Journal of Psychiatric Research 46 (2012) 492–499

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Working memory deficits affect risky decision-making in methamphetamine users with attention-deficit/hyperactivity disorder

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ARTICLE INFO

Article history:
Received 4 October 2011
Received in revised form
19 December 2011
Accepted 5 January 2012

Keywords:
Amphetamine
Attention deficit disorder with hyperactivity
Cognitive processes
Drug abuse
Short-term memory
Dysexecutive syndrome

ABSTRACT

Methamphetamine (MA) use and Attention-Deficit/Hyperactivity Disorder (ADHD) commonly co-occur and are independently associated with dysregulation of frontostriatal loops and risky decision-making; however, whether their comorbidity exacerbates risky decision-making is not known. This study evaluated 23 participants with histories of MA dependence and ADHD (MA+ADHD+), 25 subjects with MA dependence alone (MA+ADHD−), and 22 healthy adults (MA−ADHD−), who completed the Iowa Gambling Task (IGT) as part of a larger neuropsychiatric research evaluation. Results showed a significant interaction between ADHD, MA, and working memory, such that individuals with working memory deficits in the MA+ADHD+ cohort demonstrated the strongest propensity to select cards from "disadvantageous" versus "advantageous" decks on the IGT. This effect was not better explained by other psychiatric, substance use, neuromedical, or cognitive factors. Findings suggest that working memory deficits may moderate the expression of risky decision-making in MA users with ADHD.

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1. Introduction

Risky decision-making is common in individuals with substance use disorders, who often continue to use alcohol and drugs despite the high probability of it having adverse long-term consequences on their social (e.g., interpersonal relationships; Gardner and Steinberg, 2005), emotional (e.g., depression; Bechara and Damasio, 2002) and physical (e.g., infectious disease; Hardy et al., 2006) health. Methamphetamine (MA) users are therefore ostensively at risk for deficits in decision-making in the laboratory and in their everyday lives. Chronic MA use is associated with a disruption of the dopamine-rich prefrontostriatal circuits (Volkow et al., 2001) that are essential to a number of different cognitive and motor processes, including decision-making (Rogers et al., 1999; van Gaalen et al., 2006). Indeed, several lines of research now suggest that MA-associated prefrontostriatal pathophysiology may underlie aspects of risky decision-making among some chronic MA users (Rogers et al., 1999; Volkow et al., 2001). Bechara and colleagues (2001) first reported evidence of laboratory-based decision-making deficits in MA users on the Iowa Gambling Task (IGT; Bechara, 2007). Specifically, MA users were significantly more likely to select cards from "disadvantageous" (i.e., high immediate value cards, but with greater risk of long-term penalties) versus "advantageous" (i.e., lower immediate value cards, but with reduced risk of long-term penalties) decks on the IGT than healthy adults (Bechara et al., 2001). Moreover, MA users tend to perform worse on laboratory measures of decision-making compared with users of alcohol (Gonzalez et al., 2007) and other illicit substances, such as cocaine (Simon et al., 2002) and opiates (Rogers et al., 1999). Functional neuroimaging studies of MA dependent individuals show decreased prefrontal and parietal activation during tasks of decision-making (Paulus et al., 2001, 2003). Speaking to the real-world implications of such deficits, altered prefrontal and parietal brain response to decision-making tasks predicts relapse in MA dependent individuals (Paulus et al., 2005).

MA misuse co-occurs with a variety of psychiatric disorders that are characterized by frontostriatal systems alterations and therefore might impact decision-making, including Attention-Deficit/Hyperactivity Disorder (ADHD). Approximately 40% of adult MA users report a lifetime history of ADHD (Jaffe et al., 2005), as compared to prevalence rates of 3–5% in the general population (Kessler et al., 2006). Elevated rates of lifetime ADHD diagnoses among adult MA users may reflect a self-medicating attempt to

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doi:10.1016/j.jpsychires.2012.01.006

ameliorate their symptoms, most notably inattention (Sim et al., 2001), although the literature is not entirely consistent in this regard (Wilens et al., 2003). ADHD is associated with structural and functional abnormalities in frontostriatal neural circuitry (Faraone and Biederman, 1998), including prefrontal cortical thinning (Almeida et al., 2010; Castellanos and Proal, 2009; Makris et al., 2007) and reduced caudate volumes (Hesslinger et al., 2002; Castellanos et al., 1996; Makris et al., 2010; Seidman et al., 2006). ADHD is also associated with prefrontal and subcortical gray matter reductions in adults who have been diagnosed with ADHD in childhood, regardless of whether the diagnosis persists into adulthood (Proal et al., 2011). The neuropsychological profile of ADHD in adults includes deficits in multiple aspects of attention (e.g., sustained) and executive functions (Woods et al., 2002). At the behavioral level, ADHD adults show increased impulsivity and engagement in high risk behaviors, including gambling (e.g., Breyer et al., 2009) and reckless automobile driving (e.g., Thompson et al., 2007). To this end, adults with ADHD also demonstrate impaired performance on tasks that mimic real-life decision-making (e.g., Malloy-Dinz et al., 2007; Mantyla et al., 2010). Mantyla et al. (2010), for example, found that adults with ADHD exhibit impairment (i.e., opting for choices that produce disadvantageous outcomes) on laboratory tasks of decision-making compared to healthy adults, which imaging studies suggest may be associated with decreased activation in the ventromedial prefrontal cortex in this population (Ernst et al., 2003).

Despite the elevated rates of ADHD among MA users and their overlapping cognitive and neural substrates, only two prior studies have examined the neuropsychological functioning of MA users with comorbid ADHD. Sim et al. (2001) found that MA users with ADHD symptomatology showed incremental deficits on neurocognitive tasks of executive functions and working memory compared to MA users without ADHD symptoms. Jaffe and colleagues (2005) found no effect of childhood symptoms of ADHD on the baseline neurocognitive performance of MA dependent individuals; however, MA dependent participants who endorsed ADHD symptomatology failed to show improvements on tests of attention and working memory at one-month follow-up from treatment of MA. Although these two prior studies suggest that comorbid ADHD may exacerbate the cognitive deficits observed in MA users, especially in the domains of executive function and working memory (Sim et al., 2001; Jaffe et al., 2005), we aimed to extend this research by specifically examining the effects of comorbid ADHD and MA on risky decision-making. We hypothesized that MA dependent individuals with comorbid ADHD would demonstrate an increased propensity for risky decision-making (i.e., making choices that produce disadvantageous outcomes) on a well-validated laboratory task (i.e., the IGT) as compared to MA dependent individuals without ADHD and healthy adults.

A secondary aim was to evaluate the possible moderating effects of working memory on MA-associated decision-making deficits. According to Bechara and Martin (2004), working memory may play a critical role in the expression of risky decision-making in substance abusers. At the level of cognitive functioning, working memory impairment likely makes it difficult to adequately maintain, monitor, and evaluate information relevant to making decisions "online." Such online processing difficulty thus increases the likelihood of impulsive decision-making in favor of immediate, short-term rewards (Bechara and Martin, 2004). At the level of neural systems, the overlapping demands of working memory and decision-making on prefrontostriatal loops (perhaps along with the posterior parietal cortex and its connections with the striatum) may play a role in this association (Bechara and Martin, 2004). In support of this contention, Bechara and Martin found that working memory deficits were inversely correlated with performance on the IGT in a mixed group of substance abusers that included MA dependent persons (Bechara and Martin, 2004). Similarly, studies in healthy adults show that experimental manipulation of working memory load is associated with impaired performance on the IGT (e.g., Hinson et al., 2002; Jameson et al., 2004; Pecchineda et al., 2006). Hinson, Jameson, and Whitney (2002), for example, showed that conditions of high working memory load were associated with increased selections from the disadvantageous decks on a modified version of the IGT (see also Pecchineda et al., 2006). Using the same modified version of the IGT task, Jameson and colleagues (2004) found that verbal buffering alone did not interfere with IGT performance, suggesting that the executive aspects of working memory are critical to decision-making (Jameson et al., 2004). Taken together, these studies provide evidence in support of Bechara and Martin's contention that working memory plays a critical role in the expression of impaired decision-making (Bechara and Martin, 2004). Considering these conceptual factors and the neuropsychological profile of ADHD and MA, it was hypothesized that working memory deficits would interact with ADHD to amplify risky decision-making in MA users.

2. Methods

2.1. Participants

A total of 70 individuals were drawn from a larger cohort ($N = 386$) that was recruited as part of a National Institute on Drug Abuse (NIDA)-funded research study that examined the central nervous system effects of MA on individuals with and without human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection. Twenty-five participants who met DSM-IV diagnostic criteria for both MA dependence and ADHD (ADHD; MA+ADHD+) during their lifetime were the primary group of interest. These participants were hand-matched based on relevant demographic characteristics (i.e., age, gender, years of education and ethnicity) to 23 participants who met lifetime diagnostic criteria for MA dependence, but did not endorse any symptoms of ADHD (MA+ADHD−). Exclusion criteria for these two groups included meeting DSM-IV diagnostic criteria for the following: alcohol dependence within the last year; abuse of illicit substances other than MA (e.g., cocaine, opioids) within the last year; and/or dependence on elicit substances other than MA within the last five years. We also included 22 comparison adults, all of whom reported minimal use (<1 g) of MA in their lifetime and met none of the diagnostic criteria for ADHD (MA−ADHD−). Individuals in both MA+ groups met criteria for MA dependence in their lifetime and continued to meet criteria for an MA diagnosis (abuse or dependence) within the 18 months prior to assessment. Given the high frequency of comorbid alcohol abuse and cannabis use disorders in MA users, individuals with such histories were not excluded from the study. Participants were required to be abstinent from illicit substances for at least ten days prior to assessment by self-report. A urine toxicology screen was conducted on all participants to confirm recent abstinence of any illicit substances that may influence neuropsychological test performance. Individuals with histories of neurological diseases (e.g., seizure disorders, closed head injuries with loss of consciousness greater than 30 min, central nervous system neoplasms, opportunistic infections) or severe psychiatric illnesses (e.g., schizophrenia) that possibly affect cognitive functioning were also excluded from the study.

The participants' demographic, psychiatric, and clinical characteristics are displayed in Table 1. Participants in all three groups were comparable with regard to age, ethnicity, gender, and total years of education ($ps > 0.10$). Rates of current major depressive

Table 1
Demographic, psychiatric, and clinical characteristics of study groups.

Variable	MA−ADHD− ($N = 22$)	MA+ADHD− ($N = 25$)	MA+ADHD+ ($N = 23$)	p
Demographic characteristics				
Age (years)	43.0 ± 14.3	40.2 ± 6.2	40.0 ± 5.9	0.50
Education (years)	11.9 ± 1.7	12.0 ± 1.4	12.2 ± 2.5	0.90
Sex (% male)	20 (90.9)	24 (96.0)	21 (91.3)	0.74
Ethnicity (% white)	13 (59.1)	15 (60.0)	17 (73.9)	0.50
Estimated VIQ	97.0 ± 8.6	97.7 ± 11.0	93.3 ± 13.8	0.37
Psychiatric characteristics				
ADHD (%)				
Current	–	–	16 (69.6)	–
Lifetime only	–	–	7 (30.4)	–
Subtypes				
Combined	–	–	14 (60.9)	–
Hyperactive	–	–	7 (30.4)	–
Inattentive	–	–	2 (8.7)	–
ASPD (%)	0 (0.0)	3 (12.0)	10 (43.5)	<0.001**
Depression (%)				
Current MDD	1 (4.6)	5 (20.0)	4 (17.4)	0.28
Lifetime MDD	6 (27.3)	8 (32.0)	16 (69.6)	0.01*[a]
BDI-II (total score)	4.1 ± 5.1	14.1 ± 11.6	16.3 ± 11.7	<0.001**
Working memory impaired (%)	4 (18.2)	9 (36.0)	5 (21.7)	0.33
Clinical characteristics[b]				
HIV seropositive (%)	0 (0.0)	16 (64.0)	16 (69.6)	0.68
AIDS diagnosis (%)	–	10 (62.5)	8 (50.0)	0.48
Detectable plasma (%)	–	8 (53.3)	7 (50.0)	0.86
Nadir CD4	–	251.7 ± 235.2	207.9 ± 157.7	0.68
Current CD4	–	672.9 ± 375.3	647.0 ± 500.0	0.27
ARV Status (%)	–	14 (87.5)	10 (62.5)	0.10
HCV Seropositive (%)	0 (0.0)	6 (24.0)	9 (39.1)	0.26
Total Bilirubin (mg/dl)[c]	–	0.938 (0.5, 1.1)	0.743 (0.5, 0.8)	0.16
APRI[c]	–	0.4 (0.20, 0.61)	0.29 (0.19,0.50)	0.16

Note: ADHD = Attention-Deficit/Hyperactivity Disorder; APRI = AST-to-platelet ration index; ARV = Antiretroviral; ASPD = Antisocial Personality Disorder; BDI-II = Beck Depression Inventory-II; MDD = Major Depressive Disorder; HCV = Hepatitis C Virus; HIV = Human Immunodeficiency Virus; VIQ = Verbal Intelligence Quotient. Current ADHD = past 12 months. Current MDD = past 30 days.

[a] MA−/ADHD−> MA+/ADHD−, MA+/ADHD+.

[b] All clinical characteristics are calculated using the two MA+ groups. [c] Numbers represent medians and interquartile ranges. *$p < 0.05$; **$p < 0.001$. All numbers represent means and standard deviations unless otherwise noted.

Table 2
Substance use characteristics of study groups.

Variable	MA−ADHD− ($N = 22$)	MA+ADHD− ($N = 25$)	MA+ADHD+ ($N = 23$)	p
MA characteristics[a]				
Current diagnosis	0 (0.0)	2 (8.0)	2 (8.0)	0.38
First use (age)[b]	–	25.0 ± 7.9	22.8 ± 7.3	0.33
Last use (days)[c]	–	120 (46.5, 240)	60 (7, 180)	0.45
Cumulative use (grams)[c]	–	1267 (333, 5556)	1064 (378, 3306)	0.26
IDU use (%)	0 (0.0)	10 (40.0)	13 (56.5)	0.25
Substance use disorders[d]				
Alcohol (%)				
Abuse	5 (22.7)	7 (28.0)	6 (26.1)	0.92
Dependence	4 (18.1)	10 (40.0)	9 (39.1)	0.21
Cannabis (%)				
Abuse	4 (18.1)	7 (28.0)	6 (26.1)	0.71
Dependence	2 (9.1)	5 (20.0)	3 (13.0)	0.55
Cocaine (%)				
Abuse	0 (0.0)	2 (8.0)	5 (21.7)	0.05*
Dependence	0 (0.0)	6 (24.0)	6 (26.1)	0.04*
Methamphetamine (%)				
Abuse	0 (0.0)	1 (4.0)	2 (8.7)	0.35
Dependence	0 (0.0)	25 (100.0)	23 (100.0)	<0.001**
Opioid (%)				
Abuse	0 (0.0)	1 (4.0)	1 (4.3)	0.62
Dependence	0 (0.0)	0 (0.0)	0 (0.0)	–
'Other' drugs (%)[e]				
Abuse	1 (4.5)	8 (32.0)	6 (26.1)	0.11
Dependence	0 (0.0)	2 (8.0)	4 (17.4)	0.06

Note: ADHD = Attention-Deficit/Hyperactivity Disorder; IDU = Injection Drug Use; MA = Methamphetamine.

[a] MA characteristic comparisons were restricted to the 2 MA+ groups.

[b] Numbers represent means and standard deviations.

[c] Numbers represent medians and interquartile ranges.

[d] Substance use disorders are defined as meeting criteria for a DSM-IV diagnosis current (past 30 days) or lifetime.

[e] 'Other' drugs refer to Hallucinogens, Inhalants, PCP, and Sedatives. Numbers represent total number of participants (n) and percentages unless otherwise noted. *$p < 0.05$; **$p < 0.0001$.

disorder (MDD) were comparable across all three groups; however, as might be expected, rates of lifetime history of MDD were significantly higher in the MA+ADHD+ group compared to the MA+ADHD− and MA−ADHD− groups ($p < 0.05$). Further the two MA+ groups endorsed significantly higher current depressive symptoms on the BDI than the comparison group ($p < 0.001$). The participants substance use characteristics are displayed in Table 2. The three groups had similar rates of remote substance use disorders (e.g., alcohol, cannabis, opioids), although the MA+ADHD+ and MA+ADHD− samples exhibited significantly higher lifetime histories of cocaine dependence than the MA−ADHD− group ($p < 0.01$). The two MA+ groups reported comparable MA use parameters (e.g., total grams used, total number of days used); ADHD+ and ADHD− individuals in the MA+ groups did not report any significant differences in age of initiation of MA use nor time (i.e., days) since last use of MA ($ps > 0.10$).

2.2. Materials and procedure

The study was approved by the University's human research protections program, and all participants provided written, informed consent. Participants completed the computerized version of the IGT (Bechara, 2007) as part of a comprehensive neuropsychological battery. The IGT is a laboratory measure that is designed to mimic "real-world" contingencies of reward and punishment (i.e., winning and losing money); the goal of the task is to maximize profit on a loan of play money. The participant is given the option to select cards from four decks (decks A, B, C, and D), which yield different financial outcomes. The task consists of 100 trials, which are commonly divided into five blocks with 20 choices in each block. Choices from two "advantageous" decks (decks C and D) result in small gains with some small loses, but ultimately yield modest long-term gains. Choices from the other two decks (decks A and B) result in immediate high gains but ultimately lead to substantial losses (e.g., −$250 after 10 trials), thus choices from these two decks are considered 'disadvantageous.' Raw scores were converted to demographically adjusted T-scores using the published test manual. The participant's total net score (i.e., the total number of advantageous choices minus the total number of disadvantageous choices across all five blocks) was used as a primary dependent variable.

2.3. Standard neuropsychological assessment

Participants were also administered a standardized neuropsychological battery that included tests of *episodic memory*, *executive functions*, *verbal fluency*, *speed of information processing*, and *working memory*. The *working memory* domain was operationalized using two neurocognitive tests, the Spatial Span subtest of the Wechsler Memory Scale-3rd Edition (WMS-III; The Psychological Corporation, 1997) and the Paced Auditory Serial-Addition Task (PASAT; Gronwall, 1977; Gronwall and Sampson, 1974). The Spatial

Span board features 10 cubes with numbers (1–10) printed on the sides of the cubes facing the examiner. The examiner taps the cubes in a specified sequence and asks the examinee to tap the same sequence (in the same order and subsequently in reverse order). For the PASAT, a set of randomized digits (1–9) is serially presented auditorily via computer. Subjects are asked to add the current number to the number that preceded it and respond with the sum of these two numbers, and continue that pattern for the entire channel. Thus, after each new digit is presented, a new total is achieved. Performance is indexed by the number of total correct responses. For both tests, raw total scores were converted to demographically adjusted *T*-scores (e.g., Heaton et al., 2004). To definite working memory impairment, the *T*-scores were converted to blinded clinical ratings (see Woods et al., 2004), which range from 1 (above average, *T*-score < 55) to 9 (severe, *T*-score < 20). A clinical ratings cut-point of >5 was used to classify individuals as "impaired," which is consistent with prior research in MA, enhances the clinical relevance of our study, and provides an empirically-based method upon which to base our pair-wise comparisons. Nevertheless, it is important to note that our primary findings remained unchanged when we used average working memory *T*-score rather than clinical ratings in our statistical models.

In order to examine the specificity of the working memory effects on the IGT, we also analyzed data from a series of standard clinical neurocognitive tests from the battery. Tests of *episodic memory* included the delayed recall trials of the Hopkins Verbal Learning Test-Revised (HVLT-R; Benedict et al., 1998) and the Brief Visuospatial Memory Test-Revised (BVMT-R; Benedict, 1997). Measures of *executive functions* included Trailmaking Test Part B (TMT; Army Individual Test Battery, 1944), preservative responses on the Wisconsin Card Sorting Test (WCST-64; Kongs et al., 2000), and the inhibition trial on the Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001). *Verbal fluency* measures included the Controlled Oral Word Association Test (COWAT-FAS; Benton et al., 1983; Gladsjo et al., 1999) and semantic verbal fluency (animals; Benton et al., 1983). The *speed of information processing* domain included Trailmaking Test Part A (TMT; Army Individual Test Battery, 1944), Digit Symbol and Symbol Search from the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; The Psychological Corporation, 1997), and the color naming trial on the D-KEFS. The clinical ratings procedure referenced above was also used to operationalize impairment in each of these neurocognitive domains.

2.4. Psychiatric and medical assessment

All participants underwent a structured psychiatric assessment using the Composite International Diagnostic Interview (CIDI Version 2.1; World Health Organization, 1997) to generate current (e.g., met DSM-IV diagnostic criteria for MDD within the last 30 days) and lifetime diagnoses of MDD, and substance use disorders (e.g., abuse and dependence) per *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.) criteria. Antisocial personality disorder (ASPD) and current and lifetime ADHD diagnoses were generated using the Diagnostic Interview Schedule for the DSM-IV (DIS-IV; Robins et al., 1995). The DIS-IV assesses lifetime symptoms of ADHD and stipulates that the first onset of symptoms occurs between ages 6–10 and the DIS-IV assess for symptoms, therefore the onset of ADHD+MA+ participants' ADHD occurred prior to the onset of their MA use disorder (range of age of MA first use = 12–39 years of age) and all individuals included in the ADHD group had lifetime symptoms of ADHD. The DIS-IV also adheres to DSM-IV guidelines for a current ADHD diagnosis, which requires that an individual meet diagnostic criteria for ADHD within the last 12 months. Although a significant proportion ($n = 16$) of ADHD+ participants reported currently (e.g., within the last 30 days) experiencing ADHD symptoms, no participants in the ADHD+ groups reported currently taking stimulant medications (e.g., dextroamphetamine, methylphenidate), which was confirmed through urine toxicology screening on the day of testing. Only three participants in the non-ADHD MA group reported a history of being prescribed stimulant medications. Participants completed a set of questionnaires including the Beck Depression Inventory (BDI-II; Beck et al., 1961). Participants also received a comprehensive neuromedical evaluation, which included a review of medications, medical history, and current symptoms as well as a complete physical, a blood draw and a lumbar puncture.

By design of the larger NIDA-funded study from which participants were selected, the two MA+ groups included some individuals infected with HIV and HCV. HIV infection was determined using enzyme linked immunosorbent assays (ELISA) and a Western Blot confirmatory test. All subjects were evaluated for HCV-infection by using enzyme linked immunosorbent assays (ELISA) to asses HCV IgG in serum. The proportions of HIV+ and HCV+ participants included in the MA+ADHD+ (HIV+ $n = 16$; HCV+ $n = 6$) and MA+ADHD– (HIV+ $n = 6$; HCV+ $n = 9$) groups were comparable ($ps > 0.10$). HIV+ participants did not show any significant differences on relevant disease or treatment (e.g., CD4 count, AIDS diagnoses) characteristics ($ps > 0.10$) across MA status. Similarly, HCV+ participants were comparable on relevant HCV disease characteristics (e.g., total bilirubin; $ps > 0.10$) across the MA cells. Within the entire MA+ sample ($N = 48$), independent samples *t*-tests showed that there was no significant effect of HIV ($p = 0.275$) or HCV ($p = 0.323$) on the IGT summary score. These null findings for HIV and HCV were confirmed when examined in the MA+ADHD– and MA+ADHD+ groups separately ($ps > 0.10$) and thus infectious disease status was not used as a covariate in the statistical models.

2.5. Data analysis

A critical alpha level of 0.05 was employed for all analyses, which were conducted with JMP 9.0.2 (SAS, Cary, NC). We first conducted a multiple regression predicting IGT summary score from study group (i.e., dummy codes for MA–ADHD–, MA+ADHD–, or MA+ADHD+), working memory status (dummy codes for impaired or unimpaired), and their interaction. Follow-up pair-wise comparisons were conducted using independent samples *t*-tests with Cohen's *d* estimates of effect size. In light of long-standing recommendations to evaluate IGT deck-specific subscales and across trials as a complement to summary score analyses, we next conducted two separate mixed model MANOVAs using the raw scores from: 1) separate deck totals from A + B and C + D; and 2) the five grouped trials of (C + D) – (A + B) as the within-subjects factors (i.e., trial groupings of 1–20, 21–40, 41–60, 61–80, and 81–100), with group status (i.e., MA–ADHD– versus MA+ADHD– versus MA+ADHD+) and working memory impairment (dichotomized), and their interactions as the between-subjects factors.

3. Results

The primary multiple regression model predicting IGT summary score from study group status, working memory, and their interaction was significant (adjusted $R^2 = 0.07$, $p = 0.036$). We observed a significant main effect of group status, such that the MA+ADHD+ group was significantly more likely to select cards from the disadvantageous decks as indicated by the IGT summary score (*t-ratio* $= -3.62$; $p = 0.0006$). The main effect of working memory

impairment was not significant (*t-ratio* = −1.02; $p = 0.311$); however we did observe a significant interaction between group status and working memory impairment on the IGT summary score (*t-ratio* = −2.51; $p = 0.015$). Specifically, the MA+ADHD+ participants who were working memory impaired had significantly lower IGT summary scores (MA+ADHD+WM+; *Mean* = 35.6, *SD* = 4.2) versus all other study groups, including working memory non-impaired MA+ADHD+ participants (MA+ADHD+WM−; *Mean* = 45.4, *SD* = 5.8; *Cohen's d* = 1.94; $p = 0.002$), working memory impaired (MA+ADHD−WM+; *Mean* = 48.9, *SD* = 9.5; *Cohen's d* = 1.81; $p = 0.013$) and non-impaired MA+ADHD− participants (MA+ADHD−WM−; *Mean* = 47.3, *SD* = 7.0; *Cohen's d* = 2.03; $p = 0.003$), and working memory impaired (MA−ADHD−WM+; *Mean* = 50.3, *SD* = 9.3; *Cohen's d* = 2.04; $p = 0.015$) and non-impaired healthy adults (MA−ADHD−WM−; *Mean* = 48.6, *SD* = 8.4; *Cohen's d* = 1.96; $p = 0.003$).

A series of post-hoc analyses were conducted to examine several potentially confounding factors. First, the incorporation of comorbid DSM-IV diagnoses, including MDD (or Beck Depression Inventory) and non-MA substance use disorders (e.g., abuse or dependence; alcohol, cannabis, cocaine, opioids) in the regression models described above did not change the primary outcomes. Furthermore, these diagnoses were not independently associated with IGT summary score in these models (*ps* > 0.10). Second, we conducted identical multiple regression analyses as described above to determine whether study group status interacted with impairment in any other cognitive ability area measured. Results showed that there were no interactions between study group status and any of the other cognitive domains, including verbal fluency, episodic memory, executive functions, or speed of information processing (all *ps* > 0.10). Memory impairment was the only domain main effect that was independently associated with IGT performance in these models (*t-ratio* = −2.25; $p = 0.028$).

The mixed model MANOVA examining raw scores from decks A + B and C + D showed a main effect of IGT deck ($F(1, 64) = 0.45$; $p = 0.504$). There was not a main effect of working memory impairment ($F(1, 64) = 1.04$; $p = 0.312$) but there was a significant effect of group status ($F(2, 64) = 6.55$; $p = 0.003$) and a significant interaction between group, working memory, and IGT deck ($F(2, 64) = 3.22$; $p = 0.047$). The pair-wise comparisons, which parallel those described above for the primary analysis in showing the disproportionate effects of MA, ADHD, and working memory deficits, are displayed graphically in Fig. 1. Finally, to evaluate IGT performance across trial, we conducted a mixed model MANOVA with the five 20 item trial blocks as within-subjects factor and group status and working memory impairment as the between-subjects factor. The main effects of IGT trial block ($F(4, 61) = 3.17$; $p = 0.020$) and group status were significant ($F(2, 64) = 7.24$; $p = 0.002$). Although the main effect of working memory impairment was not significant ($F(1, 64) = 0.84$; $p = 0.363$), we did observe a significant interaction between group status, working memory impairment, and IGT trial block ($F(8, 122) = 2.20$; *Wilks' Lambda* = 0.032). Specifically, MA+ADHD+ participants who were working memory impaired preformed similarly to MA+ADHD− and MA−ADHD− participants on trials 1, 2 and 5 of the IGT but were significantly more likely to perform disadvantageously on trial 3 and trial 4 of the IGT (*ps* < 0.05). Fig. 2 plots the results of the significant group status × working memory impairment × IGT trial block interaction, across the IGT.

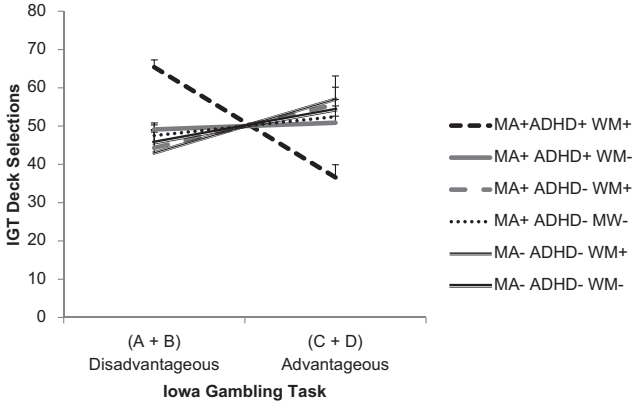

Fig. 1. IGT performance of MA−ADHD− MA+ADHD− and MA+ADHD+ individuals by working memory impairment.

4. Discussion

Results of the present study indicate that adults with comorbid MA and ADHD demonstrate an increased propensity toward risky decision-making (i.e., making choices that produce disadvantageous outcomes) on the IGT. These findings are consistent with prior studies of stimulant abusers substances, who commonly show impaired performance on the IGT, perhaps due to dysfunction in frontostriatal pathways (e.g., Bechara et al., 2001; Bechara and Martin, 2004; Gonzalez et al., 2007; Grant et al., 2000). Consistent with the prior work of Bechara and Martin (2004), our data indicate that working memory deficits interact with ADHD to amplify risky decision-making in MA dependent individuals. Specifically, MA+ADHD+ participants who were impaired on clinical measures of working memory were significantly more likely to engage in risky decision-making on the IGT. Furthermore, decision-making deficits on the IGT were *specific* to impairment in working memory, meaning no interactions were observed between MA+ADHD+ and impairment in other cognitive domains (e.g., executive functions, speed of information processing). MA+ADHD+ participants who are working memory impaired may have difficulty maintaining and evaluating information online, thereby limiting their capacity to develop, evaluate, and deploy effective decision-making strategies. In turn, this may increase their likelihood of impulsive responding and engagement in risky behaviors. These findings are consistent with prior research by conducted by Bechara and Martin (2004) in substance abusing populations, as well as studies in healthy adults (e.g., Hinson et al., 2002) indicating that working memory plays a central role in decision-making.

4.1. Limitations

The study has several limitations. Firstly, it is important to recognize that decision-making is an expansive construct of which the IGT is only one of several approaches used to define risky decision-making (Buelow and Suhr, 2009). Future research in the area of decision-making in MA users with comorbid ADHD should examine performance on other aspects of decision-making; for example, measures of delayed discounting and behavioral risk taking (e.g., Balloon Analog Risk Task) likely warrant exploration in

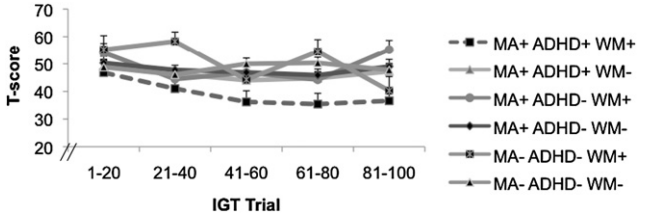

Fig. 2. IGT performance the study participants by trial blocks.

this population. Second these data are inferential in regard to the hypothesized frontostriatal pathogenesis, and as such we cannot rule out the involvement of the posterior parietal cortex, which is affected in MA (Jernigan et al., 2005) and involved in both decision-making (Paulus et al., 2003) and working memory (Mellers et al., 1995). Although the inclusion of a healthy comparison sample is a methodological strength, we are limited by the absence of a non-MA ADHD comparison group (e.g., MA−ADHD+). The omission of a pure ADHD group limits the extent to which we can speak to the additive or synergistic effects of this comorbidity. It is possible that we simply observed an ADHD effect. Moreover, participants with remote (e.g., >5 years ago) non-MA substance use disorders were included in the "healthy" comparison sample. Although this provides a more conservative comparison group for a study of substance abuse, we cannot rule out the inclusion of such individuals may have somewhat dampened our statistical signal given the known associations between other substances of abuse and decision-making.

Another limitation of this study is that, although study exclusionary criteria were rigorous, undiagnosed conditions might have cognitive effects and therefore may have biased the results. Results also may have been biased by under-reporting of illicit substance use and/or depressive symptoms. However, post-hoc analysis showed that including lifetime history of a non-MA substance use disorder or MDD in the statistical models did not alter our primary findings. These findings are consistent with a recent study, which showed that self-reported psychiatric symptoms do not impact performance on the IGT in individuals with substance use disorders (van Toor et al., 2011).

It should be noted that, by design of the parent study, the two MA+ groups included some individuals infected with HIV and/or HCV. This is an important distinction since research shows that HIV status impacts IGT performance (e.g., Gonzalez et al., 2010; Hardy et al., 2006). A prior study conducted by Martin and colleagues (2004) showed that HIV+ substance dependent individuals were significantly more likely to make risky decisions on the IGT compared to HIV− substance dependent individuals. Analyses in the current cohort did not reveal performance differences on the IGT among our small cohort of HIV+ participants (*ps* > 0.10). Although the effect of HCV-infection on IGT performance specifically has not been previously explored, HCV has been associated with discounting of delayed rewards (Huckans et al., 2011) Nevertheless, we did not observe an HCV effect on the IGT in the current sample; as such, we contend that the inclusion of HIV and HCV infected participants in this study did not appear to have affected the findings in a meaningful way. That being said, future studies regarding the combined effects of MA and infectious disease on decision-making may be of value, particularly considering the high rates of comorbidity and prior evidence that they may have additive effects on central nervous system structure and function (e.g., Rippeth et al., 2004).

4.2. Conclusions

Despite these limitations, the findings from this study may have clinical implications. Studies show that comorbid ADHD is associated with worse clinical outcomes in substance abusing adults, including more rapid progression from substance abuse to dependence and a longer duration of substance abuse (Wilens, 2004). The propensity for MA users with comorbid ADHD to engage in risky decision-making may adversely impact substance abuse treatment outcomes. Because these individuals are strongly motivated by the lure of short-term immediate reward, they may resist seeking treatment or discontinue treatment prematurely. As such, reliance on traditional 12-step treatment programs alone may not be adequate (Wilens, 2004). MA use is associated with high rates of relapse and data suggests that at approximately 50% of MA users will relapse within the first year of sobriety (Paulus et al., 2005). MA dependent individuals with comorbid ADHD may be at increased risk for relapse because they are unable to effectively evaluate the negative consequences associated with continued MA use, therefore multimodal treatment that includes non-stimulant pharmacotherapy in addition to traditional psychotherapy may be necessary to prevent relapse in this subgroups of MA users. Careful screening and monitoring of MA users with comorbid ADHD (particularly those with compromised working memory) may facilitate compliance with the treatment plan.

In addition to clinical treatment implications, risky decision-making can have significant real-world consequences in other important functional arenas. For example, decision-making deficits may increase the likelihood of financial mismanagement (e.g., gambling), vocational difficulties (e.g., unemployment), and automobile driving accidents in MA users with ADHD. Research shows that MA dependent adults score poorly on measures of everyday functional ability (e.g., finance, transportation, medication adherence) and that these deficits are associated with executive dysfunction (Henry et al., 2010). MA users with comorbid ADHD may also be more likely to engage in high risk drug and sexual behaviors, such as sharing needles or engaging in unprotected sex, thereby increasing the risk for negative health outcomes, including HIV and HCV transmission (e.g., Darke et al., 2008; Scott et al., 2007). Treatment providers should remain cognizant that MA dependent individuals with ADHD may be at particular risk to engage in risky decision-making and intervention strategies should be tailored accordingly (e.g., working memory training; Bickel et al., 2011).

Role of funding source

This research study supported by grants P01-DA12065 (Grant), P50-DA026306 (Grant), and P30-MH62512 (Grant) from the NIH. The NIH had no further role in study design; in the collection, analysis, and interpretation of the data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Steven Paul Woods, J. Hampton Atkinson, and Igor Grant designed the study and wrote the protocol. Alexandra Rooney and Nichole A. Duarte managed the literature searches. Nichole A. Duarte undertook the statistical analysis. Nichole A. Duarte wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All authors declare they have no conflicts of interest.

Acknowledgments

The Translational Methamphetamine AIDS Research Center (TMARC) is supported by Center award P50-DA026306 from the National Institute on Drug Abuse (NIDA) and is affiliated with the University of California, San Diego (UCSD) and the Sanford-Burnham Medical Research Institute. The TMARC is comprised of: Director: Igor Grant, M.D.; Co-Directors: Ronald J. Ellis, M.D., Ph.D., Cristian Achim, M.D., Ph.D., and Scott Letendre, M.D.; Center Manager: Steven Paul Woods, Psy.D.; Aaron Carr (Assistant Center Manager); Clinical Assessment and Laboratory Core: Scott Letendre, M.D. (P.I.), Ronald J. Ellis, M.D., Ph.D., Rachel Schrier, Ph.D.; Neuropsychiatric Core: Robert K. Heaton, Ph.D. (P.I.), J. Hampton Atkinson,

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The views expressed in this article are those of the authors and do not reflect the official policy or position of the United States Government.

This research was supported by grants P01-DA12065 (Grant), P50-DA026306 (Grant), and P30-MH62512 (Grant) from the National Institutes of Health.

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