Methamphetamine Dependence and Neuropsychological Functioning: Evaluating Change During Early Abstinence*

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ABSTRACT. Objective: The purpose of this work was to assess neuropsychological functioning of individuals in early abstinence from methamphetamine dependence and to test for cognitive change over the first month of abstinence. **Method:** Methamphetamine-dependent subjects in very early abstinence from methamphetamine (4-9 days; n = 27) were compared with healthy comparison subjects (n = 28) on a test battery that evaluated five cognitive domains (attention/processing speed, learning/memory, working memory, timed executive functioning, and untimed executive functioning). A subsample of the methamphetamine-dependent subjects (n =18), who maintained abstinence for 1 month, as well as a subsample of the comparison subjects (n = 21), were retested. **Results:** At the first assessment, the methamphetamine-dependent subjects showed significantly worse performance than the comparison group on a test of processing speed; they also performed 0.31 *SD*s worse than the control group on a global battery composite score ($p < .05$). After a month of abstinence, methamphetamine-dependent subjects demonstrated slightly more cognitive improvement than healthy control subjects on the entire cognitive battery, but this difference did not approach statistical significance ($p = .33$). **Conclusions:** Our findings suggest that methamphetamine-dependent subjects do not show considerable cognitive gains in the first month of abstinence. A greater length of abstinence may be needed for cognitive improvement. (*J. Stud. Alcohol Drugs, 71,* 335-344, 2010)

METHAMPHETAMINE (MA) USE HAS been associated with various cognitive deficits (Gonzalez et al., 2004, 2007; Hoffman et al., 2006; Kalechstein et al., 2003; Monterosso et al., 2005; Paulus et al., 2003; Salo et al., 2002, 2005, 2007; Simon et al., 2000, 2002; Woods et al., 2005). In a meta-analysis of studies comparing individuals with MA abuse or dependence to healthy control subjects (Scott et al., 2007), the largest MA-associated deficits were noted in the domains of learning (d = -0.66), executive functions (d = -0.63), memory (d = -0.59), and processing speed (d = -0.52), with milder deficits in visuoconstruction (d = -0.37) and language (d = -0.34).

Despite evidence provided by meta-analytic data, which is collapsed across studies, individual MA-dependent subjects vary in the severity of cognitive deficits they exhibit (Dean and London, 2010), and not all studies of MA-abusing subjects have demonstrated weaknesses. In one study, MA-dependent subjects (n = 44), who were abstinent for a week, did not significantly differ from matched comparison subjects (n = 28) on a battery of motor functioning, verbal memory, attention/processing speed, working memory, reaction time, and executive functioning (Chang et al., 2005). Similarly, other studies did not find MA-associated weaknesses in noncomputerized neuropsychological tests (Chang et al., 2002), executive functioning (Gonzalez et al., 2004; Hoffman et al., 2006), verbal memory (Chang et al., 2002, 2005; Moon et al., 2007), and attention/working memory (Gonzalez et al., 2004).

One factor that may account for variability in the performance of MA-using subjects is the duration of abstinence from MA. It is not known whether MA-using individuals improve cognitively with abstinence and, if so, when the improvement occurs. Knowledge regarding recovery of cognitive function during abstinence could help to inform treatment interventions, particularly those that use cognitive strategies to prevent relapse (e.g., cognitive behavioral therapy). Such information could help to optimize the timing of cognitively demanding exercises.

Studies of cerebral glucose metabolism indicate that brain physiology can change substantially during abstinence from MA (Berman et al., 2008; Wang et al., 2004). In this regard, subjects who initiated abstinence from chronic MA use showed a substantial increase in local glucose metabolism, with an especially marked change in parietal cortex during the first month (Berman et al., 2008). This change may reflect

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gliosis, as hypothesized before on the basis of higher cortical glucose metabolism in abstinent MA users (abstinent weeks to several years) than in healthy control subjects (Volkow et al., 2001), and supported by evidence of higher glucose metabolism in glia than neurons in vitro (Roh et al., 1998).

Although a few longitudinal studies of cognition have been conducted in MA-using participants after the first weeks or months of abstinence in which improvements in function have been identified (Chou et al., 2007; Jaffe et al., 2005; Wang et al., 2004), these studies did not compare the performance of MA groups with control groups to account for the effects of practice on repeatedly administered cognitive tests. Thus, "improvements" in function may represent practice effects from repeated test administration, particularly on tests such as the Wisconsin Card Sorting Test (see Chou et al., 2007) in which practice effects can be large even across a 1-year interval in testing (Basso et al., 1999). Furthermore, controlled studies of cognition during abstinence may help to clarify conflicting findings from a cross-sectional study, in which MA-using participants who were abstinent for 3 months had *worse* verbal memory performance than MA-using participants who were continuously using or had relapsed during treatment (Simon et al., 2004).

To address these issues, we conducted a longitudinal study of MA-dependent subjects who initiated abstinence from MA and resided on a clinical research unit for approximately 1 month, with abstinence verified continually by urine testing. A neuropsychological test battery was administered after 4-9 days of confirmed abstinence (M = 6.19 days) and again after approximately 1 month to those participants who were willing to remain in the study. A healthy comparison group was included at both assessment times to control for practice effects in repeated measurement. Based on the meta-analytic literature showing the largest MA-associated deficits in learning, memory, executive functioning, and processing speed (Scott et al., 2007), the neuropsychological battery was heavily weighted toward these test domains.

We hypothesized that, at the first assessment, MA-dependent participants would show deficits on tests of verbal memory, executive functioning, and attention/processing speed. Because of the meager literature on the topic, we did not develop concrete hypotheses regarding neuropsychological performance after a month of abstinence. We aimed to determine if cognitive function changed during the first month of abstinence and, if so, if change differed among different cognitive domains. No similar or overlapping data are reported in any other papers.

Method

Participants

Fifty-five volunteers participated in the study; 27 met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; American Psychiatric Association, 1994), criteria for current MA dependence (MA group) but were not seeking treatment; and 28 were healthy comparison subjects with no substantial history of drug abuse or dependence (healthy comparison [HC] group). Volunteers were predominantly non-Hispanic Whites (66%), with a smaller representation of other ethnicities (African American = 16%, Hispanic = 11%, and other = 7%). All participants were recruited via advertisements placed in newspapers and on the Internet. After receiving a detailed description of the protocol, participants provided written informed consent following the guidelines of the University of California, Los Angles, Office for Protection of Research Subjects. Potential participants with current evidence or history of the following conditions were excluded on the basis of a physician-conducted history, physical examination, and laboratory tests: neurological disease (e.g., stroke, history of head trauma with loss of consciousness > 5 minutes), systemic disease, cardiovascular disease, pulmonary disease, symptomatic hepatitis or cirrhosis, or HIV infection (HIV1/HIV2 antibody screen). All participants had values within normal limits for hematocrit, plasma electrolytes, and markers for hepatic and renal function. Participants who were using prescription psychotropic medications were excluded. All subjects were administered the Structured Clinical Interview for the DSM-IV (SCID) for Axis I diagnosis (Kranzler et al., 1996). Potential MA participants were excluded if they currently met criteria for abuse or dependence on any drug other than MA, with the exception of marijuana abuse (see details in the following). Current Axis I mood or psychotic disorders (unrelated to MA dependence) were exclusionary. Phobias were not explicitly excluded. The Wender Utah Rating Scale (Ward et al., 1993) was used to retrospectively assess for symptoms of childhood attention-deficit/hyperactivity disorder but was not used for exclusion. Individuals who passed initial screening but showed frank structural brain abnormalities on magnetic resonance imaging were also excluded.

Participants in the MA group (17 men, 10 women; M_{age} = 33.90 years, SD = 7.53) all met DSM-IV criteria for MA dependence and used MA an average of 4.15 days (SD = 2.24) per week (see Table 1 for description of research participants). They also tested positive for MA in urinalysis conducted at the time of enrollment. The mean duration of regular use (i.e., three times per week or two periods of heavy episodic use per week) was 7.63 years (SD = 6.89). On days of use, the mean frequency was 5.87 (SD = 3.46) times per day, providing an intake of approximately 4.66 (SD = 5.76) grams per week. The breakdown for the usual method of MA administration was as follows: smoking (68%), snorting (12%), intravenous injection (16%), or the oral route (4%).

Two participants in the MA group met criteria for substance-induced mood disorder, and one met criteria for substance-induced psychotic disorder. Three MA partici-

Table 1. Characteristics of research participants

Variable	Entire sample (Time 1)		Subsamples (Times 1 and 2)	
	Control	MA-dependent	Control	MA-dependent
Number/group	28	27	21	18
Age, years, *M* (*SD*)	33.3 (7.9)	33.9 (7.5)	35.2 (8.0)	34.1 (6.9)
Shipley-Hartford Vocabulary score[a], *M* (*SD*)	29.4 (4.3)	28.1 (4.6)	30.3 (3.3)	28.7 (3.2)
Education, in years, *M* (*SD*)	15.1 (2.5)	12.7 (1.9)**	14.7 (2.4)	12.9 (1.7)*
Mother's education, in years, *M* (*SD*)	14.2 (2.2)	13.3 (2.6)	13.9 (2.2)	13.1 (2.8)
Wender-Utah Rating Scale, *M* (*SD*)	17.3 (18.2)	24.7 (17.2)	18.5 (20.5)	28.6 (17.6)
Ethnicity, *n*				
White	19	17	15	11
African American	7	2	4	1
Hispanic	1	5	1	4
Other	1	3	1	2
Gender, *n*				
Male	14	17	12	13
Female	14	10	9	5
Cigarette smokers, *n*	13	21**	10	14*
Duration of MA use, in years, *M* (*SD*)	–	7.6 (6.9)	–	8.0 (6.3)
Grams MA/week, *M* (*SD*)	–	4.7 (5.8)	–	5.4 (6.7)

Notes: MA = methamphetamine. [a]Taken as an index of premorbid IQ.
*Significantly different from the control group, $p < .05$; **$p < .01$.

pants met criteria for marijuana abuse but not dependence (average days of marijuana use in the last 30 days for both those with and without marijuana-abuse diagnoses was less than 2 days). In addition, one MA participant met criteria for social phobia. The diagnosis of nicotine dependence was not regularly assessed with the SCID, but most of the MA participants ($n = 21$ of 27) regularly smoked cigarettes.

Participants in the HC group (14 men, 14 women; $M_{age} = 33.29$ years, $SD = 7.88$) were naive to MA and did not meet the criteria for substance abuse or dependence (Table 1). No HC participant used a given illicit substance (other than marijuana) more than twice in their lifetime. A subset endorsed a history of infrequent marijuana use ($n = 6$). None of the HC participants met criteria for an Axis I psychiatric diagnosis, with the exception of one participant with a specific phobia of heights. Thirteen of the 28 HC participants regularly smoked cigarettes. One HC participant and one MA participant exceeded a score of 46 on the Wender Utah Rating Scale, suggestive of a history of childhood attention-deficit/hyperactivity disorder. In blood laboratory analyses, four MA participants and two HC participants tested positive for the hepatitis B virus, but no participant was determined to have clinically significant hepatic impairment as determined by liver function tests, medical examination, and review of medical history.

Nine of the MA participants who were included in the initial analyses chose not to remain in the study for a minimum of 30 days, and seven HC participants did not return to the laboratory for the second assessment (i.e., dropped out after the first assessment). After attrition, 18 MA participants and 21 HC participants completed both the first and second assessments.

Measures

The neuropsychological battery closely paralleled one that was used before, and the measures have been described in detail previously (Simon et al., 2004; also see Simon et al., 2000; the current study sample did not overlap with these studies). The areas of function and respective tests were as follows:

1. *Estimate of premorbid intellectual functioning.* The Shipley-Hartford Test of Vocabulary (Shipley, 1940) was used. It is a vocabulary test in which the participant selects the word that has the same meaning as the target word.

2. *Attention/processing speed.* Two tests were used. In the Trailmaking Test (Reitan, 1958), part A, participants draw lines to connect 25 consecutive numbers. The other test was the Stroop Test (Stroop Test–words and Stroop Test–colors; Golden, 1978). The participant read color words aloud (words) and identified the colors of the ink in which the words were presented (colors) for 45 seconds each.

3. *Working memory.* Three tests were used. In the Backward Digit Span (also known as Number Reversal, patterned after Woodcock and Johnson, 1977), the participant was asked to repeat orally, and in reverse order, digit sequences read by the experimenter. In Sentence Span (Simon et al., 2004; similar to Reading Span by Daneman and Carpenter, 1980), the participant read a series of sentences, and, after the last sentence, was to recall the last word in each of the sentences. In the Missing Digit Span test (Simon et al., 2004; patterned after Buschke, 1963), the experimenter read a string of digits aloud, followed by a string of digits that was one digit shorter; the participant was to identify which digit had been left out of the second string.

4. *Learning/memory.* In the Selective Reminding Test (a list learning alternate version adaptation of Buschke, 1973), the participant was to recall an orally presented word list on 12 consecutive trials; only words *not* recalled by the participant on the preceding trial were presented each time. In the Repeated Memory Test (Simon et al., 2004; based on stimuli from Snodgrass and Vanderwart, 1980), the experimenter presented 25 words, then 25 pictures for 1 second each; after 10 minutes (occupied by a distracter test), the participant was asked to recall and then to recognize the target from similar items.

5. *Timed executive functioning.* The Trailmaking Test, part B, is similar to the Trailmaking Test, part A, except that the participant must alternate between connecting numbers and letters in order (1-A-2-B). In the Stroop Test (Stroop Test–color/word interference), color words were printed in different colored inks, and the participant was instructed to identify the ink color while ignoring what the printed word said. In Controlled Oral Word Fluency (FAS; Borkowski et al., 1967), the participant was given three letters, one at a time, and was asked to generate a list of words that began with the specified letter. Any words were allowed as long as they were not proper names or a single word given repetitively with different endings (e.g., eat and eating).

6. *Untimed executive functioning/abstract reasoning.* The Wisconsin Card Sorting Test (Heaton et al., 1993) is a computerized test of executive functioning in which examinees categorize cards in the presence of changing environmental feedback. Participants needed to learn to change their matching strategies based on changing feedback (correct or incorrect) to be successful. In Discrimination Learning (Simon et al., 2004; similar to the concept learning subtest of the Woodcock-Johnson Psycho-Educational Battery; Woodcock and Johnson, 1977), the participant was shown a series of objects and was asked to explain how a designated object in the series differed from the other objects. The Logical Problems test (Simon et al., 2004) consisted of a series of logical problems (e.g., "If A is longer than B and C is shorter than B, what is the relationship between A and C?").

All tests—except for the Trailmaking Test, the Stroop Test, and Backward Digit Span—had alternate forms to reduce practice effects in the second test session. The Shipley-Hartford Vocabulary Test and the Wisconsin Card Sorting Test were not administered during the second assessment. In addition, the FAS test was inconsistently administered during the second assessment and could not be analyzed at that time because of small sample size. Normative data to assess severity of impairment were available for use on a few measures, including the following: Trailmaking (Bornstein, 1985; age, gender, and education adjustment), Stroop Test (Golden, 1978; age adjustment), Controlled Oral Word Fluency–FAS (Tombaugh et al., 1999; age and education adjustment), Selective Reminding (Larrabee et al., 1988; age and gender adjustment), and Wisconsin Card Sorting (Beatty, 1993; age adjustment).

Procedure

MA participants resided at the University of California, Los Angeles, General Clinical Research Center throughout the duration of the study. They were administered the first cognitive battery after at least 4 abstinent days on the research ward (M = 6.19 days, SD = 1.47). The 4-day minimum before test administration was used to allow MA to clear fully from the system (Cook et al., 1993; Harris et al., 2003). Abstinence from MA and other drugs of abuse (aside from nicotine) during the course of the study was confirmed by urine drug screens every other day. HC participants were also tested via urine screen for drug use before assessments but did not reside at the General Clinical Research Center. Once the participants provided informed consent, a physical examination was performed and a medical history taken, including collection of samples for standard blood chemistry and hematology profiles. Participants were retested with the cognitive battery approximately 1 month after their initial assessment (M = 25.44 days, SD = 3.20 for MA participants). Participants were paid $30 for participating in each cognitive assessment and received $50 more for completing both assessments. MA participants also received $60 for each week they resided at the General Clinical Research Center.

Statistical methods

Because of the number of tests performed, multivariate analyses of variance (MANOVAs) were performed for each test domain previously described: attention/processing speed, working memory, learning/memory, timed executive functioning, and untimed executive functioning. Omnibus results (Wilk's lambda) produced by the MANOVAs are reported, followed by individual t tests where appropriate. Composite cognitive-battery scores for the first assessment were constructed for each participant by standardizing each test score to the mean and standard deviation of the HC group's performance on that test; the composite score was then calculated as the mean of all standardized scores for each participant (standardized scores in which lower scores indicated better performance were multiplied by -1). Thus, composite battery scores for the MA participants represent the degree to which they deviate from the HC group's performance ($M_{\text{HC group}} = 0$). For data obtained from subjects who participated in both assessments, change scores were created by subtracting performance on the first assessment from performance on the second assessment for each test. MANOVAs were then conducted on change scores for each cognitive domain. Lastly, a composite change score was created for each participant who completed both assessments by taking the mean of the sum of his or her standardized change

scores across tests (each change score standardized to the HC sample, multiplying change scores by -1 when negative scores indicated improvement).

Results

First assessment

The two participant groups did not differ significantly in age, $t(53) = -0.29$, $p > .05$; gender, $\chi^2 = 0.34$, $p > .05$; ethnicity, White/non-White, $\chi^2 = 0.15$, $p > .05$; asymptomatic hepatitis B, $\chi^2 = 0.83$, $p > .05$; Wender Utah Rating Scale scores, $t(53) = -1.56$, $p > .05$; years of mother's education, $t(53) = 1.42$, $p > .05$; or estimated premorbid IQ, as measured by the Shipley-Hartford Vocabulary test, $t(50) = 1.07$, $p > .05$ (Table 1). The MA group had a greater proportion of smokers, $\chi^2 = 6.82$, $p < .05$, than the HC group and fewer years of education, $t(53) = 3.96$, $p < .01$, possibly because MA dependence disrupted educational engagement. Mother's education, therefore, may be a more accurate marker of educational propensity than the participant's own educational attainment (see Resnick, 1992, for similar arguments regarding educational comparisons of schizophrenic subjects).

MANOVAs comparing the performance of MA and HC participants on the first assessment were conducted on the five test domains listed and described above. A significant omnibus difference was found in the attention/processing-speed domain (Wilk's $\lambda = 2.97$, $p < .05$). Although trends toward significance were present in other cognitive domains (i.e., learning/memory, $p = .09$; timed executive functioning, $p = .09$), no other domain reached significance at the .05 level. Analysis of attention/processing-speed tests with independent-samples *t* tests revealed that the MA group performed significantly worse than the HC group on the Stroop colors subtest, $t(53) = 2.26$, $p < .05$. This effect was reduced to a nonsignificant level ($p > .05$) when participants' education was used as a covariate (see Table 2 for groups' Time 1 neuropsychological performance).

Comparison of the battery composite score between the MA and HC participants with an independent samples *t* test revealed a significant difference between the MA and HC subjects, $t(53) = 2.21$, $p < .05$, in which the MA participants performed, on average, 0.31 *SD*s worse than the control group on the entire cognitive battery. This effect was reduced to a nonsignificant level when the participant's educational attainment was used as a covariate. Lastly, within the MA group, no significant relationships were found between MA consumption variables (years of use, grams/week) and the overall battery composite score (*p*s > .05).

Because the MA withdrawal syndrome peaks within the first 24 hours but can persist for approximately the first week of abstinence (McGregor et al., 2005; consisting primarily of increased appetite and sleep, as well as dysphoria and fatigue), we sought to examine if the number of days of abstinence before the first assessment (4-9 days) was associated with cognitive performance in the MA group. Initial days of abstinence did not correlate with any of the cognitive scores at the first assessment (all *p*s > .05). Similarly, when MA subjects were categorized into early initial abstinence (Days 4-6) or later initial abstinence (Days 7-9), this independent variable was not significantly related to any of the cognitive domains in the first assessment (all Wilk's λ *p*s > .05) or the composite battery score ($p > .05$). Thus, a systematic relationship was not present between the initial days of abstinence and the first assessment scores.

Table 2. Neuropsychological test performance at assessment Time 1

Domain/tests	Control *M* (*SD*)	MA-dependent *M* (*SD*)
Attention/processing speed[c]		
Trails A[a]	29.0 (11.0)	29.3 (15.5)
Stroop–words	101.7 (19.0)	102.2 (16.6)
Stroop–colors	75.6 (11.7)	68.8 (10.5)*
Working memory		
Backward digit span	4.69 (1.54)	4.33 (1.24)
Sentence span	2.50 (0.76)	2.42 (1.03)
Missing digit span	6.46 (1.86)	6.48 (1.93)
Learning/memory		
Selective Reminding Test		
Total	120.3 (15.7)	110.3 (14.3)
Intrusions[a]	2.04 (2.56)	2.64 (3.05)
Repeated Memory Test		
Word recall	4.18 (2.87)	2.56 (2.42)
Picture recall	8.11 (2.50)	5.89 (2.42)
Word recognition	14.00 (5.00)	11.30 (4.57)
Picture recognition	19.14 (4.58)	18.04 (3.91)
Timed executive functioning		
Trails B[a]	65.4 (30.2)	68.6 (27.7)
Stroop–color/word	44.7 (8.68)	38.8 (9.52)
FAS	42.9 (10.1)	44.0 (10.0)
Untimed executive functioning		
Wisconsin Card Sorting, perseverative errors[a]	12.2 (10.9)	13.5 (9.7)
Discrimination learning	22.2 (7.02)	20.0 (7.02)
Logical problems	6.26 (1.63)	5.74 (1.85)
Composite battery score[b]	0.01 (0.60)	-0.31 (0.45)*

Notes: Sample size for the control group was *n* = 24-28 per test; for the methamphetamine (MA) group *n* = 25-27, with the exception of the Wisconsin Card Sorting test with some missing data (*n*s = 13 and 18, respectively). Unless specified, higher scores indicate better performance. FAS = Controlled Oral Word Fluency. [a]Higher scores indicate worse performance; [b]mean of all test scores standardized (*z*) to the control sample; [c]significant omnibus statistic for multivariate analysis of variance.
*$p < .05$.

Change between first and second assessments

Within the MA group, those participants who remained in the study and received the second assessment ($n = 18$) did not significantly differ from those who dropped out before the second assessment ($n = 9$) in terms of age, gender, ethnicity, smoking status, years of education, mother's years of education, Wender Utah Rating Scale score, asymptomatic hepatitis (none dropped out), years of MA use, grams of MA used/week, or estimated premorbid IQ (all *p*s > .05).

Similarly, the MA completers did not differ from those who dropped out in terms of first assessment cognitive domain scores (Wilk's λ $p > .05$) or composite cognitive battery scores ($p > .05$). Within the HC group, those participants who provided data at the second assessment ($n = 21$) were slightly older than those who dropped out of the study ($n = 7$; remain age = 35.19, drop-out age = 27.57, $p < .05$) and had marginally higher premorbid IQ estimates (remain Vocabulary = 30.25, drop-out Vocabulary = 26.20, $p = .06$); but these groups did not differ by gender, ethnicity, smoking status, years of education, mother's years of education, Wender Utah Rating Scale score, or asymptomatic hepatitis (none dropped out). With respect to the first assessment cognitive domains, the HC subjects who completed the second assessment differed from those who dropped out in the attention/processing-speed domain (Wilk's λ $p < .05$), in which those who dropped out had a slightly better performance than completers on the Stroop words test ($p < .05$). These two HC groups did not differ in other cognitive domains ($p > .05$) or composite scores ($p > .05$).

The MA and HC participants who completed the second assessment did not differ significantly in age, gender, ethnicity, years of mother's education, Wender Utah Rating Scale scores, asymptomatic hepatitis, or estimated premorbid IQ (ps > .05). As with the larger groups that completed the first assessment, the MA group had a higher proportion of smokers than the HC group ($p < .05$), and the HC group had more years of education than the MA group ($p < .05$). The interval between the first and second testing sessions was significantly longer for the HC subjects ($M = 43.50$ days, $SD = 15.81$) than the MA subjects ($M = 25.44$ days, $SD = 3.20$, $p < .01$) because of scheduling delays associated with retesting of the HC subjects. To investigate whether these differences in time between sessions affected change in cognitive scores, pairwise correlations were conducted between testing interval and change scores (test performance at the second assessment minus performance at the first assessment for each participant); none of these correlations were significant across all subjects (all ps > .05). However, when these correlations were calculated in the MA group alone, a greater interval between testing sessions (more days) was associated with *more* improvement between testing sessions on the Repeated Memory Test–picture recognition and the Logical Problems test, and *less* improvement on the Backward Digit Span test (ps < .05). Within the HC group, testing interval was uncorrelated with all cognitive change scores (all ps > .05).

To assess for differences between the HC and MA groups in change of cognitive performance between testing sessions, MANOVAs were conducted on within-subjects change scores (performance on Assessment 2 minus performance on Assessment 1) for each cognitive domain (Table 3). This was equivalent to conducting multiple repeated-measures analyses while also controlling for Type I error rate. No omnibus differences were found in change scores by cognitive domain (all Wilk's λs < 1.36, ps > .10). Similarly, no omnibus dif-

TABLE 3. Test performance of subjects who participated at two assessment times

Domains/tests	Time 1 Control *M* (*SD*)	MA *M* (*SD*)	Time 2 Control *M* (*SD*)	MA *M* (*SD*)
Attention/processing speed				
Trails A[a]	29.8 (11.5)	31.2 (18.5)	27.9 (10.2)	23.5 (4.3)
Stroop–words	101.6 (19.3)	100.2 (15.5)	105.2 (21.3)	104.8 (15.0)
Stroop–colors	73.0 (11.8)	67.1 (9.9)	75.9 (12.0)	72.4 (9.1)
Working memory				
Backward digit span	4.43 (1.33)	4.22 (1.06)	5.05 (1.83)	4.06 (1.16)
Sentence span	2.57 (0.60)	2.44 (1.04)	2.90 (0.70)	2.71 (0.92)
Missing digit span	6.14 (1.77)	6.61 (1.94)	6.24 (1.76)	6.67 (1.61)
Learning/memory				
Selective Reminding Test				
Total	120.9 (12.1)	108.2 (13.2)	117.1 (15.9)	113.1 (18.6)
Intrusions[a]	1.89 (2.64)	3.18 (3.52)	2.29 (2.83)	2.88 (2.78)
Repeated Memory Test				
Word recall	3.57 (2.18)	2.83 (2.79)	4.14 (2.87)	2.11 (1.88)
Picture recall	8.05 (2.54)	6.00 (2.77)	7.29 (2.67)	5.17 (2.53)
Word recognition	14.33 (5.07)	11.94 (4.35)	14.67 (5.09)	10.72 (4.91)
Picture recognition	19.67 (3.95)	17.56 (3.57)	20.24 (2.88)	17.61 (4.26)
Timed executive functioning				
Trails B[a]	69.5 (32.1)	72.9 (30.9)	69.0 (30.5)	69.5 (22.8)
Stroop–color/word	43.5 (7.6)	38.3 (7.8)	46.4 (10.5)	41.1 (7.5)
Untimed executive functioning				
Discrimination learning	22.0 (7.0)	19.5 (6.1)	24.8 (6.3)	21.5 (5.4)
Logical problems	6.3 (1.8)	5.5 (1.9)	7.1 (1.1)	7.4 (1.5)

Notes: Values are means (*SD*s), based on data from 19-21 participants in the control group and 19-17 participants in the methamphetamine (MA)-dependent group. The groups are subsets of larger samples that participated in Test 1. [a]Higher scores indicate worse performance.

ferences were found when the analyses were repeated using education, testing interval, or estimated IQ as covariates (all *p*s > .10).

Standardized change scores for the entire cognitive battery did not significantly differ according to group, $t(37) = -1.01$, $p = .33$, although the MA subjects did nonsignificantly demonstrate more improvement than the HC subjects (MA = 0.14; HC = -0.00). Practice/learning effects for each test, irrespective of MA or HC group, were assessed with paired-samples *t* tests (first assessment compared with the second assessment for all available subjects). Seven tests demonstrated improvement from the first to second assessment at the uncorrected .05 level (Trails A, Stroop colors, Stroop words, Stroop color/word, logical problems, discrimination learning, and sentence span). Lastly, within the MA group, MA consumption variables (years of use, grams/week) were analyzed for relation with cognitive battery change scores; no significant correlations were obtained (*p*s > .05).

Discussion

In very early abstinence (4-9 days) from MA use, MA-dependent subjects exhibited worse performance than HC subjects on one test of attention/processing speed; they also demonstrated worse performance on the cognitive battery as a whole. After approximately 1 month of abstinence, the MA subjects did not show evidence of significant improvement in any cognitive domain. Although the MA subjects did improve on the cognitive battery as a whole (0.14 *SD*s more improvement than the HC subjects), this improvement did not approach statistical significance ($p = .33$). In sum, 1 month of abstinence was not associated with considerable cognitive improvement for MA subjects.

The fact that MA subjects nonsignificantly demonstrated more improvement after 1 month than the HC subjects suggests that, with a greater length of abstinence, MA users may improve to a greater degree. For example, within the MA group, a greater number of days of abstinence was positively associated with more improvement on one test of nonverbal memory (Repeated Memory Test–picture recognition) and one test of problem solving (Logical Problems). However, a greater length of abstinence was *negatively* related to improvement on a test of working memory (Backward Digit Span) within the MA group, and it should be noted that these correlations with testing interval were not adjusted for multiple comparisons ($p < .05$, uncorrected). Thus, indications of improvement within the 1-month interval are equivocal, and additional research will be needed to determine if greater improvements can be realized with a longer length of abstinence.

Because the HC subjects outperformed the MA subjects on the overall cognitive battery during the first assessment time point, the HC subjects may have possessed a greater ability to learn and benefit from repeated testing (i.e., produce practice effects) than the MA subjects. If the HC subjects did possess such an enhanced learning ability, differential learning between groups would bias *against* finding abstinence-related improvements in the MA group (i.e., learning effect differences would mask true cognitive improvement in the MA group). Thus, it should be noted that the MA subjects nonsignificantly demonstrated greater overall improvement than the HC subjects despite this potential confound. However, because the HC subjects experienced a longer testing interval ($M = 45$ days) than the MA subjects ($M = 29$ days) because of scheduling delays getting the HC participants to return to the laboratory, it is also possible that any enhanced learning benefits for HC subjects would have been negated by their respectively longer testing interval. Nonetheless, length of testing interval was not related to cognitive change scores across subjects, nor was it related to cognitive change scores within the HC group specifically.

Across all research subjects, scores on several tests improved with repeated testing, even when these tests were administered with alternate forms. Learning effects, comfort with the testing situation, facility with task demands, and other factors can contribute to practice effects with repeated testing. As such, we strongly recommend that future research of cognitive changes during abstinence include healthy comparison groups to control for practice effects that are common in the repeated measurement of cognitive function.

During the first assessment, the MA subjects performed 0.31 *SD*s worse than the HC participants on the entire cognitive battery, with a particular weakness on one test of attention/processing speed (Stroop colors). Because most of the cognitive tests were presented in an oral or verbal format, it is possible that the MA subjects had a mild verbally mediated cognitive deficit realized across tests. The Stroop colors test is also sensitive to verbal ability because the participant needs to verbally identify ink colors. However, cognitive differences between the groups were reduced to a nonsignificant level when years of education was used as a covariate (despite the fact that the groups did not differ in estimated IQ levels or mother's education). Thus, it is possible that premorbid cognitive differences between the groups account for the majority of the variance in test scores, rather than the deficits being attributable to MA-induced toxicity. However, drug use may also reasonably interfere with successful engagement in educational activities; therefore, it is possible that educational corrections partly obscure MA-associated deficits (see Resnick, 1992, for similar considerations in schizophrenia). Drug-related educational problems in our sample would have been mostly likely to occur after high school, because most MA participants completed high school (but not college), and their heavy regular use of MA began in their early 20s. Longitudinal data collected both before and after substance abuse are needed to definitively assess the cause of MA-associated cognitive deficits in humans.

Inspection of the means and standard deviations on the first cognitive assessment revealed highly similar findings to previous studies of MA and control subjects using almost identical cognitive batteries (Simon et al., 2000, 2002). Although these previous studies did find significant differences between the MA and HC groups on multiple cognitive tests, one study had a considerably larger sample size (n = 65 per group; Simon et al., 2000), and the other study did not match the MA and the HC subjects on level of premorbid intellectual function (Simon et al., 2002). As such, we suspect that the null results currently found are partly a result of limited statistical power (small sample size) and more rigorous control of extraneous variables. Some degree of variability in the performance of MA users is also anticipated based on the multiple factors that can affect cognitive performance (e.g., premorbid variables, etc.), inevitably leading to differences between studies based on different subsets of MA subjects (Dean and London, 2010).

Normative data were available for scoring a few of the currently administered tests (Trailmaking, Verbal Fluency, Selective Reminding, Stroop, and Wisconsin Card Sorting). On the first cognitive assessment, the mean performance of the MA group generally placed in the low-average to average range (range: 16th-55th percentile). This indicates that, although the MA group did have mildly lowered scores, their mean scores did not place in the impaired range of function (e.g., ≤2nd percentile). These results are similar to the normative findings published in other MA samples by Johanson et al. (2006) and McCann et al. (2008; Stroop t scores = 43 to 46). Of note, the MA subjects in the current research were reasonably young (mean age in the early 30s) and otherwise healthy, and the mildness of their cognitive deficits may reflect brain reserve and resilience at this age of evaluation (see Satz, 1993). As studies of alcoholism have revealed interactions between age and alcohol abuse, suggesting that alcohol has greater neurotoxic effects on cognitive functions as individuals age (Rourke and Grant, 1999; Schottenbauer et al., 2007), similar interactions between MA dependence and age may be reflected in cognitive functioning.

Limitations of the current study include small sample sizes and some inequality in group characteristics. As previously described, the MA and HC groups were not equivalent in years of education, although it should be noted that years of education were unrelated to change scores between the first and second assessments. Also, although the inclusion of a control group was a strength of the current study, the HC subjects were not studied as inpatients and instead came to the laboratory on two occasions to complete the testing sessions. In contrast, the MA subjects were held on a clinical ward and were studied as inpatients to ensure sustained abstinence. The MA subjects completed daily research activities and regularly interacted with nursing and research staff; however, it is likely that MA subjects were not as active as most HC subjects who maintained work and social engagements outside of the laboratory (i.e., the MA subjects likely had more down time). Although we have no reason to believe that activity-level differences affected cognitive test scores, it is possible that the MA subjects would have demonstrated more cognitive improvement with abstinence if they were involved in consistent structured exercises, particularly treatment (no treatment was implemented in the current study). The MA group also had a higher proportion of cigarette smokers than the HC group, and smoking status has been related to cognitive performance (see reviews by Heishman et al., 1994; Mansvelder et al., 2006). Cognitive dysfunction in smokers has been related to nicotine withdrawal (e.g., Domier et al., 2007; Hendricks et al., 2006; Mendrek et al., 2006), with some effects seen very soon after the cessation of smoking (30-180 minutes). To minimize the effects of nicotine withdrawal, subjects were allowed to take breaks from the test battery and smoke as desired. Lastly, although a strength of the current study lies in the selection of subjects to exclude co-morbid conditions (e.g., other drug dependence, psychiatric diagnoses, medical conditions), it should be noted that such techniques may limit the generalizability of findings to the MA-dependent population at large, in which a high proportion of individuals have various co-morbid conditions.

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