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Misremembering Future Intentions in Methamphetamine Dependent Individuals

Jennifer E. Iudicello[1], **Erica Weber**[1], **Igor Grant**[2], **Michael Weinborn**[3], **Steven Paul Woods**[2], and **The Hiv Neurobehavioral Research Center (HNRC) Group**

[1]Joint Doctoral Program in Clinical Psychology, San Diego State University and University of California, San Diego, San Diego, California, 92183, USA

[2]Department of Psychiatry, University of California, San Diego, School of Medicine, La Jolla, California, 92093, USA

[3]School of Psychology, University of Western Australia, Crawley, WA, 6009

Abstract

Methamphetamine (MA) dependence is associated with neural abnormalities (e.g., frontal systems neurotoxicity) and corresponding cognitive deficits, including impairment in episodic memory and executive functions. This study evaluated the hypothesis that MA use is associated with impairment in memory for intentions, or prospective memory (ProM), which is an ecologically relevant aspect of episodic memory that involves the execution of a previously encoded intention at an appropriate moment in the future and is known to rely on frontal systems integrity. Thirty-nine MA-dependent individuals and 26 demographically similar non-MA-using comparison subjects were administered the Memory for Intentions Screening Test (MIST). The MA group performed significantly lower than the comparison participants on overall ProM, an effect that could not be better explained by demographics, psychiatric factors, infectious disease comorbidity, or other substance use disorders. The ProM impairment observed in the MA group was comparable on time- and event-based tasks and was marked by an increased rate of task substitution (i.e., intrusions) and loss of time (e.g., early responding) errors. Within the MA cohort, ProM impairment was associated with executive dysfunction and earlier age at first MA use. Findings suggest that individuals with MA dependence experience difficulty in the strategic components involved in the retrieval of future intentions and are discussed with regard to their implications for everyday functioning.

Keywords

Prospective memory; methamphetamine; episodic memory; executive functions; time perception; cognition

Methamphetamine (MA) is a highly addictive and neurotoxic stimulant that is associated with a number of adverse biopsychosocial consequences, including abnormalities in brain structure and function. Both animal and human research indicate that the neurotoxic effects of chronic MA exposure, while evident in several neural systems, are most prominent in the dopamine-rich fronto-striato-thalamo-cortical loops (e.g., Sonsalla, Nicklas, & Heikkila, 1989; Volkow et al., 2001). Chronic MA use has also been established as a risk factor for

Corresponding Author: S.P. Woods, Department of Psychiatry (MC: 8231), HIV Neurobehavioral Research Center and Translational Methamphetamine AIDS Research Center, 220 Dickinson Street, Suite B, San Diego, CA 92103; 619-543-5004 (ph); 619-543-1235 (fax); spwoods@ucsd.edu.

neuropsychological impairment. Approximately 40% of MA dependent individuals demonstrate neurocognitive impairment (Rippeth et al., 2004), with generally moderate deficits apparent in several cognitive domains dependent on the integrity of the frontal systems, including executive functions and psychomotor skills (Scott et al., 2007).

Nearly one-half of MA dependent individuals also demonstrate impairment in episodic memory (e.g., Rippeth et al., 2004), with a recent meta-analysis revealing medium effect sizes for chronic MA users relative to healthy adults on traditional measures of learning and delayed recall (Cohen's *d*s = −0.66 and −0.59, respectively; Scott et al., 2007). Consistent with the frontostriatal neurotoxicity of MA, the MA-associated learning and memory deficits may reflect dysregulation of the "strategic" aspects of episodic memory, which Moscovitch (1992; 1994) theorized were functions of the frontal systems that regulate executive control of encoding and retrieval (cf. the "associative/cue dependent" component, a temporolimbic function responsible for consolidation and rudimentary retrieval processes). Consistent with this hypothesis, the profile of episodic memory deficits in MA users is characterized by limited use of higher-level encoding (e.g., semantic clustering) and elevated rates of perseverations and non-semantically-related intrusion errors, but normal retention and recognition performance (Woods et al., 2005a). In further support of the strategic frontal systems hypothesis, MA-associated episodic memory deficits correlate with measures of executive functions (e.g., cognitive flexibility; Woods et al., 2005a), as well as with both neuroimaging (McCann et al., 2008; cf. Thompson et al., 2004) and neuropathological (e.g., Chana et al., 2006) markers of frontal systems neurotoxicity.

Prospective memory (ProM) is a unique aspect of episodic memory that places considerable demands on strategic encoding and retrieval process and frontal systems (McDaniel & Einstein, 2007), but has not been extensively studied in the context of MA dependence. ProM, which is colloquially known as "remembering to remember," is a multi-faceted cognitive ability referring to the initiation, retrieval, and execution of previously encoded intentions at an appropriate moment in the future. Examples of ProM in everyday life include remembering to mail the household bills, attend health care appointments, and take one's medications as prescribed. Of significant ecological relevance, ProM impairment has been established as an independent risk factor for dependence in everyday functioning activities (e.g., Twamley et al., 2008; Woods et al., 2008a), including treatment adherence (Contardo, Black, Beauvais, Dieckhaus, & Rosen, 2009; Woods et al., 2009). Drawing upon Moscovitch's (1992; 1994) aforementioned component process model, McDaniel and Einstein (2000) developed the multiprocess theory of ProM, which posits that ProM may be heavily reliant on frontally-mediated strategic/executive processes, including planning (i.e., forming and executing an intention), monitoring for the appropriate moment to initiate the intended action, inhibition of ongoing activities, and flexible switching from ongoing activities to the planned action. Consistent with this view, ProM has been associated with measures of executive functions (e.g., Carey et al., 2006; McFarland & Glisky, 2009) and prefrontal cortex activation (e.g., Brodmann's area 10; Basso et al., 2010; Burgess et al., 2001; Burgess et al., 2003; Reynolds et al., 2009). In addition, ProM impairment has been found in conditions characterized by frontal systems damage (e.g., Parkinson's disease; Katai et al., 2003).

Multiprocess theory (McDaniel & Einstein, 2000) further suggests that the strategic encoding, monitoring, and retrieval demands of a given ProM task may vary by the particular characteristics of the target cue upon which intention retrieval is based. For instance, an important distinction is often made between time- and event-based ProM (Einstein & McDaniel, 1990). While time-based ProM tasks require the execution of an intention at a specified time (e.g., taking a medication at 8:00am), event-based ProM tasks involve executing an intention upon detection of an external stimulus (e.g., mailing a letter

when you see a mailbox). Due to the absence of an overt environmental cue, time-based tasks are thought to place greater demands on cognitive control processes, most notably self-initiated monitoring of time that, under normal circumstances, strategically increases as the cue approaches (e.g., Costa, Peppe, Caltagirone, & Carlesimo, 2008). Thus, it is argued that time-based ProM may be more reliant on executive functions and the integrity of frontal systems relative to event-based ProM. In support of this notion, Raskin et al. (in press) recently showed that patients with Parkinson's disease, a classic basal ganglia disease, demonstrate disproportionate impairment in time-based ProM, which was associated with executive dysfunction.

Although the underlying neural systems and cognitive processes associated with ProM performance are consistent with those hypothesized to be adversely affected by chronic MA use, only one study to date has examined ProM in MA users. In a cohort of 20 recently abstinent MA-dependent and 20 MA-naïve individuals, Rendell and colleagues (2009) assessed ProM using the Virtual Week task, which requires the participant to remember to perform a series of actions as part of a board game (see Rendell & Henry, 2009, for a review). The MA-dependent group made fewer correct ProM responses than the MA-naïve group (Cohen's $d = 1.25$), which included a series of primarily event-based intentions, as well as time-check tasks. The MA effects remained significant after covarying for other cognitive abilities, including a standard clinical test of retrospective memory (i.e., Auditory-Verbal Learning Test).

While this study provided an important first step toward elucidating the nature and extent of ProM impairment in MA dependence, a few limitations are worth noting. First, the Virtual Week task, while a widely used and well-validated test of ProM, does little to clarify the *nature* of the time- vs. event-based ProM impairment. Specifically, most of the Virtual Week ProM tasks are functionally event-based (i.e., they require performing an action upon seeing a specific cue without relying on the passage of actual time). Second, the scoring system of Virtual Week does not allow for specific error analysis (e.g., content-based errors, poor time monitoring), which would help delineate a cognitive profile of ProM impairment, and subsequently may provide insight into the possible underlying cognitive neural systems (e.g., frontostriatal vs. temporolimbic) of MA-associated ProM impairment. Third, the Virtual Week task allows participants to choose the appropriate intention from a drop-down menu, which may reduce demands on the strategic aspects of intention search and retrieval. Moreover, although activities performed in Virtual Week may be similar to everyday tasks, the overall task is laboratory-based, and does not include a naturalistic component that could provide insight with regard to everyday ProM functioning. In addition, while Rendell et al.'s (2009) work used appropriately strict exclusion criteria to isolate a MA effect on ProM, broader inclusion criteria would be helpful in order to examine this construct in a larger, more representative sample. MA dependence is often accompanied by a number of medical conditions (e.g., HIV infection) and other substance disorders (e.g., alcohol dependence) that are themselves risk factors for ProM impairment (e.g., Carey et al., 2006), which raises important clinical questions regarding the role of such comorbidities in the expression of ProM deficits in this population. Lastly, no data were presented on the relationship between MA use characteristics (e.g., recency, age at first use) and ProM performance, which are needed to further our understanding of the clinical correlates and course of MA-associated ProM impairment.

Considering these limitations, the present study aimed to assess the nature and extent of ProM impairment in MA users using a well-validated measure of ProM (i.e., Memory for Intentions Screening Test [MIST]; Raskin et al., 2010) that allows for a more detailed analysis of the component processes of MA-associated ProM impairment (i.e., time- and event-based scales, error analyses, and recognition), and includes a semi-naturalistic ProM

task. Given the apparent strategic episodic memory deficit profile and frontostriatal pathogenesis of MA, we hypothesized that MA users would show poorer overall ProM (in the laboratory and on a semi-naturalistic task) relative to non-MA using healthy comparison subjects, and that MA-associated ProM impairment would be particularly evident on time- versus event-based tasks. In contrast, we expect the performance on the MIST recognition trial, where retrieval demands are minimized, to be relatively preserved in the MA group. Furthermore, we predicted that the ProM deficits found in the MA sample would not be better explained by other potential confounding medical (e.g., HIV infection), substance use (e.g., alcohol dependence), and demographic (e.g., sex) factors.

Method

Participants

The study was approved by the University of California, San Diego (UCSD) Human Research Protections Program, and all participants provided written, informed consent. MA-dependent participants (n = 39) were recruited from ongoing studies at the UCSD HIV Neurobehavioral Research Programs (HNRP). All participants in this sample met Diagnostic and Statistical Manual-IV (DSM-IV; American Psychiatric Association, 1994) criteria for MA dependence within the past 18 months as determined by a computerized structured clinical interview (i.e., Composite International Diagnostic Interview version 2.1; World Health Organization, 1998). Healthy comparison participants (n = 26) were drawn from an NIMH-funded study examining ProM in HIV infection (NB. all healthy comparison participants were seronegative for HIV and hepatitis C virus). Each participant underwent a comprehensive neuromedical screening that included a review of medical history and current symptoms, medical and neurological examination, and blood draw. Participants with histories of severe psychiatric (e.g., psychotic disorders) or neurological (e.g., seizure disorders) conditions were excluded. Consistent with our prior studies on MA dependence (e.g., Rippeth et al., 2004), additional exclusion criteria included meeting DSM-IV criteria for: 1) alcohol dependence within the last year; 2) other drug dependence within 5 years of the evaluation; 3) abuse within the year prior to the evaluation of drugs other than MA (e.g., cocaine, opioids); and 4) remote (i.e., > 5 years) but clinically significant history of alcohol or other drug dependence. Participants who tested positive for alcohol on a Breathalyzer or for illicit drugs (except marijuana) on a urine toxicology screen conducted on the day of testing were also excluded. HIV serostatus was determined by enzyme-linked immunosorbent assays and confirmed by a Western Blot test, whereas hepatitis C virus (HCV) serostatus was determined by standard clinical antibody detection.

Demographic, substance use, and psychiatric characteristics for the MA users and their non-MA-using healthy comparisons are displayed in Table 1. Groups did not differ on age, education, or ethnicity (all *p*s > 0.10); however, there were significantly more men in the MA group ($p < 0.001$). In regards to substance use characteristics other than MA use, the MA participants had higher prevalence rates of dependence diagnoses for cannabis and cocaine use (both *p*s < 0.05). MA-dependent participants also reported greater overall current psychological distress on the POMS and were more likely to have a history of Major Depressive Disorder (both *p*s < 0.05).

MA use and infectious disease (i.e., HIV and HCV) characteristics for the MA users are presented in Table 2. On average, participants in this group began using MA in their mid-20s, had used for approximately 4 years, and had been abstinent from MA for about 3 months. Approximately one-quarter (n = 10) of the MA sample were seropositive for HCV and one-half (n = 20) were HIV seropositive, 60% of whom had a history of AIDS-defining illness.

Procedure

Participants were administered the research version of Memory for Intentions Screening Test (MIST; Raskin et al., 2010), which is a standardized measure of prospective memory that demonstrates evidence of reliability (e.g., Woods, Moran, Dawson, Carey, & Grant, 2008b) and construct validity (e.g., Carey et al., 2006). The MIST is a 30-minute laboratory-based measure of ProM that includes four time-based and four event-based trials, during which the participant is engaged in an ongoing distracter task (i.e., a word search). Participants are also asked to complete a post-test multiple-choice recognition measure to specifically examine the retrospective memory component of the task after its completion. Error coding was as follows: 1) No Response (i.e., omissions); 2) Task Substitutions (e.g., performing an action in place of a verbal response); 3) Loss of Content (e.g., recognition of a cue, but forgetting all or part of the prescribed intention); and 4) Loss of Time (i.e., performing the correct response at the wrong time). The 24 hour trial of the MIST, which does not contribute to the Summary Score, requires participants to telephone the examiner 24 hours after their clinic visit and report how many hours they slept (Carey et al., 2006; Zogg et al., in press).

Although participants were enrolled in a variety of different ongoing studies, we were able to extract several overlapping tests of executive functions, retrospective memory, and information processing speed in order to examine the neurocognitive correlates of ProM impairment in the MA using participants. Measures of executive functions included the Wisconsin Card Sorting Test-64 card computerized version (perseverative responses; M SS = 8.0 [2.9]; Kongs et al., 2000), Trailmaking Test Part B (total time; M SS = 9.5 [2.4]; Reitan & Wolfson, 1985), and letter (total correct; M SS = 10.0 [2.5]; Benton et al., 1983) and action (total correct; M SS = 9.2 [3.1]; Woods et al., 2005b) fluency. Retrospective memory was assessed with the total learning and delayed free recall trials of the Brief Visuospatial Memory Test – Revised (BVMT-R; learning M SS = 6.9 [2.2]; delayed M SS = 7.1 [2.6]; Benedict, 1997) and the Hopkins Verbal Learning Test – Revised (HVLT-R; learning M SS = 7.0 [2.6]; delayed M SS = 6.8 [2.8]; Benedict et al., 1998). Tests of information processing speed included Trailmaking Test Part A (M SS = 9.9 [2.1]) and the Digit Symbol (M SS = 8.6 [3.0]) and Symbol Search (M SS = 9.9 [3.2]) subtests from the Wechsler Adult Intelligence Scale (3rd ed.; Psychological Corporation, 1997). Raw scores were converted to population-based z-scores and averaged across domains using standard, published methods (e.g., Cysique et al., 2009; Woods et al., 2008a).

Finally, each participant was also administered the Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1981) as an index of acute affective distress. 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, on which higher scores indicate greater affective distress. MA use characteristics (i.e., lifetime amount used in grams, total duration of use, age at first use, and recency of use) were obtained via a semi-structured timeline follow-back interview (see Rippeth et al., 2004, for more detail).

Statistical Analyses

Group differences on the MIST were examined using Wilcoxon rank-sum tests (and the unbiased Cohen's *d* measure of effect size) due to the non-normality of the data (Shapiro-Wilk *p*s < .05). Regression analyses were then conducted to determine whether any of the demographic, psychiatric, and substance use factors on which the MA and comparison groups differed confounded the MA effect on the MIST Summary Score. This approach was not possible for a few possibly confounding factors due to insufficient variability in the healthy comparison group (e.g., zero prevalence of HIV, HCV, and dependence on several

substances). For those variables, it was therefore necessary to conduct Wilcoxon rank-sum tests on the MIST Summary Score only within the MA users. Nonparametric Spearman's rho analyses were used to determine the relationship between the MIST summary score and neurocognitive tests (e.g., executive functions) and MA use variables (e.g., duration of use) within the MA group. A repeated measures ANOVA was used to test for an interaction between MA status and ProM cue type (i.e., time- and event-based) across groups. Despite the fact that the MIST variables were non-normally distributed, the results of this analysis did not differ when nonparametric statistical methods were used. Lastly, chi-square analyses were conducted to examine group differences on the 24-hour task.

Results

Table 3 displays descriptive data and the group differences for the MIST variables and error subtypes. The MA group performed significantly worse than the healthy comparison subjects on the MIST Summary Score ($p < 0.05$; Cohen's $d = 0.87$). A follow-up regression that included sex, lifetime Major Depressive Disorder, alcohol dependence, and POMS total mood disturbance, revealed that MA status ($p = 0.009$) was an independent predictor of overall ProM (adjusted $R^2 = .20$, $p = 0.003$). Similarly, within the MA group (n = 39), there was no significant effect of sex, HIV, HCV, or other substance use disorders (i.e., cannabis, opioid, cocaine, or other substance use dependence) on overall ProM (all ps > 0.10).

Within the MA group, the MIST Summary Score was significantly correlated with the executive function domain (Spearman's $\rho = 0.41$, $p = 0.03$), but not measures of learning ($\rho = 0.26$, $p = 0.16$), delayed recall ($\rho = 0.19$, $p = 0.31$), or information processing speed ($\rho = 0.17$, $p = 0.35$). A post-hoc multiple regression predicting the MIST Summary Score from the four individual tests in the executive was significant (adj $R^2 = 0.29$, $p = .02$), with TMT Part B emerging as the only significant contributor to the model ($p < .05$). Examination of associations between MA use characteristics and ProM deficits within the MA group (n = 39) revealed a significant correlation between age at first MA use and the MIST Summary Score ($\rho = 0.43$; $p < 0.01$), such that lower ProM performance was associated with earlier age at first use of MA. There were no associations between the remaining MA use characteristics (i.e., last use, total duration, and total quantity) and ProM performance (ps > 0.10).

A repeated measures ANOVA examining with MA group as the between-subjects variable and cue type (i.e., time- vs. event-based) as the within-subjects factor revealed a significant main effect of group [$F(1,63) = 11.8$, $p = 0.001$, $\eta^2 = 0.278$)], such that the MA users performed significantly worse than the non-MA users on both time and event-based ProM tasks (Cohen's ds = 0.76 and 0.64, respectively, see Table 3), and a significant main effect of cue task, whereby both the MA users and their healthy counterparts performed worse on the time-based tasks than the event-based tasks [$F(1,63) = 24.3$, $p < 0.001$, $\eta^2 = 0.158$]. However, the interaction between MA group and cue type failed to reach significance [$F(1,63) = 0.97$, $p > 0.10$, $\eta^2 = 0.015$].

Error type analyses revealed a larger proportion of Task Substitution (TS) errors (Cohen's $d = 0.91$) and Loss of Time (LOT) errors (Cohen's $d = 0.89$) in the MA group relative to the non-MA-using group (both ps < 0.01). Within the MA group, 68% of the TS errors were classified as intrusions (i.e., substitution of a novel task for the prescribed task), whereas only 11% were classified as perseverations (i.e., repetition of a task that was already completed). Seventy-one percent of LOT errors in the MA group were committed on time-based tasks and the majority (87%) were committed prior to the prescribed time (i.e., early). The occurrence of No Response and Loss of Content errors did not differ between the groups (both ps > 0.05). No significant between group differences were observed on the

recognition or word search tasks (Cohen's *d*s = 0.05 and 0.33, respectively), nor did the two groups differ in the proportion of participants who accurately completed the 24-hour delay task ($p > 0.10$).

Discussion

Consistent with our primary hypothesis, results from the current study provide further evidence for ProM impairment in individuals with MA dependence. More specifically, MA users demonstrated difficulties with the complex cognitive processes necessary for successful enactment of future intentions. These findings are consistent with the results of the Rendell et al. (2009) study, which also demonstrated that MA was associated with ProM impairment relative to non-MA-using healthy comparison subjects (Cohen's $d = 1.25$). Our study extends their findings by clarifying the nature of MA-associated ProM impairment through use of the MIST, which includes both time- and event-based tasks, a scoring system for error analyses, and a 24 hour semi-naturalistic ProM task. Moreover, our study also provides preliminary evidence of the external validity of MA-associated ProM deficits through the examination of ProM in a clinical cohort with a high rate of common comorbidities, including infectious diseases (e.g., HIV infection) and other substance use disorders (e.g., alcohol dependence). Importantly, analyses of these potentially confounding variables revealed no significant association between ProM performance in the MA-users and co-morbid disease (i.e., HIV or HCV infection) or substance use (e.g., alcohol) factors. This latter finding is consistent with prior research demonstrating no relationship between MA-associated ProM impairment and either cannabis or alcohol use (Rendell et al., 2009). It is also unlikely that the ProM impairment observed in this sample of MA-dependent individuals can be attributed to demographic factors, as the two groups were matched for age, education, and ethnicity, and post-hoc analyses did not reveal significant sex effects on ProM. Furthermore, it does not appear that psychiatric characteristics confounded the MA-associated ProM effect; while the groups differed in current affective distress (i.e., POMS Total Mood Disturbance), and histories of lifetime major depressive disorder, post-hoc analyses revealed no significant associations between these characteristics and ProM performance. Thus, despite the highly confounded nature of the study sample, the data suggested that ProM impairment could be attributable specifically to MA use rather than comorbid disease, psychiatric, or other substance use factors.

Moreover, we observed a significant correlation between age at first MA use and the MIST summary score, whereby poorer ProM performance was associated with a younger age of first MA use. This is an important finding, considering that a number of adverse outcomes may result from early onset substance use, including neurocognitive impairment (Monti, O'Leary Tevyaw, & Borsari, 2005). Adolescence is a key period for central nervous system development (Paus, 2005) and a time during which the brain may be particularly susceptible to the effects of drug use. Thus, early MA use may disrupt the maturation processes in areas responsible for higher cognitive functioning (e.g., frontal systems), which may subsequently increase the risk of neurocognitive deficits later in life. In support of this notion, Jernigan et al. (2005), observed greater frontostriatal (e.g., nucleus accumbens) volume increases in younger MA-dependent individuals, which were associated with more severe neurocognitive impairment and hypothesized to reflect neural sprouting and/or microglial activation. Another possibility is that premorbid cognitive characteristics (e.g., poorer decision making, lower brain reserve) may predispose individuals to use substances at an earlier age. Collectively, these data provide preliminary evidence regarding the importance of early clinical interventions for MA users in order to prevent future cognitive decline. There were no associations between the remaining MA use characteristics (e.g., total quantity) and ProM performance, which is consistent with previous literature indicating minimal

associations between neurocognitive impairment and MA use parameters (e.g., Chang et al., 2002; Cherner et al., 2010; Scott et al., 2007).

Regarding the possible cognitive mechanisms of the MA-associated ProM deficit, our findings indicate that executive dysfunction may play a particularly influential role. Within the MA group, ProM deficits were significantly associated with executive dysfunction, perhaps most notably, complex attention as measured by TMT B. This finding is consistent with the hypothesized cognitive and neural substrates of ProM, which is thought to rely heavily on executive functions (e.g., McDaniel & Einstein, 2000; McFarland & Glisky, 2009) and prefrontostriatal systems (e.g., Basso et al., 2010; Burgess et al., 2003). This result also converges with the findings of Rendell and colleagues (2009), who reported a significant association between ProM impairment on the Virtual Week task and cognitive impulsivity among MA users. Also consistent with the Rendell study, the association between MA-associated ProM impairment and executive dysfunction was specific; that is, ProM was not correlated with tests of retrospective memory or information processing speed. Such weak associations were somewhat surprising when considered in the context of prior research in other clinical populations (e.g., HIV; Carey et al., 2006) showing that the MIST relates to these cognitive abilities. However, when paired with the findings of Rendell and colleagues (2009), these data give credence to the executive dyscontrol hypothesis of ProM impairment in MA users.

Analyses of component ProM variables and error types revealed further evidence that MA-associated ProM failures may be primarily driven by executive (i.e., strategic) components of ProM, including inefficient encoding, monitoring, and/or retrieval of future intentions. Consistent with our hypotheses, the MA users showed poorer performance relative to the healthy comparison subjects on both the time- and event-based tasks. However, the MA-users did not perform disproportionately worse on the time-based ProM tasks, which were hypothesized to place greater demands on self-initiated monitoring and retrieval processes (McDaniel, Glisky, Rubin, Guynn, & Routhieaux, 1999). There are several potential explanations for this unexpected finding. First, it is possible that we simply overestimated the magnitude of the hypothesized interaction and were thus underpowered to detect it; indeed, the effect size for time-based tasks (Cohen's $d = 0.76$) was slightly larger than that of event-based tasks (Cohen's $d = 0.64$). Of course, the clinical and conceptual relevance of such a small effect would be highly suspect. An alternate interpretation is that, although comparable in magnitude, the time- and event-based deficits apparent in our MA sample were driven by different underlying mechanisms. The design of the MIST, which is a clinical task with overlapping trials, makes it difficult to address this possibility directly. However, prospective experimental studies might shed some light on this issue by examining the specific components of event-based tasks, such as the semantic relatedness of the cue-intention pairing (Woods et al., 2010), cue monitoring, and focality (Foster et al., 2009). An equally plausible possibility is that MA users exhibit difficulties executing future intentions regardless of the modality of the cue itself due to a common underlying mechanism. In other words, it may be that the expression of MA-associated ProM deficits depends on the extent to which the tasks impose strong strategic (i.e., "executive") demands, rather than whether the ProM task is specifically time- or event-based. For example, consistent with McDaniel and Einstein's (2000) multiprocess approach, event-based ProM tasks may depend on strategic processes (e.g., self-monitoring) and/or relatively automatic processes (e.g., involuntary attentional processes) for successful completion. As such, event-based tasks that rely more heavily on such strategic processes may be more susceptible to failure in conditions characterized by executive dysfunction (e.g., MA dependence) relative to those depending on more automatic processes (e.g., Henry, MacLeod, Phillips, & Crawford, 2004). It has also been posited that event-based tasks on the MIST may rely heavily on executive processes, as they are nonfocal and thus may impose greater executive

demands (e.g., self-monitoring of the environment for cues) relative to event-based tasks where the cue signaling the retrieval is presented more explicitly (Raskin et al., in press).

Also in support of a MA-associated deficit in the executive component of ProM (i.e., deficient strategic control of encoding, monitoring, and retrieval processes), the MA dependent individuals and their non-MA-using counterparts in our study performed comparably on the recognition subtest. Although this subtest is limited by ceiling effects, these results may indicate that MA users are able to effectively retrieve the correct cue-intention pair when the demands for self-initiated retrieval are minimized. Nevertheless, consistent with McDaniel and Einstein's (2000) multiprocess theory, the intact recognition in MA users may suggest that while they may have difficulties with the executive aspects of ProM possibly reflective of frontal systems damage, their ability to encode and retain information related to the intention itself, may be less affected. Finally, consistent with the notion that basic attentional abilities may be spared in chronic MA users (e.g., Chang et al., 2002), the MA users performed similarly to their non-MA-using counterparts on the distracter word search task, which also rules out the possibility that the observed effects may be secondary to differential attentional resources being directed toward the primary and ongoing tasks.

The most prominent error types that occurred in the MA dependent sample were task substitution (i.e., TS; repetition or intrusion errors) and loss of time (i.e., LOT; performing a task at an incorrect time) errors. Within the MA dependent group, 72% (n = 28) of the sample made one or more TS error relative to only 35% (n = 9) of the healthy comparison group. The greater proportion of TS errors within the MA user group may suggest that while they were able to correctly recognize a ProM cue at an appropriate moment, they were inefficient with regard to matching the cue-intention pair. This may suggest a breakdown in the intention encoding process (i.e., encoding the appropriate cue-intention pairing), in the ability to maintain the proper cue-intention pairing while faced with ongoing distractions, or in the intention retrieval process (i.e., retrieving the appropriate intention). In addition, post-hoc analyses revealed that the majority of the TS errors within the MA users group were intrusions, which is consistent with prior research demonstrating elevated non-semantic intrusion errors during verbal list learning in MA users (Woods et al., 2005a). This evidence, along with research demonstrating elevated intrusion rates in conditions characterized by frontal systems damage (e.g., Baldo, Delis, Kramer, & Shimamura, 2002), provides support that the MA-associated ProM deficits may also reflect similar cognitive deficits (e.g., impaired control of encoding and retrieval) and common underlying neural injury (e.g., damage to frontostriatal circuits).

MA users also showed a greater proportion of loss of time (LOT) errors relative to non-MA users. In fact, while the healthy comparison group did not make any LOT errors, 49% (n=19) of the MA-dependent individuals showed at least one error. Moreover, the majority of the LOT errors that occurred in the MA user group were on time-based ProM tasks, which may be indicative of ineffective time estimation or monitoring. Interestingly, post-hoc examination found that 87% of all the LOT errors in the MA group were due to early responding (i.e., the participant responded earlier than instructed). Considered in the context of the paper by Rendell and colleagues (2009), this finding may be attributable to MA-associated difficulties in cognitive inhibition. These time-based errors are also consistent with research demonstrating impaired time perception in stimulant dependent individuals, which may be in part, due to altered time processing or increased impulsivity (Wittmann, Leland, Churan, & Paulus, 2007). In addition, given evidence suggesting a role of the frontostriatal networks in temporal processing (e.g., Cuoll, Vidal, Nazarin, & Macar, 2004; Hinton & Meck, 2004), the time estimation and management difficulties and subsequent LOT errors in MA users may be reflective to MA-associated neural damage to the

frontostriatal networks. However, a notable limitation of this interpretation is that the MIST paradigm does not currently include an index of time monitoring. Given evidence suggesting impairment in time perception in stimulant dependent individuals (Wittmann et al., 2007), future research on ProM in MA users should incorporate various indices of time estimation, production, and monitoring (e.g., clock checking) in their assessment of ProM in order to further clarify the specific cognitive mechanisms contributing to the time-based ProM deficits.

This study also aimed to extend prior research by examining ProM in MA users with a semi-naturalistic task in which participants were instructed to call the examiner 24 hours after their evaluation and report the number of hours they slept the night before. Results showed that both the MA and the non-MA users demonstrated a high proportion of failures on the 24-hour task, which is generally consistent data from prior clinical studies (e.g., Carey et al., 2006; Zogg et al., in press). However, contrary to our expectations, the proportion of MA users who successfully completed the task (i.e., phone call with correct content within 15% of the target time) was comparable to that of the non-MA users (21% and 35%, respectively). Thus, despite laboratory evidence of performance-based ProM impairment, MA users were just as effective as their non-MA using counterparts at completing a semi-naturalistic task of the type often requested by healthcare providers. This prospective memory “paradox” is well known in the aging literature, where a similar pattern of findings among older versus younger adults is found, and is commonly attributed to the formers’ more effective use of mnemonic compensatory strategies (e.g., Rendell & Thomson, 1999). Alternatively, it is possible that we were unable to detect group differences due to the high failure rates (i.e., floor effects). Interestingly, however, post-hoc analyses revealed that within the MA user group, participants who failed to correctly execute the real-world telephone instruction task demonstrated significantly (*ps* < .05) lower scores on the MIST (i.e., Summary Score and the time- and event-based subscales), a pattern that was not seen in the non-MA-using comparison group (*ps* > .10). These findings extend prior research supporting the ecological relevance of ProM as a predictor of everyday functioning in other clinical conditions (e.g., HIV-infection; Zogg et al., in press). While only preliminary, these results provide support for MA-associated ProM impairment in the laboratory as a predictor of real-world ProM failures despite the freedom to use mnemonic strategies. Unfortunately, we did not gather data on the specific compensatory strategies used by participants in the current study, which would be an interesting future direction that might guide the development of specific treatment strategies to enhance everyday functioning in MA users with ProM impairment.

While these results demonstrate that MA use is associated with ProM impairment, and provide preliminary evidence that MA-associated ProM deficits may reflect deficient encoding or retrieval processes or inefficient time estimation and monitoring, they should be interpreted in the context of several limitations. One inherent limitation of our study is the use of self-report measures to determine the MA use characteristics (i.e., age at first use, duration and quantity of use, and last use) of our sample, which are arguably less reliable than objective measures of use (i.e., biological data). Similarly, our data are only inferential with regard to the hypothesized neural substrates of MA-associated ProM impairment, which await testing with structural and functional neuroimaging, perhaps along with relevant biomarkers of inflammation, oxidative stress, vasculopathy, and neuronal injury. This study is also limited by the complex clinical characteristics of our MA users, who had a high proportion of comorbid substance disorders and infectious disease. Although the data argue against the confounding influence of these factors on the MA effect, well-designed studies (e.g., factorial designs with well-matched groups) are needed to more carefully examine the additive (or synergistic) impact of these common comorbid risk factors on ProM (e.g., Rippeth et al., 2004).

Despite these limitations, findings from this study are likely of clinical interest, as research on the specific cognitive mechanisms that are impaired in MA users (i.e., encoding and retrieval processes) is critical in the development of effective treatment and rehabilitation strategies. For example, we found that MA-associated ProM impairment may be characterized by inefficient strategic (i.e., executive) components of ProM, including both encoding and retrieval processes. Thus, when in treatment, MA users may have difficulties learning various cognitive strategies or recalling when and how to use them, rendering them less effective. However, with knowledge of the cognitive strengths and weaknesses (e.g., encoding verbal material), a treatment provider may tailor cognitive rehabilitation strategies to the individual, making use of appropriate compensatory strategies (e.g., those that may facilitate executive processes) to ameliorate an individual's cognitive weaknesses and capitalize on his/her strengths. For example, strategies that have utilized content-free cueing devices (e.g., text-messaging), which presumably reduce the demands of executive recall abilities, have been shown to improve ProM performance of individuals with traumatic brain injury (Fish et al., 2007). In addition, findings regarding MA-associated time estimation and management deficits provide support for the use of cognitive rehabilitation strategies (e.g., routine use of calendars and alarms) in treatment in order to assist with time-dependent activities. Along similar lines, research should also examine the relationship between MA-associated ProM impairment and activities of daily living, as prior research has been demonstrated in other conditions with compromised frontostriatal systems (e.g., HIV infection; Woods et al., 2008a). As such, this may be an important target for cognitive neurorehabilitation in order to improve the overall quality of life for recovering MA users.

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Table 1

Demographic, substance use and psychiatric characteristics of the study samples.

Variable	MA Users (n=39)	Non-MA Users (n=26)	*p*-value
Demographic Characteristics			
Age (years) [a]	41.6 (8.8)	40.6 (13.8)	0.742
Education (years) [a]	12.6 (2.2)	13.4 (1.6)	0.104
Sex (% Male)	92%	42%	<0.001
Ethnicity (% Caucasian)	69%	54%	0.209
Substance Use Disorders[b]			
Alcohol dependence	44%	23%	0.090
Cannabis dependence	28%	0%	0.002
Opioid dependence	8%	0%	0.269
Cocaine dependence	36%	8%	0.017
Psychiatric Characteristics			
Current Major Depressive Disorder (%)	13%	0%	0.077
Lifetime Major Depressive Disorder (%)	59%	31%	0.026
POMS Total Mood Disturbance[c]	58.0 (34.0, 90.0)	36.0 (25.3, 56.0)	0.034

Note.

[a] Means (SD);

[b] Percent lifetime dependence;

[c] Median (interquartile range).

MA = Methamphetamine; POMS = Profile of Mood States.

Table 2

Methamphetamine Use and Disease Characteristics

	MA Users (n=39)
MA use characteristics[a]	
Age at first use (years)	24.0 (20.0, 33.3)
Last use (days)	105.0 (21.0, 187.5)
Total duration of use (years)	4.6 (1.4, 11.8)
Total quantity of use (grams)	1058.2 (293.7, 3723.4)
HIV disease characteristics[a]	
Proportion with HIV infection (%)	51%
HIV plasma viral load	1.7 (1.7, 3.6)
Current CD4 count	354.0 (249.5, 580.3)
Proportion on cART (%)	85%
Proportion with AIDS (%)	60%
Proportion with Hepatitis C Virus (%)	26%

Note.

[a]Median (interquartile range) unless otherwise indicated.

MA = Methamphetamine. HIV = Human immunodeficiency virus. CD4 = Cluster of differentiation 4. cART = combined antiretroviral therapy. AIDS = Acquired immune deficiency syndrome.

Table 3

Prospective Memory performance in the MA User and Non-MA-using samples

MIST Variable	MA Users (n=39)	Non-MA Users (n=26)	*p*-value	Cohen's *d*
Summary score	39.0 (30.0, 42.0)	42.0 (38.3, 48.0)	0.001	0.87
Time-based cues	6.0 (5.0, 7.0)	7.0 (6.0, 8.0)	0.003	0.76
Event-based cues	7.0 (6.0, 8.0)	7.0 (7.0, 8.0)	0.013	0.64
Total errors	4.0 (2.0, 5.0)	1.0 (0.0, 2.0)	<0.001	1.19
No Response	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.411	−0.12
Task Substitution	1.0 (0.0, 2.0)	0.0 (0.0, 1.0)	<0.001	0.91
Loss of Content	1.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.075	0.27
Loss of Time	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	<0.001	0.89
Recognition	8.0 (8.0, 8.0)	8.0 (8.0, 8.0)	0.740	0.05
Word Search	15.0 (13.0, 18.0)	17.0 (14.0, 19.3)	0.204	0.33
24-hour Delay (% Complete)	21%	35%	0.227	-----

Note. Data are presented as median values with the interquartile range in parenthesis unless otherwise indicated.

ProM = Prospective Memory. MA = methamphetamine. MIST = Memory for Intentions Screening Test.