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Longer Term Improvement in Neurocognitive Functioning and Affective Distress Among Methamphetamine Users Who Achieve Stable Abstinence

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Abstract

Chronic use of methamphetamine (MA) is associated with neuropsychological dysfunction and affective distress. Some normalization of function has been reported after abstinence, but little data is available on the possible added benefits of long-term sobriety. To address this, we performed detailed neuropsychological and affective evaluations in 83 MA-dependent individuals at a baseline visit and following an average one-year interval period. Among the 83 MA-dependent participants, 25 remained abstinent and 58 used MA at least once during the interval period. Thirty-eight non-MA-addicted, demographically matched healthy comparison (i.e., HC) participants were also examined. At baseline, both MA-dependent participants who were able to maintain abstinence and those who were not performed significantly worse than the healthy comparison subjects on global neuropsychological functioning and were significantly more distressed. At the one-year follow-up, both the long term abstainers and healthy comparison groups showed comparable global neuropsychological performance and affective distress levels, whereas the MA-dependent group who continued to use were worse than the comparison participants in terms of global neuropsychological functioning and affective distress. An interaction was observed between neuropsychological impairment at baseline, MA abstinence, and cognitive improvement, with abstinent MA-dependent participants who were neuropsychologically impaired at baseline demonstrating significantly and disproportionately greater improvement in processing speed and slightly greater improvement in motor abilities relative to the other participants. These results suggest partial recovery of neuropsychological functioning and improvement in affective distress upon sustained abstinence from MA that may extend beyond a year or more.

Keywords

Methamphetamine; dependence; drug abstinence; cognition; central nervous system; affective disorders

INTRODUCTION

Methamphetamine (MA) use has become increasingly prevalent in recent years, with an estimated 5.8% of people in the United States over age 12 reporting MA use at least once in their lives and 1.9 million reporting use over the past year (Substance Abuse and Mental Health Services Administration, 2007). MA is a highly addictive stimulant that is associated with numerous adverse consequences that are of considerable public health concern. For example, MA users are more likely to be unemployed or uninsured (Baberg, Nelesen, & Dimsdale, 1996), have poorer physical (e.g., infectious, dental, and cardiovascular diseases; e.g., Olsen, 1977) and mental (e.g., depression; Kalechstein et al., 2000) health outcomes, and experience a number of interpersonal difficulties (e.g., limited social networks; Cretzmeyer, Sarrazin, Huber, Block & Hall, 2003).

Research on the neurotoxic effects of chronic MA use in humans has demonstrated an association between MA exposure and abnormalities in brain structure and function, primarily within the frontostriatal and limbic systems. For example, studies have found reduced dopamine (DA) and dopamine transporter (DAT) levels in the striatum (e.g., Chang, Alicata, Ernst & Volkow, 2007; Johanson et al., 2006; McCann et al., 1998; Volkow et al., 2001a) and prefrontal cortex (Sekine et al., 2001; Volkow et al., 2001a), as well as reduced global serotonin transporter density (Sekine et al., 2006) in MA users. In addition, research has demonstrated MA-associated metabolic changes (e.g., reduced concentrations of N-acetylaspartate and total creatine) in the basal ganglia (Chang et al., 2007; Ernst, Chang, Leonado-Yee & Speck, 2000) and anterior cingulate cortex (Nordahl et al., 2002). In addition, approximately 40% of MA-dependent individuals experience neurocognitive problems (Rippeth et al., 2004), with a recent meta-analysis on the neurocognitive effects of MA demonstrating moderate deficits in the domains of episodic memory, executive functions, information processing speed, motor skills, language, and visuoconstruction (Scott et al., 2007), possibly reflective of fronto-striatal neurotoxicity. Chronic MA use is also associated with a number of psychiatric symptoms (e.g., suicidal ideation; Kalechstein et al., 2000) and has been associated with high rates of self-reported affective distress during periods of active use (e.g., Kalechstein et al., 2000; Zweben et al., 2004), acute withdrawal (Newton, Kalechstein, Duran, Vansluis & Ling, 2004), and early abstinence (e.g., 4–7 days; London et al., 2004). Moreover, MA-associated cognitive deficits and affective distress have been associated with a greater number of cognitive complaints and self-reported dependence in instrumental activities of daily living (IADLs; Sadek, Vigil, Grant & Heaton, 2007).

Despite considerable research on the neurobiological, neuropsychological, and psychiatric consequences of chronic MA use, the extent to which these problems persist following periods of abstinence remains to be determined. From a neurobiological standpoint, some studies have demonstrated persistent MA-induced DAT (Johanson et al., 2006; McCann et al., 1998) and serotonin transporter (Sekine et al., 2006) reductions for at least a year after last use, whereas other evidence suggests potential for recovery. For example, research has shown recovery of both striatal DAT levels and thalamic metabolism (Volkow et al., 2001a; Volkow et al., 2001b; Wang et al., 2004) as well as other MA-associated brain metabolism abnormalities such as reduced N-acetylaspartate (NAA) levels (Nordahl et al., 2005) with prolonged periods of abstinence (e.g., greater than nine months). Thus, these latter studies support the possibility of partial neural recovery following protracted periods of abstinence from MA.

Research concerning the persistence or recovery of MA-associated cognitive dysfunction following periods of abstinence from MA use has also been inconclusive, but this literature is hampered by a number of methodological weaknesses. Specifically, most studies have assessed relatively short periods of abstinence, used cross sectional methodologies, not

included appropriate comparison groups, and utilized abbreviated cognitive test batteries. Much of the existing cross-sectional research shows that despite periods of brief abstinence (e.g., less than 3 months), chronic MA users evidence deficits in a number of cognitive domains (e.g., attention, episodic memory, executive functions) relative to non-MA-using comparison groups (Kalechstein, Newton & Green, 2003; Simon, Dacey, Glynn, Rawson & Ling, 2004; McCann et al., 2008). However, some studies have found that MA users display comparable neuropsychological test performance to that of non-MA-using controls following slightly longer periods of abstinence (i.e., 8 months), suggesting there may be partial recovery of cognitive functioning (e.g., Chang et al., 2002). As such, it remains unclear to what extent MA-associated cognitive deficits improve over time with abstinence, and whether even longer periods of abstinence (i.e., a year or greater) may lead to further recovery of cognitive functioning. While a recent meta-analysis on MA-associated cognitive dysfunction found no association between length of abstinence and neuropsychological deficits in chronic MA users (Scott et al., 2007), this meta-analysis analyzed studies with the aforementioned weaknesses, with many not including information on length of abstinence. Therefore, further examination of abstinence-related changes using longitudinal designs is needed in order to provide a more rigorous evaluation of cognitive recovery following sustained periods of abstinence.

To our knowledge, very few studies have examined the effects of abstinence on cognitive functioning in MA users using a longitudinal design (Chou et al., 2007; Volkow et al., 2001b; Wang et al., 2004). As demonstrated in cross-sectional research, results from the existing longitudinal studies on the effects of abstinence on cognition in MA users yields some evidence for persistent cognitive deficits, but also for partial recovery of cognitive function following both short (i.e., two weeks; Chou et al., 2007) and long (i.e., greater than 6 months; Volkow et al., 2001b; Wang et al., 2004) periods of abstinence. For example, in the early stages of abstinence (e.g., two weeks) MA-dependent individuals demonstrated improvement on a measure of executive functioning (Wisconsin Card Sorting Test; WCST) relative to baseline, and this change was significantly associated with improvement in DAT binding (Chou et al., 2007). In addition, slight improvement in motor and verbal memory abilities in MA-dependent individuals has been demonstrated following nine months (Volkow et al., 2001b) and 17 months of abstinence (Wang et al., 2004) relative to healthy comparison participants. While the former study (Volkow et al., 2001b) did not find a significant association between improvement in cognitive functioning and neural recovery, the latter study found a significant correlation between cognitive improvement and recovery of thalamic metabolism (Wang et al., 2004). A clearer picture of the nature and extent of recovery may emerge with inclusion of a non-MA-using comparison group, and a more extensive battery of neurocognitive tests, which may allow a more thorough examination of abstinence-related changes in other domains of neuropsychological functioning known to be affected by chronic MA use (e.g., processing speed).

Research has also found high self-ratings of affective distress (e.g., depression, anxiety) in active MA users (e.g., Kalechstein et al., 2000), during acute withdrawal periods (e.g., Newton, Kalechstein, Duran, Vansluis & Ling, 2004) and following short (e.g., London et al., 2004) and more extended periods of abstinence (e.g., one year; Peck, Reback, Yang, Rotheram & Shoptaw, 2005). Mood disturbances are common in active MA users, and may be reflective of MA-associated neurobiological abnormalities (e.g., dysregulation within DA and serotonin systems; US Department of Health and Human Services, 1999). London et al. (2004) investigated the potential neural mechanisms underlying affective symptoms in MA abusers following a brief (i.e., 4–7 days) period of abstinence, and found that MA abusers showed significantly higher ratings of depression and anxiety than their healthy counterparts. Moreover, greater affective distress was significantly associated with dysfunction in brain regions that have been linked to mood disorders (e.g., limbic and

paralimbic regions). Treatment studies have also found evidence of recovery of negative affective symptoms following periods of abstinence. For example, Peck et al. (2005) found that behavioral therapy was effective in both reduction of MA use and depressive symptoms, which were sustained for a year following treatment admission. However, some studies have also reported persistent depressive symptoms despite successful abstinence from MA (e.g., Rawson et al., 2002). Thus, given the common comorbidity of affective symptoms and MA-dependence and the detrimental effects that mood dysregulation may have on recovery and treatment, research addressing the effects of abstinence on affective symptoms is clearly needed.

The primary aim of this study was to employ a longitudinal design to examine the effects of long-term abstinence (i.e., average interval period of 13 months) on neuropsychological functioning in MA-dependent individuals across numerous cognitive domains known to be adversely affected by MA, and to determine whether these effects are moderated by baseline cognitive functioning. A novel feature of our design was that we enrolled MA users, most of whom were abstinent approximately 1–2 months; thus, any “early recovery” had already occurred. This allowed us to focus on possible long term processes by comparing stable abstainers to relapsers (i.e., MA-dependent individuals who used at least once during the interval period). In addition, we included a healthy comparison sample to help distinguish actual improvement in neuropsychological functioning over time versus practice effects. We also sought to investigate whether long periods of abstinence from MA use may also be associated with subsequent improvements in affective symptoms including depression and anxiety, when compared to non-MA-using controls and MA-dependent individuals who used during the interval period. Consistent with evidence suggesting partial neurobiological, neuropsychological, and psychiatric recovery, it was hypothesized that, relative to non-MA-using healthy comparisons and MA-dependent individuals who continued to use, those who were able to remain abstinent for a protracted period of time would show at least partial recovery of MA-associated neuropsychological dysfunction and significant reduction in affective distress.

METHOD

Participants

Participants included 121 English-speaking individuals enrolled in the longitudinal NIDA-funded program project at the University of California, San Diego studying the individual and combined neurobehavioral effects of methamphetamine, Human Immunodeficiency Virus (HIV), and Hepatitis C virus (HCV). Participants were recruited from the San Diego community and substance abuse treatment programs. After providing written, informed consent, each participant underwent an extensive substance use interview, as well as a neuropsychological, medical, and psychiatric evaluation, both at a baseline visit, and again after an average 13-month ($SD = 5.6$, range 6 to 42 months) follow-up. Diagnoses for psychiatric disorders common in MA-using populations, including Major Depressive Disorder (MDD), Bipolar Disorder (BD), and Antisocial Personality Disorder (ASPD) were established using the Structured Clinical Interview for DSM-IV (SCID; First, Spitzer, Gibbon, & Williams, 1996). Attention – Deficit/Hyperactivity Disorder was assessed using the Diagnostic Interview Schedule (DIS; Robbins, Helzer, Croughan & Radcliff, 1981). Participants who met *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., DSM-IV; American Psychiatric Association, 1994) criteria for MA-dependence (MA-dependent) during their lifetime and within 18 months of their baseline visit based on the SCID (First et al., 1996) were included in the MA-dependent sample ($n = 83$). Participants in the MA-dependent group were subclassified as Abstinent ($n = 25$) provided that they did not report using MA during the time period between their baseline and follow-up visit (i.e., the interval period), or Non-Abstinent ($n = 58$) if the psychiatric evaluation revealed indicated any MA

use (i.e., at least one time) during that period. No individuals classified as Abstinent met *DSM-IV* criteria for MA abuse or dependence over the interval period whereas 25% of the Non-Abstinent group met criteria for MA abuse and 54% met criteria for MA dependence. Recency, duration, and quantity of MA use were determined by a detailed lifetime substance use interview. Each MA-dependent participant reported recent use within 90 days of their initial evaluation, yet were abstinent for at least 10 days prior to the day of testing verified by urine toxicology screen. The typical MA user was abstinent 1–2 months at baseline.

Due to the high prevalence of marijuana and alcohol use among MA-dependent individuals, participants with a history of cannabis abuse or dependence were included, as were individuals with a history of alcohol abuse within the last 12 months and lifetime alcohol dependence provided that they did not meet criteria within 12 months of their initial evaluation. Recency, duration, and quantity of marijuana and alcohol use were determined by a detailed lifetime substance use interview. While individuals meeting criteria for abuse of other substances (e.g., hallucinogens, sedatives, opioids) prior to the last 12 months were allowed, those with a history of recent (i.e., within the last 12 months) abuse or dependence of any other substance within 5 years prior to the date of their evaluation were excluded. In addition, individuals infected with HIV and HCV were included in the MA-dependent sample given the common comorbidity of such infectious diseases in MA-dependent samples. HIV infection was indicated by enzyme linked immunosorbent assays (ELISA) and a Western Blot confirmatory test and HCV diagnoses were confirmed through detection of HCV IgG antibody in plasma by ELISA.

A healthy comparison group of MA-, HIV-, and HCV-negative individuals was also included ($n = 38$). Healthy comparison subjects were excluded if they had a history of Antisocial Personality Disorder (ASPD), Attention Deficit Hyperactivity Disorder (ADHD), or lifetime *DSM-IV* dependence criteria for any other substances (e.g., marijuana, alcohol, cocaine). Six individuals in the healthy comparison group met criteria for alcohol abuse and six individuals met criteria for abuse of marijuana within the last 12 months. Only one participant included in the comparison sample met criteria for other substance abuse prior to the last 12 months. General exclusion criteria were prior histories of neurological (e.g., seizure disorders, closed head injuries, and cerebrovascular accidents) or severe psychiatric (e.g., schizophrenia, mental retardation) conditions.

Demographic, HIV, psychiatric, and neuropsychological characteristics for the three groups at baseline are presented in Table 1. The groups did not differ in terms of age, education, ethnicity, and sex (all $ps > 0.10$). The Abstinent and Non-Abstinent groups had comparable proportions of individuals infected with HCV and HIV (both $ps > 0.10$). HIV-infected individuals within the Abstinent ($n = 14$) and Non-Abstinent ($n = 34$) groups did not differ in terms of their HIV-associated disease characteristics including HIV plasma viral load, HIV CSF viral load, CD4 count, and nadir CD4 count, as well as proportion with acquired immune deficiency syndrome (AIDS), and proportion currently on highly active antiretroviral therapies (HAART; all $ps > 0.10$). In terms of psychiatric diagnoses at baseline, the three groups did not differ in the proportion of individuals diagnosed with lifetime major depressive disorder (MDD) ($p > 0.10$), although the Abstinent group had a greater proportion of individuals with a lifetime history of bipolar disorder ($n = 5$; $p < 0.05$). The Abstinent and Non-Abstinent groups did not differ in terms of proportion of individuals diagnosed with ASPD or current or lifetime ADHD (both $ps > 0.10$) at baseline. In addition, while there was a greater proportion of participants in the Non-Abstinent group relative to the Healthy Comparison participants who were neuropsychologically impaired at baseline ($p = 0.03$), the proportion of impaired participants within the Abstinent and Non-Abstinent groups did not differ, nor did the proportion of neuropsychologically impaired participants

in the Abstinent group versus the Healthy Comparison sample (both $ps > 0.10$). The groups did not differ in terms of estimated premorbid intelligence ($p > 0.05$).

Baseline MA, alcohol, and marijuana use characteristics, as well as the proportion of abstinent and relapse groups who met criteria for abuse or dependence on substances other than MA are presented in Table 2. The Abstinent and Non-Abstinent groups were comparable in most MA use characteristics, including reported age at first use, the total duration of use, and the total lifetime consumption of MA use (all $ps > 0.10$). Less than 50% of each group used MA intravenously, and these proportions were not significantly different ($p > 0.10$). Prior to the baseline visit, the Non-Abstinent group reported more recent MA use (mean = 40.2 days, SD = 20.1) than the Abstinent group (mean = 54.8 days, SD = 28.5; $p = 0.033$), yet both groups were abstinent for a minimum of 10 days prior to their baseline visit.

While the Healthy Comparisons were older than both MA groups at the time of their first use of alcohol, and used less alcohol overall (both $p's < 0.05$), the MA groups did not differ from each other on these variables (both $ps > 0.10$). However, the Non-Abstinent group did show a greater overall duration of use relative to both the Healthy Comparisons and the Abstinent group (both $p's < 0.001$). Relative to the Healthy Comparisons, the Abstinent and Non-Abstinent groups used a greater overall quantity of marijuana, for a longer period of time, and within fewer days prior to both of their visits (all $p's < 0.05$). In addition, while the Healthy Comparisons were on average, slightly older than the Abstinent group when they first used marijuana ($p = 0.063$), the two MA groups did not differ on this variable, nor did they differ in terms of any marijuana use characteristic (i.e., total duration and quantity of use, last use since both visits; all $p's > 0.10$). Relative to the Abstinent group, a greater proportion of the Healthy Comparison and Non-Abstinent groups endorsed alcohol use at least once during the interval period ($p < 0.001$). With regard to marijuana use over the interval period, a larger number of individuals who used MA over the interval period (i.e., non-abstainers) reported marijuana use over the interval period relative to the Abstinent and Healthy Comparison groups ($p < 0.001$).

Importantly, the Abstinent and Non-Abstinent groups were comparable with regard to the proportion of individuals who met criteria for dependence on substances other than MA (i.e., marijuana, alcohol, cocaine, and other substance use; all $ps > 0.10$). The proportion of individuals who met criteria for abuse of marijuana did not differ across the three groups ($p > 0.10$), although there were a greater proportion of individuals in the Non-Abstinent group who met criteria for alcohol and other substance abuse ($ps = 0.045$ and 0.007 , respectively) relative to the non-MA comparison sample. In addition, more individuals in both the Abstinent and Non-Abstinent groups met criteria for cocaine abuse relative to the healthy comparison participants ($p = 0.006$).

Procedure

Each participant was administered a comprehensive neuropsychological test battery including a measure of estimated premorbid verbal intelligence (i.e., reading portion of the Wide Range Achievement Test – Third Edition; Wilkinson, 1993), and measures assessing the following domains: executive functions, learning and memory, motor skills, speed of information processing, verbal fluency, working memory. Trained psychometrists administered the neuropsychological test batteries in accordance with manualized procedures, and the most comprehensive normative data available was used when possible, correcting for age, sex, education, and ethnicity when indicated. The following tests were included in each neuropsychological domain:

1. *Executive Functions*: Halstead Category Test (Heaton, Grant & Matthews, 1991; Reitan & Wolfson, 1993), Wisconsin Card Sorting Test – 64 Card Version

(WCST-64; Kongs, Thompson, Iverson & Heaton, 2000), Trail Making Test, Part B (Army Individual Test Battery, 1944; Heaton et al., 1991), and the Stroop Interference subtest of the Stroop Color-Word Test (Golden, 1978; Golden & Freshwater, 2002).

2. *Learning*: Immediate recall (i.e., Total Trials 1–3) measures from the Hopkins Verbal Learning Test – Revised (HVLRT-R; Benedict, Schretlen, Groninger, & Brandt, 1998; Brandt & Benedict, 2001) and Brief Visuospatial Memory Test – Revised (BVMRT-R; Benedict, 1997; Brandt & Benedict, 2001).
3. *Memory*: Delayed recall measures from the HVLRT-R (Benedict et al., 1998; Brandt & Benedict, 2001) and BVMRT-R (Benedict, 1997).
4. *Motor*: Grooved Pegboard Test (Heaton et al., 1991; Kløve, 1963).
5. *Speed of Information Processing (SIP)*: Digit Symbol and Symbol Search tests from the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Heaton, Taylor, & Manly, 2002; The Psychological Corporation, 1997), Trail Making Test, Part A (TMT; Heaton et al., 1991; Reitan & Wolfson, 1985), and the Stroop Color subtest of the Stroop Color-Word Test (Golden, 1978; Golden & Freshwater, 2002).
6. *Verbal*: Controlled Oral Word Association Test (COWAT-FAS; Benton, Hamsher, & Sivan, 1994; Gladsjo et al., 1999; Heaton et al., 1991) and semantic verbal fluency (animals; Benton et al., 1994; Heaton et al., 1991).
7. *Working Memory*: Letter Number Sequencing Test from the WAIS-III (Heaton et al., 2002; The Psychological Corporation, 1997) and the Paced Auditory Serial Addition Test (PASAT 50; Diehr, Heaton, Miller, & Grant, 1998; Heaton et al., 1991).

Each participant was also administered the Beck Depression Inventory (BDI; Beck & Steer, 1987) and the Profile of Mood States (POMS; McNair, Lorr & Droppleman, 1981) in order to assess the degree of mood symptoms and acute affective distress, respectively, within the sample. The POMS is a 65-item self-report measure of current mood states that includes items relating to six subscales (i.e., Tension, Depression, Anger, Vigor, Confusion, and Fatigue) and a Total Mood score. Higher scores on both the BDI and POMS indicate greater affective distress.

Data Analyses

Raw scores from individual neuropsychological tests comprising each domain were converted to demographically (e.g., age, education) corrected T-scores and used to derive neuropsychological domain T-scores and a global neurocognitive T-score in order to reduce the number of comparisons made across tests (i.e., reduce the risk of Type I error). A baseline global deficit score (GDS) was also computed for each individual in order to provide a summary index of each individual's baseline level of cognitive impairment (Heaton et al., 1994). Baseline GDS was computed by converting the demographically corrected T-scores on the individual neuropsychological test measures to deficit scores ranging from 0 (no impairment) to 5 (severe impairment). The following conversions were used to convert T-scores into deficit scores: $> 40T = 0$; $39T - 35T = 1$; $34T - 30T = 2$; $29T - 25T = 3$; $24T - 20T = 4$; $\leq 19T = 5$. The deficit scores were then averaged to derive the GDS. A cut-off score of 0.5 was used to classify individuals as neuropsychologically impaired at baseline, thus an individual who demonstrated a GDS greater than 0.5 (which corresponds approximately to the 16th percentile and a T-score of less than 40) would be classified as neuropsychologically impaired at baseline (Carey et al., 2004).

Repeated measures ANOVAs with time (i.e., baseline and follow-up) as the within-group variable and group (i.e., Abstinent, Non-Abstinent, and Healthy Comparison) as the between-subjects variable were used to evaluate abstinence-related changes in global cognitive functioning. Repeated measures ANOVAs with time (i.e., baseline and follow-up) as the within-group variable and group (Abstinent, Non-Abstinent, Healthy Comparison) and baseline cognitive functioning (i.e., Neuropsychological (NP) status; NP impaired, NP normal) as the between-subjects variables were used to examine the effects of baseline cognitive status on change in global cognitive functioning over time. Identical analyses were conducted to explore the relationship between baseline cognitive functioning and improvement or decline within the individual cognitive domains. Similarly, repeated measures ANOVAs with time (i.e., baseline and follow-up) as the within-group variable and group (i.e., Abstinent, Non-Abstinent, and Healthy Comparison) as the between-subjects variable were then used to also evaluate abstinence-related changes in self-reported affective symptoms. When applicable, follow-up analyses including paired samples t-tests and independent samples t-tests were used to examine within- and between-group differences, respectively.

Post hoc analyses were then conducted to evaluate whether co-morbid infectious diseases (i.e., HIV and HCV) moderated any changes in cognitive functioning. Specifically, repeated measures ANOVAs were conducted within the MA-use groups with time (i.e., baseline and follow-up global cognitive functioning) as the within-group variable and group (Abstinent, Non-Abstinent) and infectious disease status (i.e., HIV+/HIV- or HCV+/HCV-) as the between-subjects variables. Similar analyses were conducted to determine associations between HIV- and/or HCV-status and change in specific individual cognitive domains and affective distress when a significant or trend-level effect was observed. Cohen's *d* effect size estimates were used to determine magnitudes of between group differences in global neuropsychological functioning and individual neuropsychological ability domains. By convention, *d* values of 0.2, 0.5 and 0.8 correspond to small, medium, and large effect sizes (Cohen, 1988).

RESULTS

Global Cognitive Functioning and Individual Cognitive Domains

Examination of the extent to which interim MA status was associated with neuropsychological change over time revealed a significant effect of time [$F(1,118) = 55.12$, $p < 0.01$], but no group by time interaction [$F(2,188) = 2.11$, $p = 0.126$]. Post-hoc analyses revealed that at baseline, the Abstinent and Non-Abstinent groups performed more poorly overall (global T-score, $p = 0.004$; see Table 3) than the Healthy Comparison subjects. At follow-up, the cognitive performance of the MA group that remained abstinent was no longer distinguishable from the Healthy Comparisons in global cognitive performance ($p > 0.05$), whereas the Non-Abstinent group performed significantly worse than the Healthy Comparison subjects ($p < 0.01$; See Table 4).

When also taking into account the effects of baseline cognitive functioning, we observed a trend towards a significant time x group x baseline NP status interaction [$F(2,115) = 2.88$, $p = 0.061$; See Table 5], such that MA-dependent individuals who were cognitively impaired at baseline and remained abstinent for an average year long period showed disproportionate improvement over time relative to the other participants (See Figure 1). The magnitude of change for cognitively impaired Abstinent individuals ($d = 1.73$) was significant ($t = 3.66$; $p = 0.015$) and nearly three times the effect observed for the remaining participants (mean ES = 0.60, range 0.31 to 1.27; See Tables 3 and 4 for means and standard deviations). With regard to possible moderating factors, the extent of cognitive change over time within the Abstinent and Non-Abstinent groups was not significantly associated with MA use

characteristics (i.e., age of first use, last use prior to baseline visit, cumulative duration, and cumulative quantity; all $ps > 0.05$), nor or the presence of infectious diseases (i.e., HIV and HCV disease). In addition, change in functioning was unrelated to substance use characteristics that differed between the Abstinent, Non-Abstinent, and Healthy Comparison groups (i.e., alcohol, cocaine, and other substance abuse; all $ps > 0.05$).

Results examining the effects of time, group, and baseline cognitive performance on change in functioning over time within individual cognitive domains are also presented in Table 5. A significant three-way interaction was found for the SIP domain [$F(2,115) = 4.45$; $p = 0.014$], such that poorer baseline cognitive performance was associated with greater improvement, particularly for MA-dependent individuals who remained abstinent relative to the other participants. The magnitude of improvement for individuals who were cognitively impaired at baseline and remained abstinent over time reached significance ($t = 3.80$; $p = 0.013$; $d = 0.69$) and was significantly greater than the magnitude of change for other participants (all $ps < 0.05$; mean ES = 0.12, range -0.37 to 0.27). A trend for a significant three-way interaction was also found for measures of motor functioning [$F(2, 115) = 3.06$, $p = 0.051$], where a similar association was found between baseline cognitive status and improvement over time. Specifically, individuals who were cognitively impaired at baseline and remained abstinent again showed disproportionately greater improvement in motor abilities over time relative to the other participants. The magnitude of improvement over time reached significance ($t = 3.08$; $p = 0.028$, $d = 1.20$) and surpassed that of the other participants (all $ps < 0.05$, mean ES = 0.16 range -0.01 to 0.35). Importantly, within the Abstinent and Non-Abstinent groups, the improvement in speed of information processing and motor skills remained (both $ps < 0.05$) even when taking into account the effects of HIV and HCV disease status. Significant main effects of time were found for six of the seven neuropsychological test domains (i.e., executive functions, learning, memory, motor, SIP, and verbal cognitive domains; all $ps < 0.05$) suggesting an overall improvement in these cognitive domains over time.

Post hoc analyses revealed that at baseline, both the MA groups tended to score worse than the Healthy Comparisons on the majority of the individual cognitive domains. Specifically, both groups had significantly worse motor performance ($p = 0.003$), whereas on speed of information processing, learning, and executive functions, only the Non-Abstinent group differed significantly from the Healthy Comparisons ($ps < 0.05$; see Table 3). Importantly, the two MA groups did not differ from each other in terms of global or individual cognitive domain performance at baseline (all $ps > 0.05$). At follow-up, the cognitive performance of the MA group that remained abstinent was no longer distinguishable from the Healthy Comparisons in global cognitive performance ($p > 0.05$), whereas the Non-Abstinent group performed significantly worse than the Healthy Comparisons both in terms of global cognitive impairment ($p < 0.01$) and in virtually all individual cognitive domains (all $ps < 0.05$; see Table 4). The abstainers continued to perform worse than the Healthy Comparisons on working memory and executive functioning (both $ps < 0.05$). While the cognitive performances of the Abstinent group relative to the Non-Abstinent group did not differ significantly, the Abstinent group nonetheless showed a trend towards better performance relative to the Non-Abstinent group in terms of global cognitive functioning ($p = 0.089$), verbal abilities ($p = 0.089$), and speed of information processing ($p = 0.071$).

Mood Symptoms and Affective Distress

Examination of the effects of abstinence from MA over time on self-reported depressive symptomatology as assessed with the BDI revealed main effects of time [$F(1,117) = 8.99$, $p = 0.003$] and group [$F(2,117) = 15.80$, $p < 0.001$] as well as a significant time by group interaction [$F(2,117) = 8.71$, $p < 0.001$] that demonstrated significantly greater improvement in self-reported symptoms of depression for the Abstinent group over time relative to both

the Non-Abstinent group and the Healthy Comparison sample (See Figure 2). Within the Non-Abstinent and Abstinent groups, the improvement in depressive symptomatology was not significantly associated with either HIV or HCV disease status (both $ps > 0.05$). Paired samples t -tests indicated that only the Abstinent group showed a significant improvement in mood symptoms over time ($t = -3.79$; $p < 0.001$), whereas the Non-Abstinent group and Healthy Comparison sample did not show any improvement ($t = -0.74$; $p > 0.10$ and $t = 1.56$; $p > 0.10$, respectively). Post-hoc analyses revealed no differences between the Abstinent and Non-Abstinent groups in terms of self-reported mood symptoms on the BDI at either baseline or follow-up (all $ps > 0.05$). Relative to the healthy comparison group, both the Abstinent and Non-Abstinent groups endorsed significantly more mood symptoms ($p < 0.01$) at baseline and follow-up (See Tables 3 and 4).

Similarly, examination of the effects of abstinence on self-reported acute affective symptoms as measured by the Total Mood scale of the POMS also revealed a significant main effect of time [$F(1,116) = 4.95$, $p = 0.028$], and group [$F(2,116) = 8.81$, $p < 0.001$] as well as a significant time by group interaction [$F(2,116) = 4.72$, $p = 0.008$]. Specifically, the Abstinent group showed significant improvement in self-reported affective symptoms relative to both those who continued to use and healthy comparisons (See Figure 3). While the Abstinent group showed significant improvement in their affective symptoms over time ($t = 3.71$; $p = 0.001$), the Non-Abstinent group and Healthy Comparison sample did not show significant change ($t = -0.84$; $p > 0.10$ and $t = 1.14$; $p > 0.10$, respectively) (see Figure 3). At baseline, while the Abstinent and Non-Abstinent group endorsed significantly more mood symptoms at baseline on the POMS relative to the Healthy Comparisons, they did not differ from each other ($p > 0.10$). However, at follow up, while both the Abstinent and Non-Abstinent groups endorsed more depressive symptomatology on the BDI relative to the Healthy Comparisons ($p < 0.05$), only the Non-Abstinent group endorsed significantly more symptoms of affective distress on the POMS ($p < 0.01$). Further analyses within the Abstinent and Non-Abstinent groups revealed that the improvement in affective distress on the POMS was unrelated to infectious disease status (i.e., HIV and HCV infection; both $ps > 0.05$). In addition, correlational analyses revealed that the magnitude of improvement in affective distress over time within the Abstinent group on both the BDI and POMS was not associated with improvement in neuropsychological functioning (both $ps > 0.10$).

DISCUSSION

Chronic MA use is becoming increasingly prevalent and leads to a host of harmful health outcomes, including cognitive dysfunction and psychiatric complications. To our knowledge, this is the first controlled, longitudinal study of longer-term neuropsychiatric recovery from MA abuse (i.e., recovery that may extend beyond the first weeks of abstinence). Findings revealed that beyond whatever benefits might be seen in the first months of abstinence there appears to be a further period of neuropsychological recovery that may evolve over many months, perhaps as long as a year, of continued abstinence. This effect was noted particularly in MA users who were cognitively impaired at their first evaluation. The benefits of longer-term abstinence were also especially notable in improvement in mood and reduction in overall emotional distress.

In terms of global cognitive functioning, while we did not find statistically significant differential improvement over time for the groups, individuals who remained abstinent showed a greater *magnitude* of improvement over time ($d = 0.67$) relative to those who continued to use MA and a group of healthy comparison participants (mean $d = 0.38$). The extent of change in global cognitive functioning in both the Abstinent and Non-Abstinent groups was unrelated to MA use characteristics (i.e., cumulative quantity and duration of use), which is consistent with previous literature indicating minimal associations between

rates of impairment and MA use frequency, amount, or duration (Chang et al., 2002; Cherner et al., in press; Hoffman et al., 2006; Rippeth et al., 2004). Change in global cognitive functioning over time was unrelated to substance use over the interval period (i.e., alcohol and marijuana), substance abuse comorbidities upon which the groups differed (i.e., alcohol, cocaine, and other substance abuse), and infectious disease characteristics (i.e., HIV and HCV infection).

Interestingly, the magnitude of change observed in the abstinent group appeared to vary by baseline cognitive status. Consistent with previous estimates of cognitive impairment in MA-dependent samples (Rippeth et al., 2004), about 34% of our MA-dependent sample was cognitively impaired at baseline. However, of those who were cognitively impaired at baseline, only those who remained abstinent showed significant global cognitive improvement over time ($d = 1.73$) relative to the other participants (mean $d = 0.60$). A similar pattern emerged for improvement within the speed of information processing and motor domains whereby individuals who were cognitively impaired at baseline showed improvement within both domains following abstinence. While the improvement in global cognitive functioning and motor abilities only reached trend-level significance, the benefits of abstinence on information processing speed within cognitively impaired MA-dependent individuals was significant and of a large magnitude ($d = 1.23$), well exceeding the improvement in other subgroups (mean $d = 0.16$). The magnitude of improvement over time on tests of motor abilities was also notably higher for cognitively impaired MA-dependent individuals ($d = 1.09$) following abstinence relative to the other participants (mean $d = 0.16$). Collectively, these results provide evidence for partial recovery of neuropsychological functioning following extended periods of abstinence, particularly in cognitively impaired MA-dependent individuals.

Although these findings are preliminary, they are nonetheless consistent with previous research demonstrating neural recovery from MA damage as well as an association between neural recovery and partial cognitive improvement on measures of processing speed and motor abilities following intermediate (e.g., 9 months; Volkow et al., 2001; Wang et al., 2004) periods of abstinence. No significant effects were found for the remaining neuropsychological domains (i.e., verbal, learning and memory, executive functions), suggesting that while partial recovery may be possible in some cognitive domains, other MA-associated cognitive deficits may persist despite prolonged periods of abstinence. Alternatively, it may be that MA-associated deficits within these cognitive domains may take longer periods of abstinence (e.g., greater than a year) to show significant recovery. This possibility is consistent with prior reports of continued impairment on measures of learning, memory and executive functioning in MA-users following shorter periods of abstinence (McCann et al., 2008). As deficits in episodic memory and executive functioning are among the more prominent cognitive difficulties found in MA-users (Scott et al., 2007), research demonstrating persistent deficits in these domains despite periods of abstinence highlight potential cognitive targets for treatment (e.g., cognitive rehabilitation; for a review, see Cicerone et al., 2005) and may guide the development of effective intervention methods for MA-dependence. In addition, treatment methods may be enhanced with knowledge of the cognitive functions that do in fact show recovery following abstinence (i.e., information processing and motor abilities) as such strengths may be exploited in order to develop effective strategies used to compensate for more permanent MA-associated neuropsychological dysfunction. Moreover, given the association between MA-associated cognitive deficits and self-reported dependence in instrumental activities of daily living (IADLs; Sadek et al., 2007), the benefits of abstinence may extend beyond neuropsychological recovery and also carry beneficial effects for everyday functioning capabilities.

It is possible that a proportion of the cognitive improvement that was observed is in part due to practice effects, as significant main effects of time were found for the majority of the cognitive domains. To help distinguish between actual change versus practice effects, we included a healthy comparison sample. As mentioned above, cognitively impaired MA-dependent individuals who remained abstinent showed greater improvement over time relative to healthy comparisons in terms of global cognitive functioning, as well as on measures of information processing speed and motor abilities. The magnitude of change for those who were cognitively impaired and remained abstinent within the global, speed of information processing, and motor abilities ($d = 1.73$; $d = 0.69$; and $d = 1.20$, respectively) was considerably larger than that of the healthy comparisons ($d = 0.52$; $d = 0.19$; $d = 0.10$, respectively). These differences suggest that individuals who were cognitively impaired at baseline and remained abstinent may have improved over and beyond that which would be expected from practice effects alone.

An inherent limitation of our study was that we were unable to exclude both HIV- and HCV-infected participants from our study given our small sample sizes and the high degree of co-morbidity of these diseases in our samples. However, it is unlikely that the association between improvement in cognitive functioning and sustained periods of abstinence from MA-use is confounded by HIV and HCV disease characteristics. First, both of the MA-dependent groups (i.e., Abstinent and Non-Abstinent) were comparable with regard to proportion of HIV- and HCV-infected participants. In addition, the HIV-infected samples within the MA-dependent group were comparable with regard to all HIV disease characteristics (e.g., proportion with AIDS, proportion on HAART, current CD4 count, nadir CD4 count, HIV plasma and CSF viral loads). Moreover, including both HIV and HCV disease status as covariates in the statistical models did not change the observed relationship between MA abstinence and improvement in neurocognitive and affective symptoms (all $ps > 0.05$). Taken together, these findings suggest that our primary study effects were not moderated by infectious disease comorbidity.

Perhaps the most striking finding from our study was a significant association between abstinence and improvement in affective distress. Specifically, MA individuals who remained abstinent for an average year long period showed significant improvement in their affective symptoms relative to both those who continued to use and the Healthy Comparison sample. However, neither the Non-Abstinent group nor the healthy comparisons showed significant changes in affective distress over their interval periods. In addition, improvement in mood symptoms within the Abstinent group was found for both self-report measures of affective distress (i.e., BDI and POMS), and was unrelated to improvement in neuropsychological functioning, and substance use during the interval period (i.e., alcohol and marijuana use). These findings extend prior research suggesting partial recovery of mood symptoms following a brief period of abstinence (Newton et al., 2004) and sustained reductions in depressive symptoms following treatment and continued abstinence (Peck et al., 2005). Given previous research suggesting an association between mood symptoms and MA-associated brain abnormalities (e.g., glucose metabolism; London et al., 2004), it may be that the mechanisms underlying improvement in affective symptoms reflect spontaneous recovery of MA-associated neural abnormalities. Alternatively, it is possible that the improvement in mood symptoms are a reflection of recovery from social and physical health consequences that tend to result from active MA use. Regardless of the mechanisms underlying improvement, the benefits of abstinence on mood symptoms are considerable, and carry important clinical implications considering the common comorbidity of mood symptoms and MA dependence (e.g., Kalechstein et al., 2000) and the association between greater depressive symptoms and poorer treatment engagement and outcome (Hillhouse et al., 2007).

While data on longer-term restoration (i.e., beyond the first six months of abstinence) of neuropsychiatric functioning are scant in regard to MA, the literature on alcoholism has described such processes of very long term brain recovery (e.g., see reviews by Grant, 1987, and Rourke & Grant, 2009). For example, Grant, Reed & Adams (1987) reported that alcoholics who were abstinent about 1–2 months when first examined improved substantially after 2 years, and even those who were abstinent 18 months at first evaluation showed greater neuropsychological gains than re-tested controls. Further evidence of such slowly resolving “intermediate duration” disorders was reported by Rourke & Grant (1995). Thus, to the extent that insights from alcoholism may serve as a general model, it suggests that neural recovery, perhaps involving gradual processes of cellular repair, may characterize slow neurocognitive and affective normalization following long-term withdrawal of drugs such as MA.

In conclusion, while these results are preliminary, they nonetheless suggest that prolonged periods of abstinence may be associated with partial improvement in some cognitive domains, but not others, and significant improvement in self-reported affective distress. However, our results should be interpreted in the context of potential sample and methodological limitations. First, our results are limited by small sample sizes, which may have restricted our ability to detect significant effects in our analyses. Given this limitation, we emphasized trends in addition to significant findings. Second, we did not have data regarding MA use or treatment during the interval period, and thus we were unable to further examine the patterns of change within the Non-Abstinent group (e.g., early versus late interval MA use) or determine effects that may be attributable to treatment factors. In addition, while research has shown differences in neuropsychiatric functioning in substance (i.e., cocaine) abusing populations based on the treatment-seeking status (i.e., treatment-seeking or nontreatment-seeking) of the individual (e.g., Ball et al., 1994), we did not have data indicating to what degree the participants of this study who were not engaged in substance abuse treatment programs were attempting to reduce their MA-use and thus it is unknown to what extent this may have affected their neuropsychiatric functioning. Moreover, while a global deficit score (GDS) of 0.5 as a cutoff to determine neuropsychological impairment may be considered a relatively liberal approach to operationalizing impairment, research has demonstrated that this is a well validated approach in classifying impairment that is widely used in the HIV and substance use literature (i.e., Carey et al., 2004). Finally, another inherent limitation of this study was the lack of biological evidence of MA-use during periods of active use and during the interval period, and the subsequent use of arguably less reliable self-report substance use data to determine MA-use characteristics and to classify individuals into the Abstinent and/or Non-Abstinent groups. Future research with larger sample sizes is needed to examine longer term effects of MA abstinence on cognition, as well as to examine the potential benefits of MA abstinence on other factors such as instrumental activities of daily living. Such research will provide essential information that has been previously unexplored regarding the effects of abstinence from MA use on cognition, which may aid in the characterization of MA-associated cognitive deficits (e.g., which cognitive abilities are more resistant to recovery versus those that may recover) and may have important implications concerning the diagnosis and treatment of methamphetamine use disorders.

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Figure 1. Performance over time for groups based on baseline neurocognitive functioning

Note. AB = Abstinant; NA = Non-Abstinent; HC = Healthy Comparisons; NP = Baseline Neuropsychological Performance.

Figure 2. Beck Depression Inventory (BDI): Ratings of affective distress over time
Note. HC = Healthy Comparisons.

Figure 3. Profile of Mood States (POMS): Ratings of affective distress over time
 Note. HC = Healthy Comparisons.

Table 1

Demographic, HIV-Disease, Psychiatric, and Neuropsychological characteristics.

	MA-Dependent Groups		HC (n=38)	p-value	Group
	Abstinent (n=25)	Non-Abstinent (n=58)			
Demographic Characteristics					
Age (years)	36.2 (7.4)	38.5 (7.6)	35.4 (12.5)	0.262	NS
Education (years)	12.4 (2.8)	12.7 (2.3)	13.4 (1.7)	0.159	NS
Ethnicity (% Caucasian)	84.0%	75.9%	76.3%	0.680	NS
Sex (% men)	88.0%	91.4%	81.6%	0.373	NS
HCV (%)	28%	32%	0%	0.708 ^b	NS
HIV-Disease Characteristics					
HIV (%)	(n=14)	(n=34)			
	56%	59%	0%	0.825 ^b	NS
Proportion with AIDS (%)	50%	35%	0%	0.346 ^b	NS
Proportion on HAART (%)	50%	65%	0%	0.146 ^b	NS
Current CD4 Count ^a	312.0 (78.5, 531.0)	415.5 (173.0, 673.8)	0%	0.230 ^b	NS
CD4 Nadir Count ^a	145.0 (71.8, 295.3)	293.0 (104.2, 451.0)	0%	0.104 ^b	NS
Plasma HIV RNA/μl load ^a	2.6 (2.6, 5.1)	3.1 (2.6, 4.5)	0%	0.980 ^b	NS
CSF HIV RNA/μl load ^a	1.7 (1.7, 2.5)	1.7 (1.7, 2.7)	0%	0.891 ^b	NS
Psychiatric Characteristics					
MDD (% lifetime)	32.0% (n=8)	44.8% (n=26)	26.3% (n=10)	0.157	NS
BD (% lifetime)	20% (n=5)	0% (n=0)	0% (n=0)	0.002	A>NA, HC
ASPD (% lifetime)	20% (n=5)	19% (n=11)	0% (n=0)	0.913 ^b	NS
ADHD (% lifetime)	28% (n=7)	13.21% (n=7)	0% (n=0)	0.122 ^b	NS
NP at baseline (% impaired)	24%	38%	16%	0.049	NA>HC
WRAT-3 Reading	97.6 (12.1)	99.3 (10.1)	103.7 (9.4)	0.075	NS

Note. Means (SD) of raw scores unless otherwise indicated; MA = Methamphetamine; HC = Healthy Comparisons; HCV = Hepatitis C Virus (identified by anti-HCV IgG); HIV = Human Immunodeficiency Virus; AIDS = Acquired Immune Deficiency Syndrome; CSF = Cerebrospinal Fluid; CD4 = Cluster of Differentiation 4; HAART = Highly Active Antiretroviral Therapy (current); MDD = Major Depressive Disorder; BD = Bipolar Disorder; ASPD = Antisocial Personality Disorder; ADHD = Attention Deficit/Hyperactivity Disorder; NP = Baseline Neuropsychological Performance; WRAT = Wide Range Achievement Test; A = Abstinent; NA = Non-Abstinent; NS = Non-significant ($p > 0.05$); n/a = not applicable;

^aMedian (Interquartile Range);

^b These factors were exclusion criteria for enrollment into the HC group, thus, the *p*-value reflects comparison between Abstinent and Non-Abstinent group only.

Table 2

Substance Use Characteristics

	MA-Dependent Groups		HC (n=38)	p-value	Group
	Abstinent (n=25)	Non-Abstinent (n=58)			
MA Use Characteristics					
Age at first use	24.5 (8.1)	25.4 (13.3)	n/a	0.394 ^a	NS
Total duration of use (days)	3167 (1975)	2787 (2070)	n/a	0.439 ^a	NS
Total quantity of use (grams)	3153 (3009)	2136 (2628)	n/a	0.125 ^a	NS
Last use visit 1 (days)	54.8 (28.5)	40.2 (20.1)	n/a	0.033 ^a	A>NA
Last use visit 2 (days)	378.8 (107.6)	68.8 (102.3)	n/a	<0.001 ^a	A>NA
IV drug use ever (%)	48.0%	43.1%	n/a	0.681 ^a	NS
Alcohol Use Characteristics					
Age at first use	13.2 (5.0)	13.9 (3.2)	16.1 (3.4)	0.004	HC>A,NA
Total duration of use (days)	1503.0 (1647)	2331.1 (2167)	734.1 (689.2)	<0.001	NA>A,HC
Total quantity of use (units)	12519.8 (19224.4)	17124.5 (20990.1)	2274.3 (3365.4)	<0.001	A,NA>HC
Last use visit 1 (days)	360.5 (632.1)	418.0 (959.3)	541.1 (1482.6)	0.795	NS
Last use visit 2 (days)	389.3 (376.7)	239.7 (447.7)	539.6 (1583.4)	0.349	NS
Use over interval? (%yes)	36%	76%	83%	<0.001	HC,NA>A
Marijuana Use Characteristics					
Age at first use	14.9 (4.5)	16.2 (4.9)	17.9 (3.5)	0.063	HC>A
Total duration of use (days)	3094.7 (3843.4)	2940.9 (3418.9)	264.26 (528.3)	<0.001	A,NA>HC
Total quantity of use (grams)	2182.3 (3489.7)	1856.5 (3572.3)	40.32 (90.8)	0.005	A,NA>HC
Last use visit 1 (days)	1801.0 (3111.8)	1025.6 (1942.1)	3669.8 (4440.8)	0.002	HC>A,NA
Last use visit 2 (days)	2037.5 (3200.9)	1119.7 (2082.7)	3930.5 (4533.0)	0.002	HC>A,NA
Use over interval? (%yes)	32%	62%	22%	<0.001	NA>HC,A
Non-MA Abuse and Dependence					
Marijuana					
Dependence (% lifetime)	16.0% (n=4)	19.0% (n=11)	0% (n=0)	0.745 ^a	NS
Abuse (%) ^b	24.0% (n=6)	32.8% (n=19)	15.8% (n=6)	0.162	NS
Alcohol					

	MA-Dependent Groups			p-value	Group
	Abstinent (n=25)	Non-Abstinent (n=58)	HC (n=38)		
Dependence (% lifetime) ^c	32.0% (n=8)	29.3% (n=17)	0% (n=0)	0.807 ^a	NS
Abuse (%) ^b	36.0% (n=9)	37.9% (n=22)	15.8% (n=6)	0.045	NA>HC
Cocaine					
Dependence (% lifetime) ^d	16.0% (n=4)	15.5% (n=9)	0% (n=0)	0.956 ^a	NS
Abuse (%) ^c	20.0% (n=5)	10.3% (n=6)	0.0% (n=0)	0.006	A,NA>HC
Other substances					
Dependence (% lifetime) ^d	4.0% (n=4)	8.6% (n=5)	0% (n=0)	0.925 ^a	NS
Abuse (%) ^e	16.0% (n=4)	24.1% (n=14)	2.6% (n=1)	0.007	NA>HC

Note.

^aThese factors were exclusion criteria for enrollment into the HC group, thus, the *p*-value reflects comparison between Abstinent and Non-Abstinent groups only.

^bWithin last 12 months;

^cPrior to last 12 months;

^dPrior to last 5 years;

^ePrior to last 12 months; MA = Methamphetamine; HC = Healthy Comparisons; A = Abstinent; NA = Non-Abstinent; IV Drug Use = Intravenous Drug Use; NS = Non-significant (*p* > 0.10)

Neuropsychological performance (i.e., T-scores for global and individual cognitive domains) and psychiatric characteristics across groups at baseline).

Table 3

	MA-Dependent Groups		F	p-value	Group ^{a, b}
	Abstinent (n=25)	Non-Abstinent (n=58)			
Global	47.1 (5.1)	46.2 (6.1)	50.1 (5.2)	5.70	0.004
Cognitive Domains					
EF	47.0 (6.4)	45.7 (7.3)	49.5 (7.2)	3.35	0.038
Learning	45.8 (10.0)	44.8 (8.3)	49.5 (9.0)	3.35	0.039
Memory	46.0 (9.8)	45.3 (8.4)	48.8 (8.7)	1.87	0.158
Motor	45.8 (10.2)	44.3 (9.4)	51.3 (9.5)	6.21	0.003
SIP	48.7 (7.7)	47.7 (7.2)	51.5 (6.0)	3.48	0.034
Verbal	47.5 (9.1)	46.5 (9.8)	49.3 (8.6)	1.07	0.348
WM	47.2 (8.4)	49.0 (9.7)	50.5 (7.9)	1.02	0.363
Psychiatric Characteristics					
BDI ^c	15.5 (9.9)	12.5 (9.1)	3.4 (4.3)	21.00	<0.001
POMS ^c	79.1 (43.4)	71.1 (42.0)	38.2 (29.5)	11.11	<0.001

Note. Means (SD) of T-scores unless otherwise indicated; A = Abstinent; NA = Non-Abstinent; HC = Healthy Comparisons; EF = Executive Functions; SIP = Speed of Information Processing; WM = Working Memory; BDI = Beck Depression Inventory; POMS = Profile of Mood States; NS = Non-significant ($p > 0.05$);

^a Post-hoc analysis conducted using independent samples *t*-tests;

^b Group differences reflect a significance level of < 0.05 ;

^c Greater score denotes a greater number of self-reported symptoms.

Neuropsychological performance (i.e., T-scores for global and individual cognitive domains) and psychiatric characteristics across groups at follow-up.

Table 4

	MA-Dependent Groups		HC (n=38)	F	p-value	Group ^{a, b}
	Abstinent (n=25)	Non-Abstinent (n=58)				
Global	50.1 (3.6)	47.8 (6.3)	52.8 (5.1)	9.59	<0.001	HC>NA
Cognitive Domains						
EF	50.9 (5.8)	49.0 (7.5)	54.3 (5.8)	7.18	0.001	HC>A,NA
Learning	48.1 (8.6)	45.6 (9.7)	51.8 (9.1)	5.22	0.007	HC>NA
Memory	48.1 (8.6)	46.3 (10.0)	50.8 (9.0)	2.64	0.075	NS
Motor	48.7 (8.6)	46.6 (8.6)	52.2 (8.3)	4.95	0.009	HC>NA
SIP	52.6 (7.5)	49.1 (8.1)	52.8 (7.3)	3.32	0.039	HC>NA
Verbal	50.4 (7.2)	46.7 (9.4)	51.9 (7.9)	4.56	0.012	HC>NA
WM	48.4 (7.1)	48.1 (8.6)	53.4 (8.0)	5.42	0.006	HC>A,NA
Psychiatric Characteristics						
BDI ^c	9.0 (7.1)	11.6 (10.0)	4.5 (6.0)	8.46	<0.001	HC<A,NA
POMS ^c	55.3 (37.0)	67.0 (40.5)	43.3 (35.1)	4.41	0.014	HC<NA

Note. Means (SD) of T-scores unless otherwise indicated; MA = Methamphetamine; A = Abstinent; NA = Non-Abstinent; HC = Healthy Comparisons; EF = Executive Functions; SIP = Speed of Information Processing; WM = Working Memory; BDI = Beck Depression Inventory; POMS = Profile of Mood States; NS = Non-significant ($p > 0.10$);

^a Post-hoc analysis conducted using independent samples *t*-tests;

^b Group differences reflect a significance level of < 0.05 ;

^c Greater score denotes a greater number of self-reported symptoms.

Table 5

Raw data and repeated measures ANOVAs for global cognitive functioning and individual cognitive domains by group by baseline neuropsychological functioning.

Cognitive Domain	MA-Dependent Groups										Time x NP x Group	p-value
	Abstinent (n=25)				Non-Abstinent (n=58)							
	NP Impaired (n=6)	NP Normal (n=19)	NP Impaired (n=22)	NP Normal (n=36)	NP Impaired (n=6)	NP Normal (n=32)	Time	Time x Group	Time x NP			
HC (n=38)												
Global												
Baseline	41.26 (3.87)	48.93 (3.92)	40.33 (4.30)	49.82 (3.73)	43.70 (2.01)	51.32 (4.65)	0.000	0.011	0.006	0.061		
Follow-up	47.94 (3.14)	50.78 (3.60)	42.37 (5.03)	51.09 (4.40)	47.01 (2.69)	53.84 (4.68)						
EF												
Baseline	39.88 (2.79)	49.25 (5.53)	39.32 (5.38)	49.57 (5.34)	41.93 (3.87)	50.93 (6.77)	0.000	0.145	0.012	0.485		
Follow-up	47.00 (4.16)	52.13 (5.79)	43.52 (6.20)	52.39 (6.23)	49.98 (6.31)	55.12 (5.36)						
Learning												
Baseline	36.00 (10.86)	48.87 (7.66)	37.80 (7.31)	49.07 (5.50)	36.75 (4.08)	51.91 (7.46)	0.003	0.263	0.098	0.653		
Follow-up	41.42 (8.81)	50.18 (7.53)	39.16 (9.14)	49.46 (7.82)	42.17 (7.47)	53.63 (8.32)						
Memory												
Baseline	35.25 (9.50)	49.42 (7.23)	38.61 (7.28)	49.40 (6.11)	37.92 (6.75)	50.84 (7.42)	0.025	0.507	0.197	0.461		
Follow-up	42.25 (9.36)	49.92 (7.68)	39.91 (10.17)	50.13 (7.72)	40.75 (4.93)	52.64 (8.31)						
Motor												
Baseline	44.33 (8.66)	46.24 (10.82)	38.70 (7.89)	47.78 (8.61)	47.08 (9.18)	52.08 (9.49)	0.001	0.112	0.095	0.051		
Follow-up	54.00 (7.46)	47.03 (8.38)	41.32 (7.25)	49.86 (7.85)	47.00 (9.31)	53.20 (7.93)						
SIP												
Baseline	45.86 (6.54)	49.62 (7.91)	43.09 (6.51)	50.52 (6.16)	47.50 (4.21)	52.25 (6.03)	0.001	0.003	0.642	0.014		
Follow-up	54.08 (5.65)	52.07 (8.06)	43.92 (7.59)	52.22 (6.71)	46.08 (3.41)	54.04 (7.11)						
Verbal												
Baseline	43.08 (9.14)	48.87 (8.91)	41.11 (9.83)	49.75 (8.42)	47.33 (12.6)	49.69 (7.87)	0.001	0.071	0.149	0.563		
Follow-up	49.42 (7.15)	50.68 (7.33)	42.27 (9.06)	49.44 (8.71)	50.25 (6.55)	52.22 (8.21)						
WM												
Baseline	41.33 (5.90)	49.11 (8.26)	43.07 (9.87)	52.65 (7.76)	46.25 (6.22)	51.31 (7.99)	0.131	0.105	0.627	0.914		
Follow-up	43.08 (9.44)	50.11 (5.48)	43.14 (8.00)	51.19 (7.54)	49.25 (4.71)	54.25 (8.30)						

Note. Means (SD) of T-scores unless otherwise indicated; MA = Methamphetamine; HC = Healthy Comparisons; NP = Baseline Neuropsychological Performance; EF = Executive Functions; SIP = Speed of Information Processing; WM = Working Memory.