there are many studies of METH use in adults (see (Scott et al. 2007; Chang et al. 2007; Nordahl et al. 2003) for reviews), there are little data regarding the neuropsychological effects of METH use in adolescents. This paucity of data is surprising for two reasons. Firstly, METH users often initiate their use during adolescence, and secondly the adolescent brain exhibits gender- and region-specific developmental trajectories (Lenroot et al. 2007). As a result, the effects of METH may be different in adolescents compared with adults, and may result in sex-dependent alterations in cortical and subcortical morphometry, which may produce differential neurocognitive deficits. Given the high prevalence of methamphetamine use in some adolescent populations, especially in Hawaii, and the paucity of knowledge regarding their neuropsychological function, the current study evaluated the cognitive function of adolescent methamphetamine users and age-and-education-matched comparison subjects on a battery of neuropsychological tests. Based on prior cognitive studies performed in adult METH users,

and the limited data from adolescent rats (post-natal day 40) which showed more resistance to METH-mediated neurotoxicity, especially in the dopaminergic systems (Kokoshka et al. 2000); we predicted that adolescent METH users would exhibit similar but less severe deficits in executive function and prefrontally mediated working memory as those seen in the adult METH users.

Materials and methods

Subjects

One hundred twenty-eight subjects, including 54 METH users and 75 healthy comparison non-drug users, were screened and enrolled in the study. Subjects were included in the study only if they fulfilled the following criteria: (1) male or female ages 12 to 23 years; (2) residing on the island of Oahu, HI; (3) willing and able to comply with study procedures; (4) able to verbalize understanding of the assent form (adolescent); and (5) have parent/guardian consent (if under 18 years old). In addition, METH users had to have a diagnosis of METH abuse or dependence as determined by the National Institute of Mental Health Diagnostic Interview Schedule for Children Version-IV (NIMH DISC-IV). Exclusion criteria included, (1) premorbid confounding neurological or chronic psychiatric disorder (e.g., multiple sclerosis, stroke, schizophrenia, bipolar disorder); (2) chronic severe medical condition that can confound analysis of study (e.g., kidney/liver failure, diabetes, or HIV/AIDS); (3) on medications that may confound analysis of study; and (4) pregnancy.

For subjects 18 years or older, a written consent was obtained after the entire experiment was explained to them. For subjects between 12 and 18 years of age, parental consent and child assent were obtained after the entire experiment was explained to them. The protocol and consent and assent forms were approved by the University of Hawaii Co-operative Institutional Review Board.

All subjects were evaluated with detailed medical and drug use history during face-to-face interviews by trained research staff. A board-certified Adolescent Psychiatrist (DA) additionally interviewed and performed physical and neurological evaluations on each subject. They were also evaluated with the Teen Addiction Severity Index, the Symptom Checklist-90, and the Brief Psychiatric Rating Scale to assess for psychiatric symptoms. A psychiatrist evaluated subjects for stability and a diagnosis if they reported significant psychiatric symptoms or diagnosis (currently or in the past). The METH using subjects reported more psychiatric symptoms than controls (King et al. 2010). Psychiatric symptoms did not correlate with neuropsychological test performance in the current experiment. A urine toxicology test was also performed to ensure that the subjects did not have drugs (cocaine, amphetamine, methamphetamine, THC, opiates, or benzodiazepenes) in their system at the time of testing. The presence of drugs could confound the performance of the neuropsychological tests.

Neuropsychological tests

Standard neuropsychological tests—All subjects completed a neuropsychological test battery sensitive to functional deficits associated with injury to the frontal lobe and the striatum. The battery included measures of: (1) psychomotor speed: Trail Making Tests (TMT A: psychomotor A) and Wechsler Adult Intelligence Scale/Wechsler Intelligence Scale for Children Symbol Digit Modalities; (2) finemotor speed: Grooved Pegboard (Kleve, 1963); (3) verbal memory: Rey Auditory Verbal Learning Test (AVLT) (Rey 1941) and WAIS/WISC-IV Digit Span; (4) executive function: Stroop Color Interference Test (Stroop 1935) and TMT B; Wisconsin Card Sort Test; (5) Verbal Intelligence: Wechsler Adult Intelligence Scale/Wechsler Intelligence Scale for Children (WAIS/WISC-IV)

vocabulary test; (6) Spatial Organization: Rey Osterrieth Complex Figure Test; WAIS/WISC-IV Matrices.

California Computerized Assessment Package (CalCAP) (Miller 1990)—Since adult METH subjects were shown to have deficits on this task, all subjects also completed a customized version of the California Computerized Assessment Package as described previously (Chang et al. 2002). Briefly, the CalCAP involves computerized measurements of focused and sustained attention, and reaction time. The customized CalCAP used in the current study includes nine separate tasks. Two of the tasks measure simple reaction time and single digit recognition. Four of the tests require working memory (a one-back cued response task that the subject responded whenever “X” follows “A”; a one-back task that the subject responded when two numbers appear consecutively; a one-increment task that the subject responded when two numbers were in ascending sequence; and a two-back task that the subject responded when the current target was the same as that appeared two earlier in the sequence). Three of the tests require visual discrimination and attention (degraded words with distracters that appear in the periphery of the screen; a response-reversal task in which subjects had to ignore the center of the screen and rapidly scan for targets that appeared in the periphery; a form-discrimination task that subjects were asked to decide whether two out of three abstract forms were identical).

Statistical analyses

Data were analyzed using Systat version 10 (SAS Institute Inc., Cary, NC). Statistical significance was defined as P values < 0.05 . The t test and Fisher’s exact test were used to compare demographic characteristics of METH users and non-METH users. The neuropsychological data (Tables 1 and 2, Fig. 1) were analyzed by an analysis of covariance (ANCOVA), with METH status (METH user vs. Comparison subject), and Gender as the main factors and Age, Wechsler Vocabulary score, and Pack Years as the covariates (see below). The ANCOVAs were performed with a Bonferroni correction to adjust for multiple comparisons. Significant effects were analyzed further by Bonferroni’s post-hoc tests. Partial correlations between METH use characteristics and neuropsychological test performance and CalCAP performance were performed, with Age and Wechsler Vocabulary Score as covariates. The partial correlations were performed with a Bonferroni correction to adjust for the large number of correlations that were performed.

Results

Subject characteristics

A two-way ANOVA with Sex and METH status as the main factors showed no difference in age between the two Sexes ($F(1,72)=1.82$) or METH status ($F(1,72)=0.22$). Similarly, no difference in years of education was found with either Sex ($F(1,72)=0.15$) or METH status ($F(1,72)=0.11$). However, the METH using subjects performed 26.4% worse than the comparison subjects on the Wechsler Vocabulary test ($F(1,85)=16.56$, $p<0.0001$). In terms of other drugs used, there were no significant differences in the lifetime marijuana use (lifetime joints: METH Status: $F(1,115)=2.94$; Gender $F(1,115)=1.23$) or the number of alcoholic drinks per week (METH Status: $F(1,119)=3.54$; Gender: $F(1,119)=1.07$). There was, however, a significant difference in nicotine use (Pack Years: METH Status: $F(1,119)=42.00$, $p<0.0001$; Gender: $F(1,119)=1.21$). The data were therefore analyzed with an Analysis of Covariance, with Age, Vocabulary Scores, and Pack Years as the covariates.

The male and female METH users show no differences in their METH usage (First Use: $F(1,36)=0.05$, $p=0.83$; Frequency of Use: $F(1,36)=0.15$, $p=0.70$; Duration of Use:

$F(1,36)=1.83, p=0.24$; Lifetime Exposure: $F(1,36)=0.05, p=0.83$; Duration of Abstinence: $F(1,36)=1.46, p=0.83$).

Effects of gender on cognitive function

Females recalled more words than males on Trial 1 of the AVLT (Gender: $F(1,114)=4.14, p=0.04$), and females cumulatively recalled more words than males in the AVLT (Gender: $F(1,114)=4.97, p=0.04$). However, on the CalCAP, males had more correct responses on the 1-back ($F(1,114)=4.86, p=0.04$) and fewer incorrect responses on the 1-back cued ($F(1,114)=3.96, p=0.05$) tasks than the female subjects.

Effects of methamphetamine use on cognitive function

The METH subjects performed 15% slower on the Interference component of the Stroop Color Interference Test than the comparison subjects ($F(1,114)=4.33, p=0.04$). The METH users also performed 13% worse than the comparison subjects on the WAIS Matrices test ($F(1,105)=4.37, p=0.04$). Lastly, the METH subjects performed significantly worse on the Pegboard task, for both the dominant ($F(1,114)=7.56, p=0.01$) and non-dominant ($F(1,114)=6.75, p=0.01$) hands.

Correlations between cognitive function and methamphetamine usage

Longer duration of abstinence correlated with better immediate and delayed recall on the Rey Complex Figure Task, as well as the forward and total WAIS/WISC Digit Span Task. Longer duration of abstinence was also associated with faster performance on the Pegboard Task for the dominant hand ($r=-0.34$). Longer duration of abstinence was also associated with improved performance on the forward digit span test ($r=0.38$).

Greater average daily use and lifetime METH use correlated with poorer performance on the Matrices task ($r=-0.46$) and lower number of categories completed on the Wisconsin Card Sort Task ($r=-0.48$), and higher number of perseverative responses in the Wisconsin Card Sort ($r=0.47$), as well as perseverative errors ($r=0.45$) and non-perseverative errors ($r=0.33$) and fewer number of conceptual level responses ($r=-0.35$).

Discussion

Adolescent METH users showed worse performance on several neuropsychological tests compared to non-drug user subjects. Specifically, METH users showed cognitive deficits involving executive functions that may be partially mediated by attentional deficits. The performance deficits appear to attenuate with longer duration of abstinence.

The primary deficit in these adolescent METH users involves executive functions. First, the METH subjects performed significantly worse in the WAIS/WISC matrices test, suggesting impairment of abstract, non-verbal reasoning abilities. Second, the METH subjects required more time to complete the Stroop interference task than the non-drug users, suggesting more difficulty with and hence required more time to resolve the conflicts or inhibit the prepotent response of reading the words. In addition, matrices performance was inversely associated with greater daily METH usage. The impaired executive function in adolescents is consistent with a recent metaanalysis of studies of adult METH users, which determined that executive function was significantly affected by METH use in adults (Scott et al. 2007).

The poor performance in tests of executive function implies that METH use impairs behavioral inhibition and regulation. Several reports indicate that METH users are more impulsive than non-drug user comparison subjects. For example, METH users are more likely to engage in “risky” sexual practices (Semple et al. 2004). METH users also showed

greater impulsivity by choosing immediate over delayed rewards (Hoffman et al. 2006). Since frontostriatal systems are critical to behavioral inhibition (Stuss and Alexander 2007), and METH is known to affect the striatal dopaminergic terminals (McCann et al. 1998), which are involved in the frontostriatal circuits, the executive function deficits in our adolescent METH users might have resulted from disrupted normal frontostriatal development. Additional research should evaluate functional and morphometric alterations in the brains of adolescent METH users to address these issues.

Some of these cognitive deficits may be transient or may recover with abstinence. Longer abstinence duration was associated with better performance on the Pegboard, in the dominant hand, and better performance on the WAIS/WISC Forward and Total digit spans, but not the Backward Digit Span, suggesting that some motor and attentional deficits in adolescent METH users may improve with prolonged abstinence. These results are also consistent with improvements on cognitive function and recovery of DAT in adult METH users (Scott et al. 2007; Volkow et al. 2001c).

Although our findings suggest that frontostriatal circuits controlling attentional processes may be particularly vulnerable to the effects of METH, the current study has several limitations. First, although we have a relatively large sample size, the numbers needed for the subgroup analyses are small, particularly the adolescent male METH users. A larger sample size would afford greater statistical power for the subgroup comparisons. Second, the self-reported data regarding METH usage may not be accurate, despite the significant amount of time spent with each subject to ascertain this information. Third, the current experiment used the WAIS III for subjects older than 16 years, and the WISC-IV test for subjects younger than 16 years old. As a result, age and test type are confounded, and this confound could have been avoided with the use of the Wechsler Abbreviated Scale of Intelligence (WASI). Fourth, METH users performed poorer on the WAIS/WISC Vocabulary subtest, and hence reflected lower verbal IQ; therefore, we co-varied their cognitive performance with their vocabulary score, but some of the cognitive deficits still may be related to poorer academic achievement. These limitations are common in human subject studies and may require clarifications with future studies or in animal models.

In summary, the current study evaluated neurocognitive test performance in adolescent METH users, an important and understudied population. METH users exhibited impairments in memory and executive function. These deficits may be related to the disruption of the developing prefrontal circuitry that mediates attention and behavioral regulation. Our findings also suggest that some of the cognitive deficits may improve with prolonged abstinence; hence, prevention measures targeting the adolescent METH users may be most effective. Longitudinal studies of adolescent METH users are needed to further determine the long-term effects of METH use in adolescents.

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Fig. 1.

This figure presents the mean and standard errors for the scores for the Wechsler Matrices test (*top panel*), the Stroop Interference Task (*middle panel*), and the Wisconsin Card Sort task (*bottom panel*). The *white bars* represent the control subjects, while the *black bars* represent the METH using subjects

Table 1

Demographics and METH use characteristics of subjects (means and standard deviations)

Subject demographics	Control (n=74)		Methamphetamine users (n=54)	
	Males (n=37)	Females (n=37)	Males (n=20)	Females (n=34)
Age (years)	18.18 (0.47)	17.14 (0.55)	18.80 (0.58)	18.09 (0.42)
Education (years)	11.16 (0.39)	10.46 (0.45)	11.18 (0.34)	10.83 (0.36)
WAIS vocabulary	42.00 (2.11)	36.00 (1.96)	31.00 (3.54)	29.00 (2.25)
Methamphetamine Use characteristics				
Age of onset (years)			15.05 (0.43)	14.67 (0.34)
Frequency (days/week)			5.42 (0.47)	5.89 (0.28)
Use (grams/day)			0.58(0.08)	1.02 (0.22)
Duration of use (months)			33.79 (8.77)	25.49 (3.28)
Abstinence (days)			127.32 (71.28)	325.27 (75.95)
Lifetime exposure (grams)			658.82 (277.51)	822.95 (310.97)

Table 2

Neuropsychological test performance in METH users and control subjects (mean, standard deviations, and *F* values from the two-way ANCOVA and correlations with METH use)

Tasks	Controls	METH users	2-way ANCOVA		
			METH effect	Sex effect	METH * sex
Matrices	21.97 (0.55)	18.31 (0.72)	4.37*	0.61	0.50
Grooved pegboard					
Dominant	66.00 (1.23)	67.73 (1.67)	6.37*	3.26	2.58
Non-dominant	71.72 (1.63)	75.54 (2.45)	5.28*	0.17	0.06
Auditory Verbal Learning Test					
Trial 1	6.73 (0.23)	6.22 (0.28)	1.44	4.14*	0.19
Trials 1–5	53.97 (1.05)	49.96 (1.26)	3.55	4.97*	0.21
Stroop task					
Color	62.36 (1.47)	64.84 (1.96)	0.97	1.34	2.82
Word	47.96 (1.12)	50.02 (1.60)	0.38	3.53*	1.13
Interference	105.41(3.36)	114.59 (3.66)	4.33*	3.83*	3.09
Sequential reaction time					
1-back cued (false positives)	2.09 (0.44)	1.65 (0.28)	0.04	3.96*	0.47
1-back (true positives)	17.78 (0.39)	17.00 (0.45)	0.10	4.46*	1.68
1-increment (reaction time)	610.45 (13.13)	635.18 (14.93)	1.77	3.62	7.14**

* <0.05

** <0.01, Bonferroni corrected