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Neurocognitive impairments in MDMA and other drug users: MDMA alone may not be a cognitive risk factor

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Background: MDMA (3,4-methylenedioxymethamphetamine; "Ecstasy") is an amphetamine derivative with mild hallucinogenic and stimulant qualities. MDMA leads to serotonin (5-hydroxytryptamine; 5-HT) neurotoxicity and has been linked to cognitive impairments. It remains unclear whether these impairments are due to MDMA versus other drug use. *Method:* Neurocognitive functioning was measured in a sample of abstinent polydrug users ($n=52$) with a range of MDMA use and healthy nondrug controls ($n=29$). Participants completed a comprehensive neuropsychological battery and self-report measures of drug use. *Results:* Polydrug users performed worse than controls on spatial span and spatial working memory ($ps < .05$). Among polydrug users, lifetime marijuana use significantly predicted verbal learning and memory performance ($p < .01$), while MDMA use was not predictive of cognitive impairment. *Conclusions:* This study and our previous report (Hanson, Luciana, & Sullwold, 2008) suggest that moderate MDMA use does not lead to persistent impairments above and beyond that associated with generally heavy drug use, but polydrug use may lead to dose-related temporal and frontoparietal dysfunction. Marijuana use may be particularly problematic. Cause–effect relations are unclear.

Keywords: 3,4-Methylenedioxymethamphetamine; Ecstasy; Cognition; Drug use; Serotonin; Memory; Executive function; Marijuana.

INTRODUCTION

MDMA (3,4-methylenedioxymethamphetamine; "Ecstasy") is an amphetamine derivative with mild hallucinogenic and stimulant qualities (Davidson & Parrott, 1997; Liechti, Gamma, & Vollenweider, 2001; Vollenweider, Gamma, Liechti, & Huber, 1998). It acts acutely as a serotonin (5-hydroxytryptamine; 5-HT) releasing agent and reuptake inhibitor, eliciting an initial increase in brain 5-HT release followed by a period of decreased release after prolonged dosage (e.g., Schmidt, 1987). 5-HT regulates multiple psychological functions, including memory, sensory and motor processes, mood, and impulsivity (Feldman, Meyer, & Quenzer, 1997). Accumulating evidence suggests that MDMA is a 5-HT neurotoxin and that recreational use may be harmful (e.g., Gerra et al., 2000; Lew et al., 1996; Reneman et al., 2002).

Due to concerns about MDMA's potential neurotoxic effects, multiple laboratories have studied neurocognitive functions in MDMA users. A significant challenge in conducting such research is that MDMA users typically use multiple drugs that may impact cognition alone or in combination (e.g., marijuana, stimulants, hallucinogens; Morgan, 2000), and thus potential impacts of MDMA use cannot be examined in isolation. To address

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this issue, previous studies have often included comparison samples of other drug users with no MDMA use history (i.e., MDMA-naïve drug users). By matching groups based on exposure to other substances, researchers hope to better isolate the specificity of MDMA's effects on behavior.

The most frequently reported cognitive deficit is in verbal memory. MDMA users have demonstrated verbal recall deficits relative to *MDMA-naïve controls* (e.g., McCardle, Luebbers, Carter, Croft, & Stough, 2004; Parrott, Lees, Garnham, Jones, & Wesnes, 1998; Reneman, Booij, Schmand, van den Brink, & Gunning, 2000), *poly-drug-using controls* (e.g., Curran & Verheyden, 2003; Fox, Toplis, Turner, & Parrott, 2001b; Morgan, 1999; Morgan, McFie, Fleetwood, & Robinson, 2002), *MDMA-naïve cannabis users* (Gouzoulis-Mayfrank et al., 2000), and *alcohol users* (Curran & Travill, 1997), while recognition memory appears better preserved (Reneman et al., 2001). In addition, MDMA users have exhibited lower verbal memory performance relative to expected levels based on normative data (Hanson & Luciana, 2004; Krystal, Price, Opsahl, Ricaurte, & Heninger, 1992). Evidence of visual memory problems is less robust with some studies showing visuospatial memory deficits in MDMA users (Fox et al., 2002; Gouzoulis-Mayfrank et al., 2000; Verkes et al., 2001; Wareing, Murphy, & Fisk, 2004), yet others report similar performance among groups (e.g., Medina, Shear, & Corcoran, 2005; Morgan, 1998; Simon & Mattick, 2002; Thomasius et al., 2003).

The verbal recall deficits appear to be dose related and suggest that MDMA use may be responsible (e.g., Bhattachary & Powell, 2001; Bolla et al., 1998; Medina et al., 2005; Morgan et al., 2002). Longitudinal research has found that prolonged MDMA use may lead to further verbal memory decrements (Zakzanis & Young, 2001), although not all studies support this conclusion (e.g., Gouzoulis-Mayfrank et al., 2005; Verbaten, 2003). Moreover, several studies have reported associations between task performance and other drug use, particularly use of marijuana (e.g., Croft, Mackay, Mills, & Gruzelier, 2001; Dafters, Hoshi, & Talbot, 2004; Montgomery, Fisk, Newcombe, & Murphy, 2005).

MDMA users have also exhibited evidence of executive dysfunction. Specifically, they have shown poorer spatial working memory performance relative to MDMA-naïve controls (e.g., Fox et al., 2002; Fox, Parrott, & Turner, 2001a; Hanson & Luciana, 2004; Wareing, Fisk, Murphy, & Montgomery, 2005), and verbal fluency deficits have also been reported (Bhattachary & Powell, 2001; Heffernan, Jarvis, Rodgers, Scholey, & Ling, 2001), with some exceptions (e.g., Back-Madruga et al., 2003; Curran & Verheyden, 2003). In addition, MDMA users have shown problems with planning, set shifting, and problem solving (Dafters, Duffy, O'Donnell, & Bouquet, 1999; Morgan et al., 2002; Schifano, Di Furia, Forza, Minicuci, & Bricolo, 1998), although these findings have not always been replicated (e.g., Back-Madruga et al., 2003; Fox et al., 2002; Gouzoulis-Mayfrank, Thimm, Rezk, Hensen, & Daumann, 2003). MDMA users (and other drug users) have also shown evidence of risky decision-making and reward-related decision-making deficits possibly due to poor inhibitory control (Hanson, Luciana, & Sullwold, 2008; Moeller et al., 2007; Morgan, Impallomeni, Pirona, & Rogers, 2006; Quednow et al., 2007; Roiser, Rogers, Cook, & Sahakian, 2006).

Behavioral control seems quite relevant as a measure of interest in this population, given that it may be related to substance use outside of the laboratory. While inhibition has not been thoroughly explored, MDMA users have demonstrated a speed–accuracy trade-off on a behavioral measure of impulsivity suggesting poor inhibitory control, which was related to the extent of previous MDMA use (Morgan, 1998; Morgan et al., 2002). In another study, heavy MDMA users generated fewer problem-solving strategies while simultaneously inhibiting previously reinforced responses, despite shorter planning times (Halpern et al., 2004). Behavioral inhibition among MDMA users requires further study before general conclusions can be made.

Another interesting question is whether MDMA has differential effects on the cerebral hemispheres. Examining motor function can assist in determining lateralized patterns of disturbance within the brain. Thus far, findings among MDMA users are inconclusive given the lack of extensive research on this topic (Krystal et al., 1992). However, poorer fine motor dexterity and reduced psychomotor speed are suggested (Croft et al., 2001; Hanson & Luciana, 2004). When found, these impairments do not suggest a lateralized pattern of dysfunction.

Collectively, research on neurocognitive functioning among MDMA users provides compelling evidence of verbal memory deficits and executive dysfunction, which appear to be dose related. Whether MDMA users have deficits in behavioral inhibition or psychomotor abilities warrants further exploration; however, MDMA users have consistently demonstrated poorer accuracy on a variety of tasks. For all abilities tested, there are pronounced variations in findings across studies and among research groups likely due to differences in patterns of MDMA use between cohorts and, importantly, the influence of other drug use (Parrott, 2006). The impact of marijuana use is particularly concerning (e.g., Bolla, Brown, Eldreth, Tate, & Cadet, 2002; Pope & Yurgelun-Todd, 1996; Solowij et al., 2002; Yurgelun-Todd, Gruber, & Pope, 1996), and heavy alcohol use among youth has also been associated with decrements in neuropsychological function (e.g., Brown, Tapert, Granholm, & Delis, 2000; Sullivan & Pfefferbaum, 2005; Tapert, Granholm, Leedy, & Brown, 2002).

These findings raise a number of questions and interpretive challenges with respect to the types of pathology exhibited by MDMA users, as well as their etiologies. Given the prevalence of other drug use among MDMA users, it is difficult to unequivocally state that the observed deficits resulted from MDMA versus other drug use. The following study was designed to clarify the nature of neuropsychological deficits exhibited by MDMA users, while also considering the impact of other drug use. We examined a sample of young adult

polydrug users with a range of MDMA use (0–150 occasions of use) and a group of non-drug-using controls. Our approach was to first compare polydrug users to nondrug controls on a battery of neuropsychological tests and then to examine the dose-related impact of MDMA and other drug use through a series of hierarchical regressions.

Based on previous studies and consistent with the notion that recall is subserved by the frontal cortex, we hypothesized that polydrug users would exhibit impairments in verbal learning and memory, but not memory span, relative to nondrug controls. Polydrug users were also expected to exhibit reductions in executive skills (verbal and spatial working memory, behavioral inhibition) and psychomotor speed and dexterity. If MDMA use is primarily responsible for observed impairments, then we expected that greater MDMA use would predict poorer neuropsychological performance in each cognitive domain, even after accounting for other drug use.

METHOD

Participants

A total of 81 individuals, ages 18–35 years, were studied: (a) recreational polydrug users with a range of MDMA use (0–150 occasions of MDMA use; $n=52$); and (b) individuals with no history of drug use or psychiatric illness (healthy nondrug controls; $n=29$). A total of 41 participants (25 controls, 16 polydrug users) were recruited from undergraduate psychology courses at the University of Minnesota and received extra credit points for participation. Others (4 controls, 36 polydrug users) were recruited via posted advertisements throughout the university and metro communities and received monetary payment for participation.

Inclusion criteria included being a native English speaker, having normal or corrected-to-normal vision and hearing, and having no reported history of neurological problems, physical disease, or current pregnancy. Participants were required to be medication free aside from birth control pills. Healthy nondrug controls were excluded from data analysis if they reported >10 marijuana uses, any use of other recreational drugs, and/or if they met current or past DSM–IV (*Diagnostic and Statistical Manual for Mental Disorders–Fourth Edition, Text Revision;* American Psychiatric Association, APA, 2000) criteria for any psychiatric disorder, including alcohol or other substance abuse or dependence.

Our initial aim was to recruit two groups of drug users: (a) MDMA users and (b) other drug users without a history of MDMA use. Recruitment criteria for MDMA users consisted of multiple occasions of MDMA use, preferably >15 uses and some use within the past year. Recruitment criteria for the other drug use group were initially designed to match the drug use patterns of MDMA users (aside from MDMA) and consisted of self-reported use of at least two different substances on a regular basis and no history of MDMA use. However, in our recruitment of this community sample of drug users, moderate to heavy MDMA users were more difficult to find than in previous years, and other drug users tended to report a handful of MDMA uses. Furthermore, MDMA users tended to use other drugs more heavily. Because of these challenges, we elected to combine the two groups to form a single group of polydrug users. We examined the dose-related effects of MDMA and other drug use through appropriate statistical tests, as described below. The dose-dependent cognitive deficits reported in the MDMA literature further support this approach (e.g., Bhattachary & Powell, 2001; Bolla et al., 1998; Medina et al., 2005; Morgan et al., 2002). Within the drug use groups, a past history of a *DSM–IV* mood or anxiety disorder was acceptable, but meeting criteria for a current mood disorder was grounds for exclusion.

All participants agreed to abstain from recreational drug use for at least two weeks and to refrain from alcohol use for at least 48 hours prior to testing. Compliance was measured by self-report. Participants were permitted to use their typical amounts of tobacco and caffeine. This study was approved by the University of Minnesota's Institutional Review Board. All participants provided informed consent prior to participation.

Procedure

Eligible participants completed an initial phone screening followed by an in-person demographic and medical screening interview, completion of the Beck Depression Inventory (BDI; Beck, Ward, Mendelsohn, Mock, & Erbaugh, 1961), and a semistructured clinical interview (*Structured Clinical Interview for DSM–IV Axis I Disorders–Patient Edition, Version 2.0*; SCID-I/P; First, Spitzer, Gibbon, & Williams, 1997). Participants answered questions about their drug use histories, including a time-line follow-back procedure with specific questions addressing MDMA use. Questions were posed during a semistructured interview that used temporal cues to aid recall. Detailed information was obtained about the type, quantity, and frequency of drug use across the past 30 days, the past year, and total lifetime use for MDMA, marijuana, stimulants (including cocaine), hallucinogens, sedatives, opiates, inhalants, and other drugs (e.g., over-the-counter diet pills). Hallucinogens do not include MDMA. The total drug use variables were created by adding together the occasions of use of each class of drugs for each time period (including MDMA but excluding alcohol). The average number of alcoholic drinks per week was estimated by multiplying the participants' self-reported average drinking occasions per week and the average number of alcoholic drinks per occasion.

Participants then completed several self-report personality questionnaires and a comprehensive neuropsychological battery, including measures of memory, executive function, behavioral inhibition, motor function, and decision-making. Findings from the personality and decision-making measures are summarized in Hanson et al. (2008). The current study focuses on the remainder of the neuropsychological results.

Neuropsychological testing

General intellectual function. A pro-rated IQ estimate (Sattler, 2001) was obtained via the Wechsler Adult Intelligence Scale–Third Edition (WAIS–III; Wechsler, 1997) Vocabulary and Block Design subtests.

The following neuropsychological tests were also administered to assess a broad range of cognitive domains:

Verbal paragraph recall. Wechsler Memory Scale–Revised (WMS–R; Wechsler, 1987), Logical Memory subtest: immediate and 30-minute delayed recall (age-corrected standard scores).

Verbal word recall. Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964; Taylor, 1959): Trial I total, total of Trials I–V, immediate recall, 30-minute delayed recall, total errors.

Spatial span. Cambridge Neuropsychological Test Automated Battery (CANTAB; Fray, Robbins, & Sahakian, 1996): number of items recalled in correct sequence across trials.

Verbal memory span and working memory. WAIS–III Digit Span (Wechsler, 1997): number of digits correctly recalled in forward and backward sequence.

Verbal fluency. Controlled Oral Word Association Test (COWAT; Lezak, Howieson, & Loring, 2004): total words generated.

Verbal fluency set shifting. Alternate between "S" and "T": total words generated.

Psychomotor speed. Finger Tapping Test (Reitan & Wolfson, 1993): average number of taps per hand.

Fine motor dexterity. Grooved Pegboard Task (Lafayette Instrument, 1989): time to completion (in seconds).

Spatial working memory. Spatial Delayed Response Task (Luciana & Collins, 1997; Luciana, Collins, & Depue, 1998; Luciana, Depue, Arbisi, & Leon, 1992): This task measured working memory for the locations of spatial targets. During each of 48 trials, participants observed a central fixation point on a computer monitor for 3 s. Next, a visual cue (a black asterisk) appeared in peripheral vision for 200 ms. After the occurrence of this visual cue, the cue and fixation point disappeared, and the screen blackened for randomly interspersed delay intervals of 500 ms, 4,000 ms, or 8,000 ms. After the delay interval, the screen instantly lit, and the participant indicated the remembered location of the cue with a touch-pen device (FastPoint Technologies, Inc.). A block of 16 "no delay" trials was administered to measure basic perceptual and visuomotor processes. The average error scores for each delay condition (500, 4,000, and 8,000 ms) was recorded.

Behavioral inhibition. Go/No-Go Task (computerized task derived from Braver, Barch, Gray, Molfese, & Snyder, 2001): Participants viewed stimuli that were rapidly presented one at a time on a computer screen (160 trials). A total of 80% of stimuli (128 trials) were designated as "go" stimuli (i.e., capitalized letters), to which the participant was instructed to respond by pressing the space bar. A total of 20% of the trials (32 trials) consisted of a "no go" stimulus (i.e., a capitalized "X") to which the participant was instructed to inhibit responding. Given the higher frequency of "go" stimuli, participants are set up to hit the space bar on most trials and must inhibit this response when a "no go" stimulus occurs. For each participant, the hit rate (no. of correct go trials/total no. go trials) and false-alarm rate (no. no-go errors/total no. no-go trials) were calculated. These scores were used to estimate *d*-prime, which is a measure of overall discriminability between go and no-go trials (Wickens, 2002).

Neuropsychological battery: Data reduction

To reduce the number of comparisons, and thus the possibility of Type I error, we created composite scores when possible. A hybrid method was used (see Delis, Jacobson, Bondi, Hamilton, & Salmon, 2003, for a discussion), which uses both information about established cognitive domains (Lezak et al., 2004) and the results of reliability analyses. First, *z*-scores were derived for each individual neuropsychological task variable based on the entire sample of participants ($N=81$). Variables were *z*-scored to ensure that higher scores reflected better performance. Next, cognitive domains were determined based on theoretical grounds. *Z* scores were averaged to form composite indices for each cognitive domain. Standardized Cronbach's α coefficients were calculated to ensure that the individual subtests representing each domain were internally consistent. Composites where Cronbach's α coefficients were less than .60 were reevaluated. It was determined that some measures were better represented by standing alone.

This procedure resulted in six summary scores: (a) verbal learning and memory ($\alpha=.85$; WMS–R Logical Memory—immediate and 30-minute delayed recall; RAVLT—total of Trials I–V, immediate recall, 30-minute delayed recall, total errors); (b) verbal working memory ($\alpha=.73$; RAVLT—Trial I total; WAIS–III Digit Span—number of digits correctly recalled in forward and backward sequence; COWAT—total words recalled in standard and shift versions); (c) spatial span (CANTAB Spatial Span—number of items correctly recalled); (d) spatial working memory (Spatial Delayed Response Task—difference between 8,000-ms vs. 500-ms delay accuracy scores); (e) behavioral inhibition (Go/No-Go Task—d'); and (f) psychomotor speed and dexterity ($\alpha=.63$; Finger Tapping Test—average taps per hand across three 10-s trials each; Grooved Pegboard Task—time to completion for each hand).

Statistics

Data were analyzed using the Statistical Package for the Social Sciences (SPSS, Inc, Chicago, IL, USA), Version 14.0 for Windows. Distributions of all variables were examined prior to analysis, and some variables were log 10 transformed to meet the assumptions for parametric analysis (i.e., BDI scores; RAVLT errors; Grooved Pegboard time; drug use). Fisher's exact tests were used to compare dichotomous variables between groups (i.e., gender, race, handedness distribution). Univariate analyses of variance (ANOVAs) assessed for group differences in other demographic characteristics (age, years of education, BDI score). Since some drug use variables did not meet requirements for parametric analysis, the Mann–Whitney procedure compared drug-use characteristics between groups.

As mentioned previously, we elected to combine MDMA and other drug users into a single group of polydrug users for comparison to non-drug-using controls. Univariate ANOVAs were used to analyze differences in cognitive summary scores between polydrug users and controls. Follow-up ANOVAs were conducted on individual subtest scores when significant group differences were found on summary scores. Since polydrug users were slightly older than controls, age was entered as a covariate in group comparisons. Effect sizes are presented as partial eta-squared (η_p^2, range=0 to 1), and alpha levels below .05 were considered statistically significant.

Hierarchical regressions assessed for dose-dependent relationships between lifetime drug use and cognitive function within the polydrug use group ($n=52$). For each regression, Block 1 entered age, BDI score, and average number of alcoholic drinks consumed per week; Block 2 entered lifetime use of the most commonly used substances in this group of polydrug users (i.e., marijuana, stimulants, and hallucinogens); and Block 3 entered lifetime MDMA use to examine whether MDMA use influenced performance above and beyond other drug use. Dependent variables were the six neuropsychological summary scores. Follow-up Spearman's rho nonparametric correlations were computed for each significant regression model.

RESULTS

Demographics

As noted in the Method section, two different strategies were used to recruit study participants. Within the control group, there were fewer paid participants relative to polydrug users ($p < .001$). Because recruitment status may have impacted other observed group differences, demographic variables were compared between participants who received monetary versus extra credit point compensation. Paid versus course-credit participants were similar in their gender, race, handedness, BDI depression scores, and IQs. However, a two-way ANOVA (Group×Reimbursement Method) revealed that paid participants were, on average, 2.6 years older, $F(1, 77)=5.61$, $p < .05$, and had more education (<1 year), $F(1, 77)=5.66$, $p < .05$, than those who received extra credit points. Since the polydrug use group consisted of relatively more paid participants, paid participants also had significantly more lifetime alcohol and drug use than course-credit participants. Importantly, paid versus course-credit participants did not differ on cognitive summary scores (all p-values >.05). Further, many of the paid participants were recruited from the University community, and, thus, the sample was generally homogeneous. Given these findings, recruitment method was not considered in the remainder of the analyses.

The control sample was next compared to the polydrug sample. Controls and polydrug users were similar in gender, race, handedness distribution, education, and IQs (see Table 1). However, polydrug users were slightly older than controls, and they reported higher levels of depression symptoms than controls based on BDI scores, which can range from 0 to 63. However, the mean scores for all groups fell within the nonclinical range based on recommended interpretive cutoffs (Kendall, Hollon, Beck, Hammen, & Ingram, 1987).

MDMA characteristics and other illicit drug use

Polydrug users reported lifetime use of a variety of drugs, primarily marijuana, cocaine/other stimulants, and hallucinogens. In addition, a range of lifetime MDMA use (0–150 occasions) was observed (see Table 1 for a summary of lifetime drug and alcohol use and detailed information regarding MDMA use).

Substance use disorder (SUD) criteria were quantified via the SCID for alcohol, marijuana, MDMA, cocaine, other stimulants, hallucinogens, sedatives, inhalants, opioids, and other drugs (e.g., over-the-counter drugs). Nearly all polydrug users (98.1%) met lifetime diagnostic criteria for substance abuse/dependence, particularly for MDMA, alcohol, and marijuana. The total (lifetime) number of substances for which this sample of drug users reported either abuse or dependence, including MDMA, ranged from 0 to 7 (mean=2.8, $SD=1.6$; median=2.0; mode=2.0). In terms of current SUDs, 32 polydrug users (61.5%) had no current SUD, 13 (25%) met SUD criteria for one substance, 5 individuals (9.6%) met criteria for two substances, and 2 individuals (3.8%) met criteria for three substances. Nevertheless, these data should not be interpreted to reflect symptom-free status in the polydrug sample. Many polydrug users reported current symptoms of substance abuse and/or dependence even if these fell short of meeting current diagnostic criteria.

Comorbid psychopathology

Based on the SCID, some polydrug users met lifetime criteria for psychological disorders. Other than SUDs, the most common clinical condition observed was unipolar depression, past episode ($n=13$). Polydrug users with a history of unipolar depression ($n=13$) were

TABLE 1
Demographic and substance use characteristics of nondrug controls and polydrug users

	Controls (n=29)	*Polydrug users (n=52)*	*F or Fisher's exact*	*U*
Demographics				
Age	19.8 (2.0)	21.6 (3.8)	6.15*	
Gender ratio (male:female)	17:12	32:20	*ns*	
Race (% Caucasian)	75.9	75.0	8.70†	
% right-handed	86.2	90.4	*ns*	
Beck Depression Inventory total score	2.4 (3.6)	5.1 (4.5)	7.71**	
Years of education	13.4 (1.0)	13.7 (1.4)	0.69	
Estimated Full Scale IQ	117.6 (11.7)	118.4 (11.7)	0.09	
Vocabulary standard score	13.1 (2.6)	13.8 (2.2)	1.63	
Block Design standard score	13.0 (2.6)	12.5 (2.8)	0.61	
Substance use				
Occasions of alcohol use per week	0.6 (0.8)	2.5 (1.9)		207.0***
Drinks per occasion of use	2.1 (2.1)	5.3 (3.0)		276.5***
Occasions of drug use: past 30 days	0.0 (0.2)	16.0 (22.8)		92.0***
Occasions of drug use: past year	0.3 (1.1)	603.9 (918.3)		1.0***
Occasions of drug use: lifetime	1.2 (2.0)	3,295.3 (5,214.0)		0.0***
Marijuana	1.2 (2.0)	2,396.0 (3,504.6)		0.0***
Stimulants	0.0 (0.0)	682.0 (2,285.7)		116.0***
Hallucinogens	0.0 (0.0)	57.0 (173.7)		72.5***
Inhalants	0.0 (0.0)	22.9 (74.8)		319.0***
Opiates	0.0 (0.0)	22.2 (29.5)		145.0***
Sedatives/hypnotics	0.0 (0.0)	11.0 (35.2)		435.0***
Other drugs	0.0 (0.0)	60.4 (205.6)		348.0***
MDMA use				
Occasions of MDMA use: past 30 days[a]	0.0 (0.0)	0.1 (0.2)(range: 0–1)		710.5
Occasions of MDMA use: past year[a]	0.0 (0.0)	3.1 (6.1)(range: 0–30)		420.5***
Occasions of MDMA use: lifetime[a]	0.0 (0.0)	17.1 (27.4)(range: 0–150)		261.0***
Duration of MDMA use (months)[b]	—	31.4 (25.1)		—
Time since last MDMA use (weeks)[b]	—	50.9 (61.9)		—
Avg. no. MDMA pills per session[b]	—	1.7 (1.1)		—
Max. no. MDMA pills ever taken in one session[b]	—	3.3 (3.3)		—
No. occasions multiple MDMA doses consumed[b]	—	11.5 (25.3)		—

Note. Values are means; standard deviations are in parentheses. Aside from alcohol use characteristics, substance use means represent estimated number of occasions of use for each time period or drug. Mann–Whitney *U*s were computed between controls and polydrug users when appropriate. [a]These variables included all participants. [b]These variables included only those participants who had ever ingested MDMA ($n=34$ polydrug users).
†$p < .10$. *$p < .05$. **$p < .01$. ***$p < .001$.

compared to those with no depression history ($n=39$). No significant group differences in cognitive performance were found (all p-values >.05).

Cognitive performance in controls versus polydrug users

Statistical information and means and standard deviations of summary z-scores are presented in Table 2. Means and standard deviations from the individual subtests are presented in Table 3.

A univariate ANOVA revealed a significant group difference in spatial span, $F(1, 78)=4.12$, $p < .05$. Polydrug users demonstrated poorer spatial memory spans than did controls.

A significant group difference was also found on the spatial working memory summary score, $F(1, 78)=4.51$, $p < .05$; $\eta_p^2=.06$, with polydrug users performing worse than controls indicating that polydrug users were more negatively impacted by increasing delay intervals than were controls. In this measure of spatial working memory, two processes are of interest: (a) error scores at each delay level (500, 4,000, and 8,000 ms), and (b) the relative impact of increasing delay (memory load) on performance. Memory load is examined by computing the difference between error scores on 8,000- versus 500-ms trials and on 4,000- versus 500-ms trials. When these difference scores are examined between groups, they represent the Delay × Group interaction. As described above, the 8,000- versus 500-ms accuracy difference score was chosen for the purposes of data reduction (Luciana et al., 1998). Nevertheless, groups also varied on the accuracy difference between 4,000- and 500-ms trials, $F(1, 78)=4.69$, $p < .05$, $\eta_p^2=.06$; again, polydrug users were more negatively impacted by increasing delay intervals than were controls.

TABLE 2
Neuropsychological summary scores in controls versus polydrug users

Cognitive summary scores	*Controls (n=29)*	*Polydrug users (n=52)*	*F*	*Effect size* η_p^2
Verbal learning and memory	0.07 (0.74)	–0.04 (0.77)	0.12	.00
Verbal working memory	0.06 (0.53)	–0.06 (0.78)	0.11	.00
Spatial span	0.36 (0.91)	–0.20 (1.00)	4.12*	.05
Spatial working memory	0.32 (0.75)	–0.18 (1.08)	4.51*	.06
Behavioral inhibition	–0.09 (1.00)	0.05 (1.00)	0.56	.01
Psychomotor speed and dexterity	0.09 (0.67)	–0.04 (0.71)	1.44	.02

Note. Values are *z*-score means for each group; standard deviations are in parentheses.
*$p < .05$.

TABLE 3
Neuropsychological subtest scores in controls and polydrug users

Neuropsychological subtests			*Controls (n=29)*	*Polydrug users (n=52)*
Verbal learning and memory	WMS–R Logical Memory[a]	Immediate recall	104.8 (15.0)	103.5 (13.0)
		30-min delayed recall	103.4 (14.2)	102.7 (13.2)
	RAVLT	Total of Trials I–V	60.2 (7.0)	57.9 (7.2)
		Immediate recall	13.2 (2.0)	13.1 (2.2)
		30-min delayed recall	12.3 (2.5)	12.6 (2.2)
		Total errors	1.3 (2.0)	2.5 (3.7)
Verbal working memory	RAVLT	Trial I total	7.8 (1.9)	7.0 (2.1)
	Digit Span	No. digits forward	7.6 (1.1)	7.3 (1.2)
		No. digits backward	6.0 (1.3)	5.8 (1.5)
	COWAT	Standard version: total no. words	44.1 (10.6)	44.9 (11.1)
		Shift version: total no. words	32.7 (5.8)	33.1 (6.8)
Spatial span	Spatial Span	No. items recalled	8.0 (1.1)	7.4 (1.2)
Spatial working memory	Accuracy scores	4,000–500-ms delay difference*	1.4 (1.6)	2.2 (1.7)
		8,000–500-ms delay difference*	3.0 (1.6)	4.1 (2.3)
Behavioral inhibition	Go/No-Go Task	*d'*	2.4 (0.9)	2.6 (0.9)
Psychomotor speed and dexterity	Finger Tapping Test	Dominant hand	49.6 (6.9)	48.2 (8.4)
		Nondominant hand	46.4 (7.9)	45.5 (8.1)
	Grooved Pegboard: time to completion	Dominant hand	65.1 (7.6)	65.0 (9.6)
		Nondominant hand	69.4 (9.9)	71.6 (10.9)

Note. Unless otherwise indicated, values are raw score means; standard deviations are in parentheses. WMS–R = Wechsler Memory Scale–Revised. RAVLT = Rey Auditory Verbal Learning Test. COWAT = Controlled Oral Word Association Test.
[a]Age-corrected standard scores.
*$p < .05$.

No group differences were found on the verbal learning and memory, verbal working memory, behavioral inhibition, or psychomotor speed and dexterity summary scores.

Relationship between drug use and cognitive task performance

Spearman's rho nonparametric correlations showed that greater total occasions of drug use (including all classes of drugs) in the past 30 days ($\rho = -.53$, $p < .001$), the past year ($\rho = -.51$, $p < .001$), and lifetime use ($\rho = -.40$, $p < .01$) were significantly associated with poorer verbal learning and memory. Lifetime ($\rho = -.29$, $p < .05$) and past year ($\rho = -.30$, $p < .05$) total drug use were also negatively correlated with spatial working memory. A series of multiple regressions examined whether lifetime use of any specific drug use classes predicted performance on each of the six neuropsychological domains. Block 1 entered age, BDI depression scores, and weekly alcohol consumption. Block 2 entered lifetime occasions of marijuana, stimulant, and hallucinogen use, which were the most frequently used substances in this sample. Block 3 entered lifetime MDMA use to the model.

Lifetime drug use predicted verbal learning and memory performance above and beyond the effects accounted for by age, depression scores, and weekly alcohol use: Block 2,

$F(6, 43) = 3.86$, $p = .004$; $R^2_\Delta = 25.6\%$. Examination of the individual drug use variables indicated that greater lifetime marijuana use was significantly associated with poorer verbal learning and memory ($\beta = -.53$, $p = .003$). Lifetime stimulant use was nearly significantly associated with performance on this domain ($\beta = .32$, $p = .054$). The addition of MDMA use did not improve the model: Block 3, $F(7, 42) = 3.24$, $p = .008$; $R^2_\Delta = 0.1\%$. Each of the remaining five regressions did not attain statistical significance: verbal working memory—overall model $F(7, 38) = 1.12$, $p = .37$; spatial working memory—overall model $F = 1.32$, $p = .26$; spatial span—overall model $F < 1$; behavioral inhibition—overall model $F < 1$; psychomotor speed and dexterity—overall model $F < 1$.

Follow-up correlations showed that lifetime marijuana use was significantly negatively correlated with the verbal learning and memory summary score (see Figure 1; $\rho = -.47$, $p < .05$), as well as each of the subtests: Logical Memory immediate ($\rho = -.30$, $p < .05$) and delayed recall ($\rho = -.33$, $p < .05$); RAVLT total of Trials I–V ($\rho = -.41$, $p < .01$), immediate recall ($\rho = -.45$, $p = .001$), and delayed recall ($\rho = -.32$, $p < .05$); it was positively correlated with RAVLT total errors ($\rho = .31$, $p < .05$). Past year and past 30-day marijuana use were also significantly negatively correlated with these measures (ρs = –.30 to –.56, ps < .05 to < .001). RAVLT error scores were positively correlated with past year use ($\rho = .30$, $p < .05$) but were not correlated with marijuana use in the past 30 days. Lifetime stimulant use was not significantly correlated with verbal learning and memory, but greater stimulant use in the past year ($\rho = -.29$, $p < .05$) and the past 30 days ($\rho = -.29$, $p < .05$) was correlated with poorer performance.

Exploratory multiple regressions examining the influence of more recent drug use showed that greater past year drug use (marijuana, stimulants, hallucinogens) was predictive of poorer verbal learning and memory performance—Block 2, $F(6, 27) = 3.47$, $p = .01$; $R^2_\Delta = 36.1\%$—but past year MDMA use did not significantly improve the model ($R^2_\Delta = 1.6\%$). Specifically, greater past year use of marijuana ($\beta = -.40$, $p = .02$) and hallucinogens ($\beta = -.39$, $p = .02$) predicted worse performance. Greater drug use in the past 30 days was also predictive of poorer verbal learning and memory performance—Block 2, $F(6, 27) = 3.32$, $p = .01$; $R^2_\Delta = 35.1\%$), but, again, MDMA use did not improve the model ($R^2_\Delta = 0.1\%$). More occasions of marijuana ($\beta = -.44$, $p = .01$) and hallucinogen use ($\beta = -.01$, $p = .054$) in the past 30 days were associated with poorer verbal learning and memory.

Exploratory correlations examined whether cognitive performance was related to the lifetime number of drug use diagnoses or any of the individual MDMA use characteristics. The spatial working memory summary score was negatively correlated with the average number of MDMA pills taken per occasion of use ($\rho = -.38$, $p < .05$) and the maximum number of MDMA pills ever taken during an occasion of use ($\rho = -.34$, $p = .05$), suggesting that higher MDMA doses were associated with worse spatial working memory performance. Neither the lifetime number of drug use diagnoses nor the other individual MDMA use characteristics were significantly correlated with any of the cognitive summary scores.

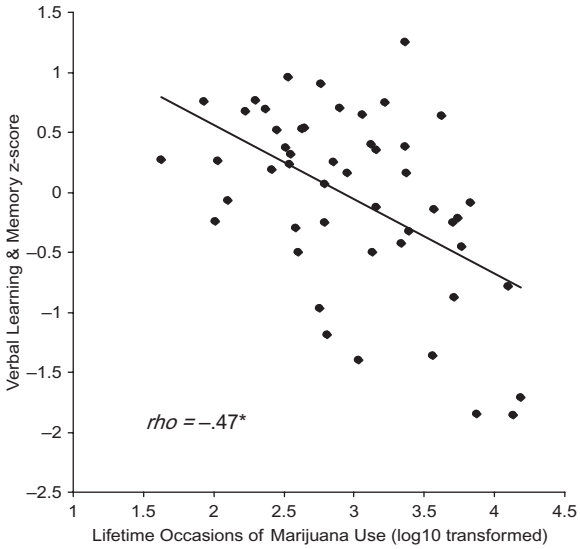

Figure 1. Greater lifetime marijuana use among polydrug users is associated with poorer verbal learning and memory. Verbal learning and memory *z*-score consisted of immediate and delayed verbal paragraph recall (Wechsler Memory Scale–Revised, WMS–R, Logical Memory) and a word list learning task (Rey Auditory Verbal Learning Test). *$p < .05$.

DISCUSSION

This study examined the neurocognitive characteristics among polydrug users with a range of MDMA use compared to nondrug controls. Our sample of MDMA/polydrug users was similar to previous samples in terms of demographics (e.g., Croft et al., 2001; Morgan et al., 2002), other drug use (e.g., McCann, Mertl, Eligulashvili, & Ricaurte, 1999; Morgan, 1999), and psychiatric history (e.g., Krystal et al., 1992; Parrott, Milani, Parmar, & Turner, 2001). Polydrug users were first compared to controls; then regression analyses examined dose–response relationships using continuous measures of drug use. The first major finding is that polydrug users performed worse than controls on measures of spatial span and spatial working memory. Second, among polydrug users, lifetime marijuana use significantly predicted verbal learning and memory performance, but MDMA use did not appear to affect performance above and beyond other drug use. Collectively, these findings suggest dose-related temporal and frontoparietal dysfunction among drug users. This dysfunction does not appear to be associated specifically with MDMA use.

Neurocognitive findings: Polydrug users versus nondrug controls

As mentioned above, we found that polydrug users demonstrated poorer spatial working memory and shorter spatial memory spans than did nondrug controls. Verkes et al. (2001) also reported shorter spatial spans

among MDMA users than among non-drug-using controls. Morgan (1998), however, reported similar spatial span among MDMA users, polydrug users, and controls. In terms of spatial working memory, polydrug users were more negatively impacted by increases in delay (i.e., poorer accuracy), suggesting greater sensitivity to increments in memory load, consistent with our previous report, which compared MDMA users to non-drug-using controls (Hanson & Luciana, 2004).

Deficits in spatial span and spatial working memory may be related to drug-induced changes in brain activation. Studies of healthy adults have demonstrated that frontal and parietal areas are activated during spatial working memory tasks (Diwadkar, Carpenter, & Just, 2000; Jansma, Ramsey, Coppola, & Kahn, 2000; Leung, Seelig, & Gore, 2004). Altered blood oxygen level-dependent (BOLD) response during spatial working memory tasks has been found in frontal, temporal, and parietal areas in adolescents and adults with alcohol use disorders and/or heavy marijuana use (Kanayama, Rogowska, Pope, Gruber, & Yurgelun-Todd, 2004; Padula, Schweinsburg, & Tapert, 2007; Schweinsburg et al., 2005; Tapert et al., 2001; Tapert et al., 2004), despite similar performance on the tasks relative to nonabusing controls. Such patterns suggest neural reorganization among substance users and that they may be compensating by engaging additional or different brain areas (e.g., Kanayama et al., 2004; Quickfall & Crockford, 2006; Schweinsburg et al., 2005). These findings also emphasize that even when neuropsychological tests do not show deficits among substance users, neural activation may differ. Importantly, some of these studies were conducted with adolescents and/or with only brief abstinence periods of several hours to a few days. Nevertheless, most of the users in this sample initiated use during adolescence, which is a time of continued neurodevelopment (Giedd et al., 1999; Gogtay et al., 2004). It is possible that the exposure to drugs during adolescence altered the course of brain development. However, longer periods of abstinence may result in normalization of cognitive function and neural activity (Quickfall & Crockford, 2006).

Together with our recent finding of reward-related decision-making deficits among MDMA users and other drug users (Hanson et al., 2008), dose-related dysfunction within the temporal, frontoparietal, and frontostriatal cortices is suggested among drug users. Furthermore, since these cognitive findings are focused within the nonverbal domain, the possibility of nondominant hemisphere dysfunction is suggested. However, many studies have reported verbal deficits among MDMA users and other drug users, so this pattern warrants further study. The impact of heavy alcohol use within the drug use group is also questioned, since heavy alcohol use has historically been associated with right-hemisphere dysfunction (Ellis & Oscar-Berman, 1989; Parsons, 1987; Zhang, Begleiter, & Porjesz, 1997), although more recent studies do not support this conjecture (Kwon, Rourke, & Grant, 1997; Sullivan, Rosenbloom, & Pfefferbaum, 2000; Wegner, Gunthner, & Fahle, 2001).

The lack of group differences in verbal learning and memory is consistent with some previous reports (e.g., Back-Madruga et al., 2003; Dafters et al., 1999; Fox et al., 2001a) but contrasts with multiple others that found verbal memory deficits among MDMA users (e.g., Fox et al., 2001b; Gouzoulis-Mayfrank et al., 2000; McCardle et al., 2004; Morgan et al., 2002). Polydrug users and controls performed similarly on verbal working memory (i.e., verbal fluency, verbal memory span), adding to the mixed literature on verbal fluency (e.g., Bhattachary & Powell, 2001; Curran & Verheyden, 2003) but supporting previous findings on verbal working memory (Bhattachary & Powell, 2001; Hanson & Luciana, 2004; Thomasius et al., 2003). The groups also performed similarly in behavioral impulsivity, consistent with previous reports (Fox et al., 2002; Thomasius et al., 2003). This area requires additional research, but thus far, behavioral inhibition (as measured by laboratory tasks) among MDMA/polydrug users appears intact. Polydrug users did not show relative reductions in psychomotor speed and dexterity, consistent with Krystal et al. (1992). Previously, we reported bilateral reductions in psychomotor speed but intact fine motor dexterity among MDMA users (Hanson & Luciana, 2004). Given the limited research on motor function, this area requires further study. Finally, it is important to note that our study compared polydrug users with a range of MDMA use (some with no MDMA use history) to controls, which may also explain some differences from previous research.

Relationship between drug use and cognitive performance

Among polydrug users, greater lifetime marijuana use significantly predicted poorer verbal learning and memory, which included measures of verbal paragraph recall and word list learning and recall. The regression model controlled for age, depression scores, and weekly alcohol consumption, and lifetime use of marijuana, stimulants, hallucinogens, and MDMA were entered as predictors of cognitive function. Lifetime marijuana use was significantly related to verbal learning and memory performance, while lifetime stimulant use was a marginally significant predictor of verbal memory. The addition of lifetime MDMA use to the regression model offered no improvement. Follow-up analyses showed that past 30 day and past year marijuana and hallucinogen use were also predictive of verbal memory performance. Lifetime drug use was not predictive of performance on other neuropsychological domains (i.e., verbal and spatial working memory, spatial span, behavioral inhibition, and psychomotor speed and dexterity).

Overall, this suggests a dose-response relationship between heavier lifetime drug use and poorer verbal learning and memory, but it does not provide convincing evidence that MDMA, specifically, is associated with cognitive decline. Although marijuana use was

most strongly related to performance, use of stimulants and hallucinogens also appeared to have an impact on cognition. Nevertheless, exploratory correlations revealed that higher doses of MDMA ingested on each occasion of use were associated with poorer spatial working memory performance. Previous studies have linked cognitive deficits to the extent of MDMA exposure, suggesting that MDMA use is responsible (e.g., Bhattachary & Powell, 2001; Bolla et al., 1998; Morgan, 1999; Morgan et al., 2002); others did not find dose–response relationships between MDMA use and cognitive decline (e.g., Daumann, Fischerman, Heekeren, Thron, & Gouzoulis-Mayfrank, 2004; Gouzoulis-Mayfrank et al., 2005; Verbaten, 2003).

Indeed, some evidence suggests nonimpairment among MDMA users relative to controls on multiple tasks and within some subgroups. Possible explanations for variability within the literature include differences in MDMA use characteristics, polydrug use, premorbid vulnerabilities, and environmental influences (Parrott, 2006), as well as methodological differences. These variables likely moderate the degree of damage or impairment detected subsequent to MDMA use (Huether, Zhou, & Rüther, 1997). Further, the degree of environmental stress likely interacts with premorbid susceptibilities to determine the degree of impairment, consistent with a diathesis-stress model (Parrott, 2006).

As previously discussed, evidence suggests that other drug use is associated with cognitive deficits (e.g., Croft et al., 2001; Dafters et al., 2004; Montgomery et al., 2005). Studies of cannabis (e.g., Bolla et al., 2002; Pope & Yurgelun-Todd, 1996; Solowij et al., 2002; Yurgelun-Todd et al., 1996), cocaine, amphetamine, and opiate users (see Rogers & Robbins, 2001; Verdejo-Garcia, Lopez-Torrecillas, Gimenez, & Perez-Garcia, 2004) have shown dose-related memory, attention, visuospatial, psychomotor, and/or executive dysfunction. Of particular note is a meta-analysis of marijuana users that reported subtle but persistent deficits in learning and memory, while other cognitive domains appeared intact (Grant, Gonzalez, Carey, Natarajan, & Wolfson, 2003). Cognitive deficits are particularly prominent following chronic, heavy marijuana use (e.g., 25–45 years of use), as opposed to shorter term use (e.g., 8–10 years of use; Fletcher et al., 1996; Solowij et al., 2002). Neuroimaging studies of marijuana users have also detected changes in temporal lobe activity, although research in this area has been limited (see Quickfall & Crockford, 2006, for a review). However, in many studies, performance is evaluated after only 19–72 hours of abstinence from marijuana, and, thus, impairments may be due to the enduring presence of marijuana or its metabolites within the brain (i.e., "drug residue") or to withdrawal effects. Furthermore, Pope, Gruber, Hudson, Huestis, and Yurgelun-Todd (2001) found that cognitive abilities returned to normal within one month of abstinence from marijuana.

Heavy alcohol use is also common among drug users and has been associated with similar cognitive deficits (e.g., Brown et al., 2000; Sullivan & Pfefferbaum, 2005; Tapert et al., 2002). In the current study, weekly alcohol use was not a significant predictor of cognitive performance. Nevertheless, these findings emphasize the challenge of attributing deficits to any particular drug. Had we studied MDMA users alone and compared them to controls, we might have concluded that MDMA use is associated with cognitive impairment. Because we included a number of relatively heavy drug users with a range of MDMA use, we were able to examine the dose-related impact of MDMA and other substance use, as supported by the literature.

Limitations

Certain methodological and ethical issues present interpretive challenges in studies of drug users (Curran, 2000; Morgan, 2000). First, legal and practical issues limit the measurement of functioning prior to drug use initiation, and long-term drug administration in a controlled environment would be unethical. Therefore, researchers rely on naturalistic studies and retrospective reports, and it is difficult to confirm whether MDMA or other drug use is responsible for any differences. Second, to differentiate between the acute and residual effects of substance use versus longer lasting effects, the current study required a two-week period of abstinence from drugs and a 48-hour period for alcohol. Due to financial constraints, drug use histories were obtained via self-report; nevertheless, self-report generally corresponds with biological assays (Schifano et al., 1998; Thomasius et al., 2003). Third, "ecstasy" tablets sometimes contain other drugs (Curran, 2000), but previous evidence suggests that 85–90% of pills contain a 100–150-mg recreational dose of MDMA (Schifano et al., 1998).

Our sample reflects the difficulty of recruiting individuals matched for extent of drug use; we found that individuals who had used MDMA, especially in large amounts, also tended to use other drugs more heavily. Clearly, other drug use should be carefully considered in this type of research. In addition, many of the MDMA users had minimal MDMA use within the past year, and some drug users had minimal use of other drugs within the past year. Therefore, some participants might be expected to have normal cognitive functioning given this period of sobriety, and a sample with more recent use might yield different findings. Also, "other drug users" without any MDMA use were challenging to find, lending further rationale for examining dose–response relationships between drug use and cognitive performance in a combined group of drug users.

Our sample consists of young adults who may have more cognitive reserve; older and more chronic users might be expected to show more cognitive deficits. In addition, participants were recruited from two primary sources: university undergraduate courses and the university/metro community. While the sample is generally homogeneous, we cannot be certain that the study is free of bias in motivation for participation or honesty in self-report of drug use. Nevertheless, participants receiving compensation through course credit versus monetary payment did not differ in their performance on the six cognitive domains tested.

Finally, it is unclear whether the cognitive deficits reported in this study would have any clinical significance, although a subset of individuals performed in the low average to mildly impaired range in learning and memory. While motivational factors could be involved, memory performance at this level is likely to impact their daily functioning in academic and work settings.

CONCLUSION

In conclusion, this study and our previous report (Hanson et al., 2008) suggest that moderate MDMA use does not lead to persistent impairments above and beyond generally heavy drug use, but polydrug use may lead to dose-related temporal, frontoparietal, and frontostriatal dysfunction. Furthermore, marijuana use appears to have a particular impact on verbal learning and memory, and use of stimulants and hallucinogens may also play a role. Future research should expand on the cognitive domains that have not been as thoroughly explored (e.g., behavioral impulsivity, decision making, motor function). To better ascertain premorbid functioning, longitudinal studies should begin prior to the highest risk period for substance use initiation and continue through young adulthood and into middle adulthood to determine whether cognitive impairments persist or worsen after drug use has ceased (e.g., Tapert & Brown, 1999; Tapert et al., 2002).

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