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ECSTASY (MDMA) EXPOSURE AND NEUROPSYCHOLOGICAL FUNCTIONING:
A POLYDRUG PERSPECTIVE

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ABSTRACT

Use of ecstasy (3,4-Methylenedioxymethamphetamine, MDMA) is becoming an increasing health problem across the United States. Numerous studies have demonstrated that ecstasy is a selective serotonin neurotoxin in several animal species and in humans. However, until recently, the cognitive consequences of ecstasy use have been relatively unknown. Studies to date have consistently demonstrated deficits in verbal memory among ecstasy users; while only some have examined impairments in visual memory, working memory, abstract reasoning, planning, attention, and problem solving. To date, there are no published studies that adequately assess the effects of ecstasy exposure on cognitive functioning while controlling for other drugs of abuse, gender, and demographic variables known to be associated with cognitive performance. The primary goal of the proposed project was to assess the relationship between exposure to the psychoactive drug ecstasy and cognitive functioning among 65 men and women. It was hypothesized that increased lifetime and past year ecstasy exposure would be related to poorer performance on cognitive tasks after controlling statistically for consumption of other drugs and potential confounding factors such as age, education, gender, premorbid intelligence, and ethnicity. The primary finding was that increased ecstasy exposure was significantly related to poorer verbal memory and learning ability, while no such relationship was found between executive functioning. Furthermore, gender was found to moderate the relationship with ecstasy exposure and cognitive functioning, including verbal memory retention, visual memory ability, working memory, visual fluency, and cognitive inhibition.

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CHAPTER 1: BACKGROUND AND SIGNIFICANCE

Prevalence and Patterns of Ecstasy Use

The nation's top monitoring systems indicate that ecstasy use is increasing throughout the United States (HHS, 1999). The U.S. Customs Service (USCS) also reported that seizures of ecstasy tablets increased from 750,000 in 1998 to approximately 9.3 million in 2000 (Community Epidemiology Work Group [CEWG], 2001). Lifetime ecstasy consumption among United States high school seniors has increased since 1994 from 6% to 11% in 2000; and 8.2% have used it during the past year (Zickler, 2001). This trend is true for young adults as well. A nationally representative sample of college students (N=14,724) revealed a substantial increase in past year ecstasy consumption from 1997 (2.8%) to 1999 (4.7%), with a subsample (including ten colleges) showing continued growth in 2000 (10.6% lifetime prevalence) (Strote, Lee, & Wechsler, 2001).

This rise in ecstasy use is also evident in the state of Ohio (where the current research was conducted). The Ohio Substance Abuse Monitoring Network reported that ecstasy use in central Ohio is increasing among young people between the ages of 15 and 25, homosexuals, and African Americans in areas such as Cleveland, Akron-Canton, and Columbus, Ohio (OSAM, 2001; Cincinnati was not included in the survey). Furthermore, ecstasy is increasingly being used in Ohio outside of the traditional "rave" or dance club setting, and now includes settings such as home, school, and small parties or gatherings (OSAM, 2001). Thus, ecstasy abuse across the United States has dramatically increased during the past decade and is becoming an mounting health care crisis due to ecstasy's detrimental physical and potential acute and chronic psychological and

neuropsychological effects (e.g., Fox, Toplis, Turner, & Parrott, 2001; Mathais & Zickler, 2001; McCann, Eligulashvili, & Ricaurte, 2000).

Psychopharmacological Properties of Ecstasy

The synthetic drug 3,4-Methylenedioxymethamphetamine (MDMA, the primary compound in pills known as “ecstasy”) is structurally similar to methamphetamine and the hallucinogen mescaline. MDMA affects brain neurochemistry by binding to serotonin (5-hydroxytryptamine, 5-HT) transporters, preventing serotonin reuptake from nerve terminals and thus increasing serotonin in the synaptic space and increasing serotonin receptor activation (Parrott, 2001). Although the primary effect of MDMA action is on serotonin, it can also increase activation of other neurotransmitters including dopamine, noradrenaline, acetylcholine and histamine (Parrott, 2001). Ecstasy is relatively fast acting: a response typically occurs within thirty minutes of ingesting one pill, and lasts between 3 and 5 hours. Individuals who use ecstasy report improved mood, feelings of closeness, sensual and perceptual enhancement, increased insight, and greater energy (Solowij, Hall, & Lee, 1992). Negative side effects include increased heart rate and blood pressure, jaw clenching, anxiety, and confusion (e.g., Tancer & Johanson, 2001).

Serotonin Neurotoxicity and Ecstasy Use: Animal Studies

Numerous studies have demonstrated MDMA (ecstasy) induced selective serotonin damage in brain areas including the frontal cortex, hippocampus, striatum, occipital cortex, and brain stem of several animal species, including rats (Broening et al., 1991;

O'Shea et al., 1998; Scheffel et al., 1992; Sharkey, McBean, & Kelly, 1991; Stone et al., 1986; Ricaurte et al., 1993), squirrel monkeys (Hatzidimitriou et al., 1999), rhesus monkeys (Taffe et al., 2001), and baboons (Scheffel et al., 1998). For example, a recent study demonstrated significant reduction (34%) of serotonin in the rat hippocampus fourteen days after treatment with MDMA (Sprague, Preston, Lefiheit, & Woodside, 2003). It is also noteworthy that nonhuman primates appear to be more susceptible to the neurotoxic effects of MDMA than lower mammals. That is, dosages necessary to produce neurotoxicity in primates are lower than those required for serotonin damage in rats (Ricaurte, Yuan, & McCann, 2000). Furthermore, in contrast to the recovery of serotonergic functioning evident in most rats after MDMA administration, monkeys who were administered MDMA twice a day for four days continued to show destruction of serotonin neuron terminals and abnormal patterns of serotonin terminal regrowth seven years later (Fischer, Hatzidimitriou, Wlos, Katz, & Ricaurte, 1995; Hatzidimitriou et al., 1999). Application of interspecies scaling principles suggests that dosages of MDMA required to cause serotonin neurotoxicity in animals fall within the range of recreational ecstasy use by humans. In monkeys this dose of 5 mg/kg is sufficient. The equivalent dose in humans is 1.28 mg/kg or 96 mg in a 75-kg individual, which is well within the range of the typical (75-125) mg dose taken by ecstasy users (O'Shea et al., 1998; Ricaurte, Yuan et al., 2000). Reports of maximum dosages among human ecstasy users have been as high as 2000 mg of MDMA in one sitting (although this is relatively rare) (Zakzanis & Young, 2001). Thus, based on animal research, humans who use ecstasy are at risk to develop lasting damage to their brain serotonergic systems.

Serotonin Neurotoxicity and Ecstasy Use: Human Studies

Recent converging lines of evidence have indicated that ecstasy (MDMA) is a selective serotonin neurotoxin in humans as well. Although there is currently no direct method of measuring serotonin neurotoxicity in living human brains, studies have utilized indirect measures including: measuring the concentration of 5-hydroxyindoleacetic acid (5-HIAA, a major metabolite of serotonin) in cerebrospinal fluid (CSF), imaging studies including positron emission tomography (PET) measuring McN-5652 (a serotonin transporter ligand), pharmacological challenge studies (described below), and neuropsychological studies (e.g., McCann et al., 2000).

Studies utilizing CSF have found selective reductions in cerebrospinal fluid 5-hydroxyindoleacetic acid (serotonin metabolite) among recreational ecstasy users compared to controls (with no differences in major metabolites of dopamine and norepinephrine) (McCann, Ridenour, Shaham, & Ricaurte, 1994; Bolla, McCann, & Ricaurte, 1998).

Ecstasy consumption has also been demonstrated to reduce regional cerebral brain electric activity (measured by EEG) in the anterior temporal and posterior orbital cortex (Frei, Gamma, Pascual-Marqui et al., 2001). More recent research utilizing imaging techniques, such as PET and SPECT, have also demonstrated serotonin depletion among abstinent ecstasy users (McCann et al., 1998; Reneman et al., 2000; Ricaurte, McCann, Szabo, & Scheffel, 2000), and in two studies the level of McN-5652 (a serotonin transporter ligand) was correlated with cumulative lifetime dosage of ecstasy (McCann et al., 1998; Ricaurte, McCann et al., 2000). Reneman and colleagues (2002), utilizing

SPECT, found lower densities of post-synaptic 5-HT_{2A} in the frontal, parietal, and occipital lobes among recent MDMA users (average length of abstinence was 3.3 weeks). The study also found that ex-MDMA users demonstrated higher 5-HT_{2A} receptor density in the frontal and parietal lobes (temporal lobe was not examined) compared to recent MDMA users, and increased occipital 5-HT_{2A} density, representing possible compensatory upregulation. Recent research has also demonstrated preliminary evidence of hippocampal dysfunction among recently abstinent ecstasy users (Daumann, Fimm, Willmes, Thron, & Gouzoulis-Mayfrank, 2003; Jacobsen, Mencl, Pugh, Skudlarski, & Krystal, In Press). In contrast, two studies utilizing PET, as well as SPECT and MRI, failed to find regional or global cerebral blood flow differences between ecstasy users and controls (Chang et al., 2000; Gamma, Buck, Berthold, & Vollenweider, 2001).

Pharmacological challenge studies have also provided useful techniques to determine whether ecstasy produces serotonin neurotoxicity in humans. Because serotonin is involved in the regulation of prolactin, cortisol and growth hormone secretion, abnormal hormone regulation can be an indication of serotonin neurotoxicity. With few exceptions (McCann et al., 1994), studies have found altered neuroendocrine function, including blunted plasma prolactin and cortisol responses (Gerra et al., 2000; Gerra et al., 1998; McCann et al., 1994; Price et al., 1989).

One criticism of the research on the neurotoxic effects of ecstasy in humans is that studies were retrospective in design so the observed serotonin abnormalities may have been preexisting. Still, only ecstasy (MDMA) and other amphetamine analogs have demonstrated selective serotonin neurotoxicity in animal and human studies (McCann et al., 2000) in ecstasy-naïve subjects. Thus, one can have confidence that the resultant

abnormalities were from MDMA use. Therefore, in combination, these imaging, cerebral spinal fluid, and pharmacological challenge studies suggest that ecstasy causes some serotonin (5-HT) injury in humans (McCann et al., 2000). It remains to be seen exactly what dosage is necessary and sufficient to produce serotonin damage, or what extent of damage is necessary to observe clinically relevant cognitive changes in human ecstasy users.

Neuropsychological Effects of Ecstasy

Serotonin is involved in several behavioral domains including the regulation of mood, sleep, vigilance, memory and learning, feeding, and sexual behavior (Naughton, Mulrooney, & Leonard, 2000). Further, because animal and human imaging studies have demonstrated ecstasy-induced damage in the temporal lobes (including the hippocampus), frontal lobes (including dorsolateral and orbital frontal cortex in humans), the parietal lobe, and brain stem (in animals) (Fischer et al., 1995; Frei et al., 2001; Hatzidimitriou et al., 1999; McCann et al. 1998; McCann et al., 2000; Reneman et al., 2002; Taffe et al., 2001), it is suspected that long-term ecstasy use may result in memory, working memory, attention, and executive functioning deficits. Because of this hypothesis, the cognitive effects of ecstasy use have gained attention during the last few years (Morgan, 2000).

The most consistent finding of neuropsychological studies is that ecstasy users demonstrate decrements in verbal learning and memory compared to ecstasy-naïve controls (Fox et al., 2001; Morgan, 1999; Morgan, McFie, Fleetwood, & Robinson, 2002; Rodgers, 2000; Zakzanis & Young, 2001). Furthermore, there is preliminary evidence in

abstinent ecstasy users that this verbal memory deficit is correlated with the extent of serotonin damage (measured by CSF 5-HIAA) (McCann et al., 1999; Reneman, Booij, Schmand, van de Brink, Boudewijn, 2000). Bolla and colleagues (1998) collected data from 24 abstinent ecstasy users, whose lifetime consumption ranged from 25 to 300 tablets, and 24 ecstasy-naïve controls. They found that greater cumulative lifetime dose of ecstasy was associated with impaired immediate and delayed verbal memory and learning, and delayed visual memory. Interestingly, differences in memory ability were not found when they compared the ecstasy group to the control group without taking dosage into account. Thus, within the ecstasy group, increased consumption was related to poorer performance.

Studies assessing the effects of ecstasy consumption on visual memory ability are not as consistent in demonstrating deficits. Although the majority of the studies have found visual memory deficits (Bolla et al., 1998; Fox et al., 2001; Gouzoulis-Mayfrank et al., 1999; Rodgers, 2000; Verkes et al., 2001), one study did not find any difference in performance between cannabis and ecstasy users (Croft et al., 2000), and three studies found no visual memory deficits in ecstasy users compared to controls (Krystal & Price, 1992; Wareing, Fisk & Murphy, 2000; Zakzanis & Young, 2001).

Up until the past few years, research has focused primarily on the relationship between ecstasy and memory while ignoring other cognitive domains, such as attention, problem solving, planning, and reasoning. Of the newer studies that did assess attentional functioning, one found deficits in sustained attention (the ability to maintain consistent performance over time) (McCann et al., 1999) and divided attention (the ability to attend simultaneously to competing stimuli) (Gouzoulis-Mayfrank et al., 1999),

while one did not find any difference in divided attention (Thomasius, Petersen, Buchert et al., 2003). There are also conflicting results related to selective attention: one study did find differences (Gouzoulis-Mayfrank et al., 1999), while one did not (Morgan, et al., 2002). Attentional capacity appears to remain unimpaired (Croft et al., 2000; Gouzoulis-Mayfrank et al., 1999; Thomasius et al., 2003). Finally, Zakazanis and colleagues (2002) found very little differences in groups in attentional ability when comparing ecstasy users to drug-naïve controls, but did find significant bivariate relationships between selective attention and lifetime ecstasy consumption (Zakazanis, Young, & Radkhoshnoud, 2002).

There is also conflicting evidence regarding the relationship between ecstasy use and frontal lobe functioning (e.g., working memory, planning, abstract reasoning, concept formation, and fluency) among ecstasy users. Studies have found deficits in working memory ability (Croft et al., 2000; Fox et al., 2001; Gouzoulis-Mayfrank et al., 1999; Morgan et al. 2002; Wareing, Fisk & Murphy, 2000), while two studies only found working memory deficits among “heavy” ecstasy users (Daumann et al., 2003; Gouzoulis-Mayfrank et al., 2003). Planning and logical reasoning impairments among ecstasy users have been reported (Milani & Shifano, 2000; Gouzoulis-Mayfrank et al., 1999), although others did not identify such impairments (Fox et al., 2002; Gouzoulis-Mayfrank et al., 2003; Morgan, 1999; Zakazanis, Young, & Radkhoshnoud, 2002). Verbal fluency results have also been mixed, with one study finding a reduction in verbal fluency among ecstasy users (Fox et al., 2002) and one reporting negative findings (Morgan et al., 2002).

Thus far, it appears that concept formation (Fox et al., 2002; Fox, Parrott et al., 2001; Gouzoulis-Mayfrank et al., 2003; Thomasius et al., 2003; Turner et al., 1999; Verkes et

al., 2001) and sequencing ability (Morgan et al., 2002; Thomasius et al., 2003) remain relatively unimpaired among ecstasy users. Still, the current literature on the cognitive consequences of ecstasy use have yielded variable results as to whether or not this drug is associated with impairments in visual memory, different aspects of attention, working memory, and several measures of executive functioning.

One factor that complicates the interpretation of existing cognitive studies is that the range of severity of ecstasy use and use of other drugs of abuse are substantially different across samples. The vast majority of these studies dichotomized participants into groups that had “never used ecstasy” or “used ecstasy,” even though several of these studies found significant bivariate correlations between frequency of ecstasy use and cognitive performance (Bolla et al., 1998; Croft et al., 2000; Gouzoulis-Mayfrank et al., 1999; Gouzoulis-Mayfrank et al., 2003; Fox et al., 2001; Morgan, 1999; Zakzanis & Young, 2001; Zakzanis, Young, & Radkhoshnoud, 2002). Also, studies examining differences between groups of ecstasy users who have different levels of exposure have found that “heavy” users demonstrate more severe cognitive deficits compared to “light” users (Fox et al., 2001; Gouzoulis-Mayfrank et al., 2003; Verkes et al., 2001).

In addition, several studies did not control for frequency of drug use besides ecstasy (Bolla et al., 1998; Gouzoulis-Mayfrank et al., 1999; Krystal & Price, 1992; McCann et al., 1999; Parrott & Lasky, 1998; Reneman, et al. 2000; Rodgers, 2000; Zakzanis & Young, 2001). Considering the high rate of polydrug use among ecstasy users, particularly alcohol, cannabis, cocaine, and other amphetamines (e.g., Fox, Toplis et al., 2001; Parrott, Sisk, & Turner, 2000), it is difficult to determine whether the observed cognitive deficits among ecstasy users were due to ecstasy use, other drugs, or the

combination of both. Studies that have attempted to control for other drugs of abuse have yielded variable results: some have found that ecstasy use predicts cognitive functioning after comparing to a polydrug control group (Fox, Toplis et al., 2001; Morgan, 1999; Verkes et al., 2001), while others did not find impairment after comparing to marijuana-using control group (Croft et al., 2000; Rodgers, 2000).

The present study will substantially add to the current literature in clarifying the relationship between cumulative exposure to ecstasy (from no use to heavy lifetime use) and various cognitive abilities (including visual and verbal memory, auditory working memory, selective attention, impulsivity, cognitive disinhibition, planning and sequencing, verbal and visual fluency, and abstract reasoning), while statistically controlling for the effects of other drug use and potentially confounding demographic variables that are related to cognitive ability. Furthermore, this project is unique in that only two published studies (Bolla et al., 1998; McCann et al., 1999) have been conducted in the United States to examine the neuropsychological consequences of ecstasy use. The remaining studies have been conducted in European countries and Australia. Regional effects are important considering the potential differences in drug use environments, ecstasy pill content, and overall frequency of ecstasy consumption between the United States and European countries and Australia.

Finally, very few studies have examined gender differences in the functional consequences of ecstasy consumption. This is important because there are gender differences in markers for serotonergic integrity in MDMA users, in which women have relatively more impaired serotonergic functioning compared to men (McCann et al., 1994; OSAM, 2001; Reneman, Booij et al., 2001). However, Bolla (1998) found that

women in their sample demonstrated *fewer* decrements in memory performance with increasing lifetime dose of ecstasy compared to men (Bolla et al., 1998).

The Present Study

The goal of the present study was to examine the relationship between past year and lifetime exposure to “ecstasy” (MDMA) and cognitive functioning (including verbal memory, visual memory, auditory working memory, selective attention, and executive functioning abilities) among 65 men and women after controlling for other recreational drug use, premorbid intelligence, and demographic variables known to be related to cognitive ability (age, gender, and ethnic identification). Furthermore, this study will examine whether gender is a potential moderator of the relationship between cognitive functioning and ecstasy use.

Specific Aims

1. **Aim:** To examine the relationship between lifetime and past year exposure and maximum dosage of ecstasy and verbal memory, visual memory, auditory working memory, selective attention, and executive functioning abilities (including cognitive inhibition, planning and sequencing, abstract reasoning, and verbal and visual fluency) after controlling for other recreational drug use, premorbid intelligence (reading ability), and demographic variables known to be related to cognitive ability (age, gender, and ethnic identification). **Hypothesis:** It was hypothesized that increased ecstasy exposure (lifetime, past year, and maximum dosage) would be related to poorer performance on the

aforementioned cognitive tasks after statistically controlling for lifetime (or past year) consumption of other drugs and potential confounding factors such as age, gender, premorbid IQ, and ethnicity.

2. **Aim:** This study also assessed whether gender moderates the relationship between ecstasy exposure and cognitive functioning. **Hypothesis:** It was hypothesized that women will demonstrate higher degrees of dose-dependent deficits compared to the men.

CHAPTER 2: RESEARCH DESIGN AND METHODS

Ecstasy Use and Marijuana Use Bins

Participants were recruited using a quota sampling technique, based on bins, or categories of lifetime ecstasy use. The purpose of recruiting using this classification system was to ensure that I had adequate numbers of participants across the expected range of ecstasy use to inform the study of dosage effects on neuropsychological functioning. (When these categories were combined, they spanned the entire range of users; therefore, data were analyzed utilizing a continuous variable reflecting lifetime ecstasy exposure.)

At the time of data collection, the two studies on functional consequences of ecstasy use that were conducted in the United States included individuals who had used ecstasy for an average of 5 years, with a range of 1-20 times a month, and a total of 25-725 uses during their lifetime (Bolla et al., 1998; McCann et al., 1999). Thus, the estimated average usage would be twice a month for five years (or 120 tablets total). Originally, this was used as the high end of the “moderate” usage category for the current study’s

classification system. However, once data collection proceeded, it was found that individuals' use in the "high" bin far exceeded 120 tablets. I reexamined the literature and found that more recently published studies demonstrated much higher ranges of ecstasy consumption among current users (although these studies were conducted in Europe and Australia). For example, Thomasius et al. (2003) found an average lifetime use of 1033 tablets among male current users and 600 among female current users. Gouzoulis-Mayfrank and colleagues (2003) found an average of 503 lifetime pill consumption among "heavy users" and an average of 40 pills used among "moderate users." Therefore, I decided to increase the "moderate" bin to include 61-200 (as opposed to 60-120) tablets and changed the "high" bin to 201 or more lifetime tablets in order to capture a broader range of ecstasy users.

Thus, the final bins were filled as follows: 8 men and 9 women who never used ecstasy; 9 men and 10 women who reported "low" usage (meaning they used ecstasy between 1 and 60 tablets during their lifetime); 8 men and 6 women who reported "moderate" usage (lifetime consumption of 61 to 200 tablets); and 9 men and 6 women who reported "heavy" usage (lifetime consumption over 200 tablets).

The "no" ecstasy usage bin was filled with controls according to their marijuana usage. As stated previously, the vast majority of ecstasy users (nearly all) also take other drugs. Recent studies have been conflicting as to whether ecstasy users demonstrate cognitive deficits when marijuana consumption is controlled for (Croft et al., 2000; Rodgers, 2000); therefore we included a control group matched according to lifetime marijuana consumption. "Low" marijuana usage was between 1-500 joints, "moderate" was 501-1500 lifetime joints, and "heavy" was 1501-10,000 lifetime joints. (The

marijuana bins were created based on the distribution of lifetime marijuana use among the first 28 ecstasy users recruited to participate in the current study.) Again, data from participants across all bins (from “no” use to “heavy” use) were combined to represent a continuous variable of lifetime ecstasy exposure. (In addition, past year and maximum dosage is measured as a continuous variable.)

Participants, Recruitment, and Screening

Participants were recruited through advertisements in a locally owned, free newspaper that has a wide audience throughout the Cincinnati metro area. In addition, advertisements soliciting individuals who have used ecstasy during the past year and individuals who have not used ecstasy during their lifetime were given out at local clubs, bars, universities, treatment centers, and community centers. Potential participants called the given phone number and were screened to determine their eligibility.

Exclusion criteria included: major medical or neurologic illnesses (mental retardation or significant developmental disorder, epilepsy, brain tumor, traumatic brain injury, multiple sclerosis, history of stroke, cerebral palsy, Parkinson’s disease, or chronic hypertension or diabetes), reported premorbid psychiatric conditions (Axis I psychotic or mood disorder prior to abusing drugs such as ecstasy), or use of prescribed medications that affect cognition (e.g., sedating medications). Participants were required to be fluent English speakers (so that the cognitive tests described below are valid), 18 years of age or older, and had to fall within one of the categories of ecstasy exposure (described in detail above).

They were also administered a brief semi-structured interview to assess their lifetime ecstasy consumption. Those who had used ecstasy must have used it within the previous eighteen months, but not within one week prior to their participation in the study. For those participants who stated they never used ecstasy, their lifetime marijuana consumption was assessed. These estimations determined which bin (see above) of lifetime ecstasy or marijuana exposure the participant fit in.

If an individual met the inclusion criteria, they were asked if they would be willing to participate in a paid (\$30 plus \$5 parking reimbursement) research study at the University of Cincinnati that would involve two hours and forty-five minutes of their time, including an interview, self-report questionnaire, and neuropsychological testing. Participants were required to remain abstinent from ecstasy and other drugs of abuse for one week [in order to reduce symptoms associated with drug withdrawal and sleep deprivation (Bolla et al., 1998; Zakzanis, & Young, 2001)]. The participant's length of abstinence was measured on two separate occasions during the study session. Of the potential participants who meet the above inclusion criteria, 34 men and 31 women participated.

Protocol

All aspects of this study were approved by the Institutional Review Board at the University of Cincinnati. Prior to beginning the study, informed consent was obtained and participants were assigned a research number.¹ Confidentiality was preserved by assigning participant numbers to all individuals and storing questionnaires, interview items, and completed neuropsychological tasks with only the participant number on them,

¹ Participants had the right to waive signing the informed consent document (per the IRB's request), in which case the P.I. and a research assistant signed the informed consent document as witnesses that informed consent was obtained.

separate from the informed consent forms. Information obtained from the phone screen was shredded after the participant was recruited and data were entered.

The study protocol was counterbalanced. All the participants began by filling out a brief background questionnaire that further assessed inclusion and exclusion criteria for the study, as well as length of abstinence. Half the participants began with the questionnaire and drug use interview and then were administered the neuropsychological battery, while the other half of the participants began with the neuropsychological battery and then completed the questionnaire and drug use interview. The Principal Investigator conducted the interviews and administered the standardized neuropsychological tests. Following completion of the study, participants received a payment of \$30, \$5 parking reimbursement, referrals to local drug and alcohol treatment centers (if interested), and informational pamphlets related to ecstasy use provided by the National Institute on Drug Abuse.

Interview/Self-Report Questionnaire

Instruments included in the psychological battery are standardized, well-normed tests. Data were collected in conjunction with a larger study that also examined the subjective effects of ecstasy, patterns of use, and health and psychological consequences of ecstasy exposure. The instruments were chosen to assess drug dependence symptoms and frequency of substance abuse, as well as psychological symptoms expected to be related to ecstasy use such as depression, anxiety, impulsivity, and novelty-seeking (Morgan, 1998; Morgan, 2000; Parrott, Sisk, & Turner, 2000; Schifano et al., 1998; Schifano, 2000). The current study utilized only a portion of the data, which included

measures that assessed substance dependence, frequency of drug use, and neuropsychological ability. Therefore, only these particular measures are described in detail below.

Frequency of Drug Use

In order to reduce the memory load on retrospective reports of drug use, a modified version of the *Time-Line Follow-Back* (Sobell, Maisto, Sobell, & Cooper, 1979) technique was used, utilizing memory cues of holidays and personal events over the past year. A semi-structured interview was then conducted in order to measure lifetime drug use frequency. First, the participants were asked whether or not they have *ever* tried any of the drugs (see below for the full list). If they answered “yes,” then age of first use was assessed. The participants were then asked their average weekly or monthly use each year up until the past year. Memory cues such as developmental milestones, school grades, graduations, jobs changes, and household moves were utilized. This was then combined with the past year use data in order to calculate lifetime drug exposure.

The following drug categories were assessed: ecstasy, marijuana, alcohol, sedatives (including barbiturates, ‘downers,’ valium, Xanax, Ativan), stimulants (cocaine, crack cocaine, amphetamine, and methamphetamine), hallucinogens (PCP, LSD, peyote, mushrooms), opioids (heroin, opium), and inhalants (paint, glue, household cleaners, nitrous oxide, gas). The participant’s drug use was measured by the number of standard units (tablets for ecstasy; standard drinks for alcohol; joints for marijuana; grams for stimulants; number of hits for inhalants, hallucinogens, and opioids; and pills for

sedatives). Maximum dosage per session of ecstasy, and all of the aforementioned drugs, was also assessed according to the listed standard units.

Substance Abuse/Dependence

It was beyond the scope of the current study to conduct diagnostic interviews to assess symptoms of substance abuse and dependence for all drug categories. Instead, the *Substance Abuse Subtle Screening Inventory-3rd Edition* (SASSI-3) was administered to assess drug dependence. Scores obtained reflecting diagnostic criteria were not utilized as variables in the primary analysis; however, they are provided for descriptive purposes. The SASSI-3 is comprised of 26 face-valid items that ask the frequency of behaviors associated with substance abuse, and 62 true or false items, the majority of which are “subtle” and do not directly relate to substance abuse (Miller & Lazowski, 1999). The true or false items give rise to eight scales, five of which are used in the decision rules process. The Symptoms of Substance Misuse (SYM) scale assess abuse patterns. The Obvious Attributes (OAT) scale reflects an individual’s willingness to acknowledge behaviors and characteristics correlated with substance use disorders. The Subtle Attributes (SAT) scale reflects a personal predisposition to develop a substance dependency, independent of attempts to enhance presentation. The defensiveness (DEF) scale measures the refusal to acknowledge problems, whether the refusal is unconscious or purposeful. The Supplemental Addiction Measure (SAM) differentiates defensive people with a substance use disorder from defensive people who do not have a substance use disorder. A positive score on any of these five subscales will produce a positive categorization of Substance Dependence.

Neuropsychological Battery

Instruments included in the neuropsychological battery are standardized and well-normed tests. These tests have been used often in studies of cognitive functioning in substance abusers and have been found to be sensitive to the deficits in verbal and visual memory, executive functioning (cognitive disinhibition, sequencing and planning, verbal and visual fluency, and abstract reasoning), attention, and working memory observed in these populations (Croft et al., 2000; Fox et al., 2001; Gouzoulis-Mayfrank et al., 1999; Wareing et al., 2000; Zakzanis & Young, 2001).

Premorbid Intellectual Functioning. The *Wide Range Achievement Test- 3rd Edition* (WRAT3) (Wilkinson, 1993) yields an estimate of current reading ability. This test is administered by an evaluator and takes approximately five minutes to complete; the participant simply reads words off a list presented to them. For this project, the reading section standard score served as an estimate of premorbid intellectual functioning and quality of education.

Working Memory and Attention. The *Ruff 2 & 7* is a standardized instrument that measures sustained attention (ability to maintain consistent performance over time) and selective attention (the ability to select relevant stimuli while ignoring distracters) (Ruff & Allen, 1996). The T-scores scores used for the current study reflected the speed and accuracy of the individuals' sustained and selective attention. The *Letter Number Sequencing* (LNS) from the WAIS-III was used to assess auditory working memory ability (Wechsler, 1997). The scaled-score on LNS was used for the current project to reflect the ability to hold and manipulate auditory information.

Executive Functioning. *Cognitive Inhibition.* The *Color-Word Interference Test* measures the ability to inhibit overlearned responses. For this project, participants were administered the *Color-Word Interference Test* from the *Delis-Kaplan Executive Function System* (D-KEFS; Delis & Kaplan, 2001). The D-KEFS is a standardized battery of executive functioning tasks, which includes a modified Stroop Task. It requires the participant to name aloud the color of the ink in which the word is printed; in addition, participants must change the rule system to reading the word when a word has a box around it. The contrast scaled score for participants' performance on the inhibition/switching task vs. combined color/naming performance was utilized in this study.

Planning and Sequencing. The *Trail Making Test Part A and Part B* (TMT A & B) are tasks that requires visual scanning, attention, sequencing and psychomotor speed. The TMT is sensitive to diffuse brain damage (Lezak, 1995). Participants must first draw lines to connect consecutively numbered circles as fast as they can (Part A). Participants are then given Part B, on which they must alternate between consecutively numbered and lettered circles on a work sheet as quickly as they can (e.g., 1-A-2-B). The residualized score (obtained from regressing TMT A T-score onto TMT B T-score) was utilized in the current study, which reflected performance on TMT B after controlling for processing speed (TMT A).

Reasoning and Problem Solving. The *Matrix Reasoning* test from the WAIS-III assesses nonverbal reasoning and problem solving ability (Wechsler, 1997). Participants were presented with a booklet of visual patterns that they need to complete by choosing one of five choices. The scaled score was utilized as the unit of measure.

Design and Verbal Fluency. Design and verbal fluency were assessed using the *Delis-Kaplan Executive Function System* (D-KEFS; Delis & Kaplan, 2001). The D-KEFS Design Fluency task requires participants to create as many unique visual designs as they can in a limited amount of time. Total score and design accuracy scaled scores were used. The Verbal analog to this task requires participants to generate as many words that begin with specific letters (e.g., “F”) or that fall into a specific semantic category (e.g., “Animals”) as they can in a limited amount of time. The scaled scores obtained for total phonemic fluency and categorical fluency were used in the regressions.

Visual Memory. The *Benton Visual Retention Test-5th Edition* (BVRT) is a standardized measure of visual memory and visuoconstructional ability (Sivon, 1992). The test materials consist of ten cards, each of which contains several geometric figures. In the copy condition, the participants are asked to copy each design as accurately as they can with the stimuli in front of them. In the recall condition, participants are shown a card for 10 seconds, the card is hidden, there is a fifteen second delay, and participants are asked to draw the figures that they were shown. The residuals obtained after regressing the BVRT copy condition raw score (number of errors) onto the BVRT recall condition raw score (number of errors) were utilized in order to reflect visual memory ability after controlling for visuoconstructional ability.

Verbal Memory. The *California Verbal Learning Test, 2nd Edition* (CVLT-2) measures verbal learning and memory using a 16-item word list, which includes items drawn from four semantic categories (Delis, Kramer, Kaplan, & Ober, 2001). The CVLT-2 variables of interest in this study were: total recall T-score (across five learning trials), short and long-delay free recall z-score, retention variable, and the recognition

discriminability z-score. The retention variable was calculated by subtracting the long delay free recall raw (LDFR) score from the trial 5 raw score, divided by the total of LDFR and trial 5.

Statistical analysis

Neuropsychological and psychological instruments were scored and then 20% of the participants' files were double-checked for accuracy. If an error was found on an instrument within the file, all 65 of that particular instrument were then double-scored. Errors were found on the following instruments: Trail Making Test, D-KEFS Color/Naming Interference Test, D-KEFS Verbal Fluency, D-KEFS Visual Fluency, RUFF 2&7, WRAT-2 Reading, and SASSI-3. Thus, these instruments were double-scored.

Prior to data analysis, the various instruments were entered into the statistical program SPSS© (2000). Data were entered into two separate databases by trained research assistants to ensure accuracy. These two databases were then compared utilizing SAS©, and any discrepant entries were checked a third time and corrected. Upon preliminary analysis, outliers and missing values were examined as a final data entry check.

As stated earlier, the first outlined hypothesis was that increased ecstasy exposure would be related to poorer performance on cognitive tasks (verbal memory, visual memory, auditory working memory, attention and concentration, and executive functioning abilities) after statistically controlling for consumption of other drugs and

potential confounding factors such as age, gender, education, premorbid IQ (reading ability), and ethnicity.

These hypotheses were examined both at the bivariate and multivariate level. In the preliminary analyses, the bivariate relationships (assessed by Pearson product-moment correlations) were examined in order to gain an understanding of the simple relationships between cognitive functioning and ecstasy use (including past year frequency, lifetime frequency, and maximum dosage). Kendall's tau correlations were examined in addition to Pearson product-moment correlations in order to examine any potential monotonic non-linear relationships. (Unless otherwise noted, Pearson product-moment correlations are reported.)

The primary analyses included a series of multiple regressions that tested whether ecstasy exposure was significantly associated with cognitive functioning. Ordinary least squares (OLS) multiple regressions were utilized because the dependent variables were approximately normally distributed (Gardner, Mulvey, & Shaw, 1995; McCullagh & Nelder, 1989). Covariates in the regressions included: age, standard reading score from the WRAT3, years of education, ethnic identification, gender, and lifetime frequency of use of drugs other than ecstasy, in standard units (including alcohol, marijuana, sedatives, opioids, stimulants, hallucinogens, and inhalants). The primary independent variable was the previously discussed continuous ecstasy lifetime exposure variable. A series of regressions was also run to examine whether past year ecstasy use and maximum ecstasy dosage were related to cognitive functioning (past year drug use and demographic variables were included in the models as covariates).

The dependent variables of interest included the scores on the multiple neuropsychological instruments: Letter Number Sequencing scaled score, BVRT recall total errors (residuals of BVRT recall after controlling for constructional ability), CVLT-2 total recall T-score, CVLT-2 short and long delay free recall z-score, CVLT-2 retention, CVLT-2 recognition discriminability z-score, Ruff 2&7 total speed T-score, Ruff 2&7 total accuracy T-score, Matrix Reasoning scaled score, D-KEF Color/Word Interference inhibition/switching vs. combined color/naming contrast scaled score, Trail Making Test B completion time T-score (residuals of TMT B after controlling for TMT A), D-KEFS Verbal Fluency FAS total and Category scaled scores, and D-KEFS Design Fluency total designs and accuracy scaled scores. Standard multiple regression was utilized in order to examine the unique variance each variable accounted for in the models. Interpretations about statistical significance were made if $p < .05$.

To address the second stated goal, assessing whether gender moderates the relationship between cognitive functioning and ecstasy use, a variable representing the interaction between gender and ecstasy exposure was examined in a secondary series of regressions (which was added to the above regression models separately according to past year, lifetime, and maximum ecstasy usage). If gender moderated the relationship between ecstasy use and neuropsychological functioning, then the bivariate relationships and scatterplots were reexamined separately according to gender in the subset of participants who used ecstasy. Interpretations about statistical significance among the bivariate correlations were made if $p < .10$ level due to reduced power resulting from the smaller N (26 for male ecstasy users and 22 for female ecstasy users). The results of the

correlations and graphical representations of the statistically significant interactions are provided in the multivariate results section.

Results

Results: Demographic, Drug Use, and Neuropsychological Data

Demographic Information: Frequencies

The two groups (48 ecstasy users and 17 marijuana-using controls) did not differ significantly in length of education [$F=1.5(1,64)$, $p<.2$], with a mean of 12.5 years for the control group ($SEM=.45$, range=9-16 years) and 13 years for the ecstasy group ($SEM=.23$, range=10-16 years). The groups were also similar in their verbal ability [$F=.03(1,64)$, $p<.8$], with a mean WRAT-3 Reading scaled score of 105.9 among the controls ($SEM=2.6$, range=83-123) and 105.4 among the ecstasy users ($SEM=1.1$, range=83-118). The control group and ecstasy group were also similar in age [$F=.35(1,64)$, $p<.6$], with a mean of 23 years for both groups (range 18-35). The majority of the ecstasy group was single (58.3%), while 33.3% were in a committed relationship but not married and 8.3% were separated or divorced. Similarly, 76.5% of the control group was single, while 17.6% were in a committed relationship, and 5.9% were married. The majority of the ecstasy users were employed full or part-time (58.3%), while 22.9% were unemployed, and 18.8% were students. The majority of the controls were students (47%), while 35.3% were employed full or part time, and 17.6% were unemployed.

The groups did differ significantly in their ethnic identification [$F=7.4(1,64)$, $p<.008$]. Further, the men and women in the control group significantly differed in their ethnic

identification [$F=5.4(1,64)$, $p<.04$]. See Table 1 for the breakdown of ethnic identification according to group.

 Insert Table 1 About Here

Dependence Criteria, Abstinence Data, and Drug Use: Frequencies

The majority of the ecstasy users (89% of the men and 59% of the women) and the marijuana using control group (63% of the men and 56% of the women) scored in the “high probability” range for drug dependence according to the SASSI-3. The average length of abstinence from all drugs for the control group was approximately one month ($M=31$ days, $SD=89$, range=7-378 days) and 15 days for the ecstasy group ($M=15$ days, $SD=17$, range=7-117 days). (For the vast majority of participants, marijuana was used more recently than any other of the aforementioned drugs.) The average length of abstinence from ecstasy among the ecstasy users was just over five months ($M=161$ days, $SD=128$, range=11-491 days).

Participants in the control group had never tried ecstasy, methamphetamine, mushrooms, opioids, or inhalants, while many members of the ecstasy group had. See Table 2 for a detailed presentation of the percentage of participants in both groups who used any of the assessed drugs (including ecstasy, alcohol, marijuana, cocaine, methamphetamine, sedatives, opioids, LSD/PCP, mushrooms, and inhalants) according to group.

 Insert Table 2 About Here

Table 3 provides a description of the type and frequency of drug use (including only participants who used each drug) during the past year, and Table 4 provides similar lifetime drug use data according to group (ecstasy vs. control). In general, the ecstasy group demonstrated higher rates of use compared to the control group, with the exception of marijuana and alcohol. Among the ecstasy users, the average maximum dosage was 4.3 tablets (median= 3, SD= 4.3, range=1-24).

Insert Tables 3 and 4
About Here

Neuropsychological Variables: Frequencies

Table 5 provides the means, standard deviations, and ranges for the scores on the various neuropsychological tests according to group.

Insert Table 5 About Here

Table 6 represents the percentage of individuals who were considered to be impaired (data on the percentage of participants who fell 1 SD below the mean and greater than 1.5 SD's below the mean, shown separately) on the various neuropsychological tests according to group.

Insert Table 6 About Here

Results: Bivariate Relationships

See Table 7 for the significant bivariate (Pearson Product moment correlations) relationships between the neuropsychological and ecstasy dosage variables.

Past Year Ecstasy Use. In general, increased use of ecstasy during the past year was significantly correlated with poorer verbal learning and memory ability. More specifically, increased past year use was significantly related to lower scores on the CVLT-2 first trial performance, total immediate recall, short and long delay free recall, retention and recognition discriminability. There was a trend observed between increased errors on the BVRT and past year ecstasy use ($r=.22$, $p<.08$). No other neuropsychological variables were significantly related to past year ecstasy use. (See Figures 1, 2, and 3 to examine the scatterplots representing the bivariate relationships between past year ecstasy use and CVLT-2 total recall, long delay free recall, and recognition discriminability.)

 Insert Figures 1, 2, and 3
 About Here

Lifetime Ecstasy Use. Increased lifetime ecstasy use was significantly related to poorer performance on the first trial of the CVLT-2. However, upon examination of non-linear relationships, significant Kendall's tau correlations were observed between lifetime ecstasy use and poorer performance on CVLT-2 trial 1 ($t_b = -.24$, $p<.01$), total recall ($t_b = -.28$, $p<.001$), short delay free recall ($t_b = -.24$, $p<.01$), long delay free recall ($t_b = -.30$, $p<.001$), recognition discriminability ($t_b = -.20$, $p<.03$). This suggests that lifetime ecstasy use has a significant non-linear relationship with verbal memory and learning ability and

that, in general, poorer performance is associated with increased use. In accord with past year ecstasy use, lifetime ecstasy use was not significantly related to any of the other cognitive domains.

Maximum Ecstasy Dose. There were no significant Pearson Product moment correlations between maximum ecstasy dosage and any of the neuropsychological variables. However, when Kendall's tau correlations were examined, a significant relationship was demonstrated between increased maximum ecstasy dosage and poorer performance on CVLT-2 long delay free recall ($t_b = -.22, p < .03$).

Thus, at the bivariate level, poorer verbal memory ability and increased ecstasy usage (particularly past year) were related, while ecstasy use did not demonstrate a significant relationship with any of the other cognitive domains (visual memory, selective attention, working memory, and executive functioning).

Insert Table 7 About Here

Other Drug Use. Although not a focus of the present study, the bivariate relationships between frequency of past year (Table 8) and lifetime (Table 9) drug use of the aforementioned drug categories and neuropsychological functioning are presented. In general, none of the other drugs demonstrated the consistent relationships with the verbal memory indices that were seen for past year ecstasy use. Again, past year and lifetime use of drugs other than ecstasy served as control variables in the multivariate analyses.

Insert Tables 8 and 9
About Here

Results: Multivariate Relationships

See Table 10 for the t and p values for the multivariate relationships between the neuropsychological and ecstasy dosage variables (past year, lifetime, and maximum dosage).

 Insert Table 10 About Here

Past Year Ecstasy Use. As noted on the table, increased past year ecstasy use was significantly related to poorer performance on CVLT-2 total recall [$t(64) = -2.00, p < .05$], long delay free recall [$t(64) = -2.79, p < .007$], and recognition discriminability [$t(64) = -2.14, p < .04$] after statistically controlling for past year consumption of other drugs (including alcohol, marijuana, sedatives, opioids, stimulants, hallucinogens, and inhalants) and potential confounding factors such as age, education, gender, premorbid IQ, and ethnicity. Past year ecstasy use was not significantly related to any of the other neuropsychological variables, including CVLT-2 retention and short delay free recall.

Interaction Between Gender and Past Year Use. Significant interactions between gender and past year ecstasy use were observed for the following variables: CVLT-2 retention [$t(64) = -2.21, p < .03$], D-KEFS color/work interference test (inhibition/switching versus color/naming) [$t(64) = -2.21, p < .03$], and WAIS-III letter number sequencing task [$t(64) = -2.21, p < .03$]. For the CVLT-2 retention variable, once the gender by ecstasy use interaction was added to the model, increased ecstasy use was significantly related to poorer retention [$t(64) = 2.92, p < .005$]. Visual examination of the scatterplots and correlations revealed that the higher ecstasy use among the men was significantly related to poorer verbal memory retention ($r = .46, p < .02$), while there

was no significant correlation for the female ecstasy users ($r=.002$, $p<.99$). (See Figure 4 for the scatterplots according to gender.)

 Insert Figure 4 About Here

A similar pattern was found for letter number sequencing (LNS). When the interaction between gender and ecstasy use was taken into account, it was found that increased ecstasy use was significantly related to poorer performance on the working memory task [$t(64) = -2.37$, $p < .02$]. Visual examination of the scatterplots revealed that the increased ecstasy use was related to poorer auditory working memory among the men, while the opposite was true for the women, although neither of the correlations were statistically significant ($r=-.22$, $p<.28$; $r=.13$, $p<.58$, respectively). (See Figure 5 to examine the scatterplots.)

 Insert Figure 5 About Here

The opposite pattern was found for the D-KEFS Color Word Interference Test (inhibition switching/switching vs. combined color/naming score). Increased ecstasy usage was unexpectedly associated with better cognitive inhibition [$t(64) = 3.27$, $p < .002$] after controlling for the gender by ecstasy use interaction. Visual examination of the scatterplots and the correlations revealed that the female ecstasy users' performance was poorer with increased ecstasy use, although this was not statistically significant ($r=-.30$, $p<.17$). In contrast, among the men, better cognitive inhibition on this switching task, was associated with increased ecstasy consumption ($r=.56$, $p<.003$). (See Figure 6 to

examine the scatterplots of past year ecstasy use and D-KEFS inhibition task according to gender.)

 Insert Figure 6 About Here

Similar to the bivariate results, after controlling for the gender-by-ecstasy interaction variable, a trend was noted between poorer performance on the BVRT recall task (after controlling for constructional ability) and past year ecstasy use [$t(64) = 1.75, p < .08$]. However, no interaction between gender and ecstasy use was observed [$t(64) = -1.38, p < .17$]. The men in the sample demonstrated a significant correlation between past year ecstasy use and increased errors, while there was no relationship between women's BVRT performance and ecstasy use ($r = .33, p < .10$; $r = .02, p < .94$, respectively).

Lifetime Ecstasy Use. Increased lifetime ecstasy use was significantly related to poorer performance on short delay free recall [$t(64) = -2.21, p < .03$] and recognition discriminability [$t(64) = -2.30, p < .03$] after controlling for other drug use, length of abstinence from ecstasy, and the other aforementioned demographic variables. Consistent with the past year ecstasy usage findings, lifetime ecstasy consumption was not significantly related to other areas of cognitive functioning after controlling for use of other drugs and demographic variables.

Interaction Between Gender and Lifetime Ecstasy Use. After controlling for the gender interaction, increased lifetime ecstasy consumption was significantly associated with poorer retention on the CVLT-2 [$t(64) = 2.21, p < .03$], and the interaction variable was also significant [$t(64) = -2.21, p < .03$]. The results were similar to the interaction

between gender and past year ecstasy use. Bivariate analysis revealed that although there was no relationship between lifetime ecstasy use and retention among the women, the men performed worse with increased lifetime consumption ($r = -.22$, $p < .33$; $r = .35$, $p < .07$, respectively). A similar pattern was found for performance on long delay free recall. Poorer performance on CVLT-2 long delay free recall was associated with increased lifetime ecstasy consumption [$t(64) = -3.05$, $p < .005$], with a significant interaction [$t(64) = 2.67$, $p < .01$]. Bivariate analysis revealed that this dose relationship was significant among the male ecstasy users, but not the women ($r = -.39$, $p < .05$; $r = .07$, $p < .76$, respectively).

An opposite pattern was found for visual fluency. Increased lifetime ecstasy consumption was unexpectedly related to improved performance [$t(64) = 2.42$, $p < .02$], with a significant interaction between gender and lifetime consumption [$t(64) = -2.36$, $p < .03$]. Again, a significant bivariate relationship was found among the male ecstasy users but not the female users ($r = .38$, $p < .06$; $r = -.25$, $p < .27$, respectively).

Maximum Ecstasy Dose. There were no observed significant multivariate relationships between maximum ecstasy dosage and verbal memory ability. However, increased dose was unexpectedly significantly related to better performance on the WAIS-III Letter Number Sequencing task (working memory) [$t(64) = 2.14$, $p < .04$].

Interaction Between Gender and Maximum Dose. There were no observed interactions between gender and maximum dosage in relation to neuropsychological functioning.

Other Drug Use. The pattern of the multivariate relationships between frequency of past year, lifetime, and maximum dosage of the aforementioned drug categories and

neuropsychological variables did not differ from the presented bivariate results. In general, none of the other drugs demonstrated consistent relationships with the verbal memory indices as past year ecstasy use did, while some were significantly related to other areas of cognitive functioning such as visual memory, verbal fluency, visual design fluency, and selective attention. (Refer back to Tables 8 and 9 to review the pattern of bivariate relationships between other drugs of abuse and neuropsychological functioning in this sample.)

Discussion

Purpose of the Present Study

The intent of this study was two-fold: 1) to examine whether there is a dose-dependent relationship between ecstasy exposure and neuropsychological functioning in a sample of ecstasy users and marijuana-using controls, while controlling for potentially confounding demographic variables and frequency of other drug use; and 2) to examine whether gender moderated the relationship between ecstasy exposure and cognitive functioning.

Findings: Ecstasy Exposure and Cognitive Functioning

The primary finding was that ecstasy exposure was significantly related to poorer verbal learning and memory ability, while no such dose-dependent relationship was observed between ecstasy exposure and executive functioning (including selective

attention, verbal and visual fluency, sequencing ability, nonverbal abstract reasoning, and cognitive inhibition). In addition, gender was found to moderate the relationship between ecstasy consumption and verbal memory retention, long delayed free recall, auditory working memory, visual fluency, and cognitive inhibition.

More specifically, increased past year and lifetime ecstasy use were significantly related in a dose-dependent fashion to poorer performance on immediate, short, and long-delayed verbal memory and recognition ability. It should be noted that as a group the ecstasy users performed in the average range on several of the CVLT-2 indices. The ecstasy group mean was approximately 0.5 SD below the mean on the CVLT-2 trial 1, total recall, short and long-delay free recall, and recognition ability. However, there was also a large range of performance among the ecstasy users (from as low as 3 SD below the mean to 1.5 SD above the mean). Further examination of the data revealed that a significantly larger percentage of the ecstasy group compared to the marijuana-using control group was considered impaired (defined as performing 1.5 SD or more below the mean according to published norms) on the following CVLT-2 variables: total recall, short delay free recall, and long delay free recall. (Refer back to Table 6.)

This finding is consistent with recent studies that found verbal memory impairments with relatively intact executive functioning abilities among abstinent ecstasy users compared to polydrug and drug-naïve controls (Fox et al., 2002; Gouzoulis-Mayfrank et al., 2003; Morgan et al., 2002; Thomasius et al., 2003). Gouzoulis-Mayfrank and colleagues (2003) compared the neuropsychological functioning of 60 ecstasy users (30 “heavy” and 30 “moderate” users) to 30 controls.

They found that heavy ecstasy users (with average use of 500 pills) performed significantly more poorly on verbal memory tasks compared to moderate ecstasy users and controls, while no group differences were observed on working memory, executive control, planning ability, and visual scanning tasks. Further, they found a dose-dependent relationship between lifetime ecstasy use and immediate verbal recall while controlling for amphetamine, cannabis, and LSD use (although the other areas of cognitive functioning were not examined for dose-dependent relationships and demographic variables were not included in the model). Therefore, the current study expanded upon these recent studies that assessed group differences between ecstasy users and controls by demonstrating *dose-dependent* relationships between ecstasy use and memory functioning after carefully controlling for frequency of other drug use, verbal ability, education, ethnicity, gender, and age.

Findings: Interaction Between Gender and Ecstasy Exposure

The current study found that visual memory was not significantly related to ecstasy exposure among the group of ecstasy users and marijuana-using controls. The current literature is inconsistent regarding visual memory deficits among ecstasy users. Some have found deficits (Bolla et al., 1998; Fox et al., 2001; Gouzoulis-Mayfrank et al., 1999; Rodgers, 2000; Verkes et al., 2001), while others have not (Croft et al., 2000; Krystal & Price, 1992; Wareing, Fisk & Murphy, 2000; Zakzanis & Young, 2001). One potential reason for this discrepancy is potential moderator variables such as frequency of alcohol consumption (which this study found to be significantly related to visual memory deficits). Gender may also moderate the relationship between ecstasy use and visual

memory ability. I found a trend ($p < .10$) towards a relationship between increased errors on the BVRT recall task and increased ecstasy consumption among only the men in the sample. Further, Gouzoulis-Mayfrank et al. (2003) found visual memory deficits among “heavy” ecstasy users compared to controls in a prominently male sample (63 men vs. 27 women). Alternatively, the BVRT task may not have been sensitive enough to detect subclinical deficits. Other studies that have utilized more complex visual memory tasks, such as visual paired associates, did demonstrate deficits among ecstasy users (Bolla et al., 1998; Rodgers, 2000).

Gender was also found to moderate the relationship between ecstasy consumption and verbal memory retention, long delayed free recall, auditory working memory, visual fluency, and cognitive inhibition. Correlational analysis and visual inspection of the scatterplots revealed that, among the men, increased ecstasy use (past year and lifetime) was significantly related to poorer retention on the CVLT-2, while the women ecstasy users did not demonstrate this relationship. This pattern was also true for CVLT-2 long delayed recall, in which increased lifetime ecstasy exposure among the male ecstasy users was significantly related to poorer delayed recall, while there was no dose-dependent relationship among the women.

This gender pattern is in contrast to my hypothesis that women would demonstrate greater memory impairment, which was based on imaging studies that have demonstrated that women have more impaired serotonergic functioning compared to men after using ecstasy (McCann et al., 1994; OSAM, 2001; Reneman Booij et al., 2001). However, the current results are in general agreement with Bolla and colleagues (1998), who found that men in their sample showed greater decrements in memory performance

with increased lifetime dosage compared to women. Of course, it is important to note that the other verbal memory indices, including total recall, short and long delay free recall, and recognition discriminability, were significantly related to past year ecstasy consumption among both the men and women in the current sample.

Although initial analyses did not reveal significant relationships between past year or lifetime ecstasy exposure and working memory, after controlling for the interaction between gender and past year ecstasy use, a significant relationship was found between increased use and poorer working memory performance. Visual inspection of the scatterplots revealed that this relationship was more pronounced among the men in the sample. This is consistent with Gouzoulis-Mayfrank et al. (2003) who found no differences between ecstasy using and polydrug-control groups in working memory ability, but did find a relationship between poorer working memory ability and heavy ecstasy consumption among their primarily male sample (21 men, 9 women).

The men in the sample also demonstrated dose-dependent relationships with visual fluency and cognitive inhibition, although the relationship was opposite what was expected (with increased dosage related to better performance). The predicted patterns (higher dose and poorer performance) were demonstrated among the women, although they were not statistically significant. One possible explanation is that the male ecstasy users performed more quickly on these tasks and thus produced more designs and got further on the modified Stroop task, compared to marijuana-using controls and female ecstasy users. It is notable that ecstasy users were actually less accurate as a group on design fluency compared to marijuana-using controls. (See Table 6.) Therefore, they may perform quickly but sacrifice accuracy.

Very few studies to date have used gender as a control variable or examined whether it is a potential moderator variable. Therefore, the current finding that gender moderated the relationship between ecstasy exposure and cognitive functioning is important to consider when interpreting current studies that compared groups of ecstasy users to polydrug controls. Further, future studies are necessary to examine this discrepancy between imaging studies that found worsened serotonergic functioning among women and neuropsychological studies that have demonstrated decreased performance among men, rather than women.

Findings: Neuropsychological Functioning and Other Drug of Use

One criticism of current research on the cognitive effects of ecstasy consumption is that polydrug use is the norm (e.g., Parrott, Sisk, & Turner, 2000), making it difficult to determine whether cognitive deficits are due to ecstasy or other substances. In order to address this issue, the current study carefully measured and statistically controlled for frequency of other drug use. I found that increased past year consumption of alcohol and marijuana were significantly related to poorer verbal memory recognition discriminability (although at the multivariate level, marijuana was no longer a significant predictor of recognition ability). No other drugs of abuse were consistent predictors of verbal memory ability, including total recall, short or long delayed recall, retention, or recognition ability.

Unlike ecstasy consumption, past year alcohol use was significantly related to poorer performance on visual memory, visual fluency, and selective attention tasks in addition to verbal recognition memory ability. This is consistent with previous studies

that demonstrated verbal memory, visual memory, attention, and visuospatial deficits among alcohol dependent individuals (e.g., Sullivan, Rosenbloom, Lim, & Pfefferbaum, 2000). These findings also highlight the importance of controlling for other drugs of abuse that have been known to be related to impaired cognitive functioning (e.g., Selby & Azrin, 1998). Therefore, the overall pattern of deficits associated with other drugs of abuse, which included visual memory (alcohol), selective attention (alcohol, opioids, hallucinogens), and visual (alcohol) and verbal fluency (opioids, stimulants), was dissociable from the effects of ecstasy, which was generally limited to verbal learning and memory ability in this sample.

Implications

The results of the current study lend further evidence to the recent hypothesis proposed by Fox et al. (2002) and Gouzoulis-Mayfrank et al. (2003) that the temporal lobe, including the hippocampus, is particularly sensitive to the neurotoxic effects of ecstasy consumption. Although imaging studies have demonstrated a global decrease in serotonin density among MDMA users (e.g., Reneman et al., 2001; Reneman et al., 2002), animal studies have demonstrated selective vulnerability of serotonin neurotoxicity in the hippocampus, compared to the neocortex and parietal lobes of MDMA-exposed rats (Sharkey, McBean, & Kelly, 1991; Sprague et al., 2003). Research on non-human primates has also found the largest decrease in serotonin density in the hippocampus compared to other brain areas seven years after MDMA administration (Hatzidimitriou et al., 1999). Furthermore, more recent imaging research conducted on humans has shown preliminary evidence that MDMA use is associated with

hippocampal dysfunction (Daumann et al., 2003; Jacobsen et al., in press). For example, in a recent pilot study, Jacobsen and colleagues (in press) found reduced activation of the left hippocampus during a working memory task (*n*-back) among six recently abstinent adolescent MDMA users. These findings support the need for further research examining the relationship between hippocampal functioning, serotonin density, and verbal memory ability among male and female ecstasy users.

Another notable implication of the present study is that past year ecstasy use was a more consistent predictor of verbal memory functioning compared to lifetime consumption and maximum dosage. One possible explanation for this finding is that accurate recall of lifetime ecstasy use may be too difficult, particularly considering the noted memory deficits among ecstasy users. In order to reduce the memory load of retrospective recall of drug use, the current study utilized a modified version of the *Time Line Follow-Back* (Sobell, Maisto, Sobell, & Cooper, 1979) method to assess frequency of drug use. Thus, considering the demonstrated memory impairment among ecstasy users accurate lifetime recall may be too difficult, and past year use may be the most appropriate measure to assess the dose-dependent relationship between ecstasy use and cognitive functioning.

There are also prevention and treatment implications of the current findings, especially considering that the observed dose-dependent verbal memory decrements existed among a sample that was otherwise physically healthy, well-educated, and young. There is a clear need for psychoeducation aimed at informing adolescents and young adults of the negative dose-dependent impact that recreational ecstasy use has on new learning and memory ability. These results also give further merit to

employing neuropsychological testing, particularly focused on memory ability, in treatment planning or psychological evaluations among ecstasy users. At a minimum, given the high rate of ecstasy use among young adults, past ecstasy use should be assessed when neuropsychological examinations are conducted in clinical practice.

Limitations of this Study

As with any study, the current research has methodological limitations that need to be considered. One consistent critique of research focused on the cognitive effects of substances is that cognitive impairment might actually precede and place individuals at risk for drug abuse rather than being the result of abuse. However, it is important to note that animal research has demonstrated MDMA induced neurotoxicity and altered brain functioning in several species, including primates (e.g., O'Shear et al., 1998). Although poor executive functioning may be a risk factor for using drugs/alcohol (e.g., Nigg, Glass, Wong, Poon, Jester, et al., 2004), it was not related to cumulative lifetime or past year frequency of ecstasy use in this sample. Further, the observed relationship between ecstasy use and memory impairment was demonstrated above and beyond the effects of other drugs. Thus, one can feel reasonably confident that the neurotoxicity of ecstasy is a contributing factor in the observed relationship. Still, I agree that this issue is a continuing problem in studying the cognitive and psychological effects of drug use among humans. A longitudinal research study following drug-naïve individuals would be necessary to conclusively examine which comes first, cognitive impairment or drug use.

Another potential weakness is that this study did not utilize urinalysis or hair analysis when assessing length of abstinence. Still, there were several aspects of the study design that maximized the reliability of the self-reported frequency of use and last day of abstinence measures including: guaranteed confidentiality (names were not used, including on the informed consent), privacy (no third parties were present), and last date of use was asked on two separate occasions (on paper-and-pencil questionnaire and during semi-structured interview). In addition, self-report of drug use has been widely utilized and accepted by the scientific community as a valid assessment of drug use frequency, including length of abstinence (Harrison & Hughes, 1997). The current study utilized the *Time Line Follow-Back* to assess length of abstinence and drug use frequency. This technique has been established as a well validated self-report instrument to assess drug-use behavior in four key ways: a) high re-test reliability, b) high convergent and discriminant validity compared to other established measures, c) high agreement with informants, and d) high agreement with patient's urine assays (Fals-Stewart, O'Farrell, Freitas, McFarlin, & Rutligliano, 2000).

In addition, all naturalistic studies examining the effects of ecstasy are challenging due to variance in ecstasy tablet content (e.g., Winstock, Wolff, & Ramsey, 2001). The current study did not collect ecstasy tablets from participants to test pill content. However, there was an observed dose-dependent relationship between ecstasy tablets and memory functioning. It is unlikely that other substances in the tablets would co-vary in a pattern that would consistently predict memory impairment among participants. In addition, the current study did not examine the effects of drug administration (e.g., oral versus inhaled MDMA) or combinations of drugs (e.g.,

consuming alcohol concurrently with ecstasy). Therefore, future studies are needed to closely examine the effects of drug combinations, or potential cumulative effects of drug combinations such as alcohol and ecstasy, on cognitive functioning.

Finally, the current results represent a sample of relatively young, well-educated primarily Caucasian ecstasy users, while the marijuana-using controls had a significantly higher percentage of male African-American participants. Although ethnicity was statistically controlled for in the multivariate analysis, the results cannot necessarily be generalized to populations that substantially differ from the current sample in their drug use or demographic variables. Still, this is one of the first neuropsychological studies on ecstasy users conducted on a sample collected from the community (as opposed to a sample of undergraduate students) conducted in the United States that controlled for important demographic and drug use variables. Further research on larger, nationally represented samples of ecstasy users would help clarify other potential moderator variables.

Future Directions

Due to the high rate of ecstasy use among high school and college students, future research examining the relationship between new learning and memory and academic performance is warranted. This study also demonstrates the need for further studies that examine the relationship between serotonergic functioning, cognitive ability, and frequency of ecstasy use. Additional imaging and neuropsychological studies examining gender effects are needed to help further elucidate whether ecstasy differentially affects men and women. Finally, future longitudinal and large-scale

cross-sectional research is crucial to determine whether recovery of cognitive functioning occurs with sustained abstinence from ecstasy.

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Table 1: Breakdown of Ethnic Identification According to Group and Gender (Controls).

	<u>Ecstasy Group</u>		<u>Control Group</u>	
<u>Ethnic Identification</u>	<u>% Men</u>	<u>% Women</u>	<u>% Men</u>	<u>% Women</u>
Asian American	3.8	0	0	0
African American	7.7	13.6	22.2	62.5
Hispanic	0	0	0	12.5
Caucasian	76.9	86.4	66.7	25
Native American	0	0	0	0
"Other"	11.5	0	11.1	0

Table 2. Percentage of Participants Using Drugs According to Category and Group.

<u>Drugs</u>	<u>Ecstasy Group</u>		<u>Control Group</u>	
	<u>N</u>	<u>%</u>	<u>N</u>	<u>%</u>
Ecstasy- Lifetime	48	100%	0	0%
Ecstasy- Past Year	47	98%	0	0%
Alcohol- Lifetime	48	100%	17	100%
Alcohol- Past Year	45	94%	17	100%
Marijuana- Lifetime	48	100%	17	100%
Marijuana- Past Year	44	92%	17	100%
Cocaine- Lifetime	37	77%	2	12%
Cocaine- Past Year	25	52%	2	12%
Methamphetamine- Lifetime	21	44%	0	0%
Methamphetamine- Past Year	13	27%	0	0%
Sedatives- Lifetime	22	46%	2	12%
Sedatives- Past Year	14	29%	1	6%
Opioids- Lifetime	23	48%	0	0%
Opioids- Past Year	11	23%	0	0%
LSD/PCP- Lifetime	35	73%	2	12%
LSD/PCP- Past Year	15	31%	0	0%
Mushrooms- Lifetime	41	85%	0	0%
Mushrooms- Past Year	24	50%	0	0%
Inhalants- Lifetime	29	60%	0	0%
Inhalants- Past Year	12	25%	0	0%

Note: Individual participants are represented in multiple rows of the table.
Percentages are not mutually exclusive.

Table 3. Past Year Drug Frequency (in Standard Units) According to Group†

<u>Drugs</u>	<u>Ecstasy Group</u>			<u>Control Group</u>		
	<u>M (N)</u>	<u>SD</u>	<u>Range</u>	<u>M (N)</u>	<u>SD</u>	<u>Range</u>
Ecstasy	15 (47)	23	1-116	0	0	0
Alcohol	421 (45)	446	14-1,836	328 (17)	428	2-1,254
Marijuana	504 (44)	835	1-3,650	280 (17)	224	5-728
Sedatives	28 (15)	42	1-150	2 (1)	0	2
Opioids*	21 (10)	50	1-164	0	0	0
Cocaine	12 (24)	25	.01-110	54 (2)	70	4-103
Methamphetamine	8 (12)	19	.03-67	0	0	0
LSD/PCP	4 (14)	4	1-18	0	0	0
Mushrooms	8 (24)	19	1-91	0	0	0
Inhalants	24 (12)	31	3-104	0	0	0

Note: Individual participants appear in multiple rows of the tables. Frequency is calculated according to standard units (see Methods section). † Indicates mean frequencies were calculated *only* for participants who reporting using the specific drug at *least one time* in during the past year, the number of participants who met this criteria is denoted in parenthesis (N). *Indicates that frequency includes heroin and opioids.

Table 4. Lifetime Drug Use Frequency According to Group†

<u>Drugs</u>	<u>Ecstasy Group</u>			<u>Control Group</u>		
	<u>M (N)</u>	<u>SD</u>	<u>Range</u>	<u>M (N)</u>	<u>SD</u>	<u>Range</u>
Ecstasy	267 (48)	482	1-2,310	0	0	0
Alcohol	3,442 (48)	4,582	10-19,670	2,373 (17)	4,096	35-13,845
Marijuana	3,453 (48)	5,807	2-31,440	2,069 (17)	3,541	6-14,894
Sedatives	152 (20)	304	2-1,290	1.5 (2)	.7	1-2
Opioids*	79 (22)	127	1-464	0	0	0
Cocaine	76 (36)	178	.01-844.7	649.6(2)	912	4.2-1,295
Methamphetamine	13.2 (21)	23	.03-78.6	0	0	0
LSD/PCP	112 (36)	229	1-1,317	2.5 (2)	.7	2-3
Mushrooms	19 (40)	40	1-233	0	0	0
Inhalants	87 (29)	178	1-710	0	0	0

Note: Individual participants appear in multiple rows of the tables. Frequency is

calculated according to standard units (see Methods section). † Indicates mean

frequencies were calculated *only* for participants who reporting using the specific drug at

least one time in during the past year, the number of participants who met this criteria is

denoted in parenthesis (N). *Indicates that frequency includes heroin and opioids.

Table 5. Mean, Standard Error of Measurement, and Range of Neuropsychological Variables

Variable	Ecstasy Group			Control Group		
	M	SEM	Range	M	SEM	Range
BVRT Recall (total correct)	7.8	.21	5 - 10	8.2	.31	6 - 10
BVRT Recall (number errors)	2.8	.31	0 - 9	2.2	.43	0 - 6
CVLT-2 Variables Trial 1 (z-score)	-.65	.13	-3 - 1.5	-.15	.27	-1.5 - 2.5
Total Recall (T-score)	45.1	1.35	24 - 61	51.1	2.12	37-73
Short Delay Free Recall (z-score)	-.57	.14	-2.5 - 1	-.006	.15	-1 - 1
Long Delay Free Recall (z-score)	-.57	.16	-3 - 1.5	.006	.20	-1.5 - 1.5
Retention (see formula in text)	.006	.002	-.20 - .53	.002	.002	-.14 - .17
Recognition Discriminability (z-score)	-.40	.13	-2 - 1	-.003	.19	-1.5 - 1
D-KEFS Inhibition Switching vs. Combined Color/Naming (scaled)	9.6	.36	4 - 18	9.3	.62	4 - 14
D-KEFS Verbal Fluency FAS (scaled)	10.5	.38	3 - 17	11.6	.67	7 - 16
D-KEFS Verbal Fluency Category (scaled)	11.8	.46	5 - 19	12.2	.77	6 - 18
D-KEFS Visual Fluency Total Correct (scaled)	10.7	.47	3 - 17	10.5	.56	7 - 15
D-KEFS Visual Fluency Accuracy (scaled)	7.9	.43	1 - 12	9.1	.47	4 - 12
Trails B time (T-Score)	52.7	1.57	33 - 74	53.5	3.22	29 - 74
WAIS-III Matrix Reasoning (scaled)	10.8	.39	5 - 16	10.5	.76	4 - 15
WAIS-III Letter Number Sequencing (scaled)	10.1	.31	6 - 17	10.5	.73	6 - 18
RUFF 2&7 Total Speed (T-score)	46.3	1.29	29 - 67	48.7	1.90	35 - 62
RUFF 2&7 Total Accuracy (T-score)	44.9	1.49	20 - 58	45.4	1.8	24 - 54

Note: BVRT = Benton Visual Retention Test. CVLT-2 = California Verbal Learning Test- 2nd edition. D-KEFS= Delis-Kaplan Executive Functioning System.

Table 6. Percentage of Participants Who Were Impaired on the Various Neuropsychological Tasks.

Variable	Ecstasy Group (%)		Control Group (%)		χ^2 †
	-1 SD Below	>-1.5 SD Below	-1 SD Below	>-1.5 SD Below	
CVLT-2 Variables					
Trial 1 (z-score)	43.8%	25.0%	35.3%	11.8%	1.29
Total Recall (T-score)	31.3%	18.8%	5.9%	0%	3.72*
Short Delay Free Recall (z-score)	35.4%	20.8%	5.9%	0%	4.20**
Long Delay Free Recall (z-score)	45.8%	37.5%	23.5%	5.9%	4.92**
Recognition Discriminability (z-score)	33.3%	14.6%	23.5%	5.9%	0.88
D-KEFS (scaled-scores)					
Inhibition Switching vs. Color/Naming	33.3%	16.7%	47.1%	17.6%	.008
Verbal Fluency FAS	16.7%	8.3%	11.8%	11.8%	.94
Verbal Fluency Category	14.6%	10.4%	11.8%	11.8%	.008
Visual Fluency Total Correct	25.0%	14.6%	11.8%	11.8%	.08
Visual Fluency Accuracy	47.9%	37.5%	35.3%	11.8%	3.92**
Trails B time (T-Score)	14.6%	0%	17.6%	11.8%	5.85**
WAIS-III Matrix Reasoning (scaled)	22.9%	8.3%	23.5%	17.6%	1.12
WAIS-III Letter Number Sequencing (scaled)	22.9%	8.3%	11.8%	11.8%	.94
RUFF 2&7 Total Speed (T-score)	25%	18.8%	23.5%	5.9%	1.61
RUFF 2&7 Total Accuracy (T-score)	31.3%	14.6%	17.6%	11.8%	.09
BVRT Recall (number errors)	-2 Points Below Expected	-2 Points Below Expected	-2 Points Below Expected	-2 Points Below Expected	χ^2
	37.5%	23.5%	23.5%	23.5%	1.09

Note: CVLT-2 = California Verbal Learning Test- 2nd edition. D-KEFS= Delis-Kaplan Executive Functioning System. BVRT=Benton Visual Retention Test. “1 SD Below” and “>-1.5 SD Below” indicate that performance is one or more standard deviations, or greater than 1.5 SD, below the mean according to published norms, respectively. † χ^2 differences were calculated to determine whether there was a significant difference percentage of impaired participants (defined as >1.5 SD below the mean) between the groups. “-2 Points Below Expected” is based on the BVRT publisher’s suggestion to subtract an individual’s score from their expected scores. A difference of two+ points indicates a “suspected visual impairment.” *p<.10. **p<.05.

Table 7. Simple Relationships Between Neuropsychological Predictors (Standardized Scores) and Ecstasy Usage Variables (Past Year, Lifetime, and Maximum Dosage).

	<u>Past Year</u>	<u>Lifetime</u>	<u>Max Dose</u>
BVRT Recall Total Errors	$r = .22$	$r = .07$	$r = .10$
CVLT-2 Trial 1 Recall	$r = -.26^*$	$r = -.29^*$	$r = -.14$
CVLT-2 Total Recall	$r = -.33^{**}$	$r = -.19$	$r = -.18$
CVLT-2 Short Delay Free Recall	$r = -.26^*$	$r = -.19$	$r = -.13$
CVLT-2 Long Delay Free Recall	$r = -.40^{***}$	$r = -.13$	$r = -.18$
CVLT-2 Retention Variable	$r = .29^*$	$r = .02$	$r = .08$
CVLT-2 Recognition Discriminability	$r = -.32^{**}$	$r = -.19$	$r = -.21$
D-KEFS Inhibition/Switching vs. Color/Naming	$r = .14$	$r = .04$	$r = -.09$
D-KEFS Verbal Fluency FAS	$r = .13$	$r = .18$	$r = .16$
D-KEFS Verbal Fluency Category	$r = -.01$	$r = .11$	$r = .07$
D-KEFS Visual Fluency Total Score	$r = .08$	$r = -.05$	$r = -.07$
D-KEFS Visual Fluency Accuracy	$r = -.13$	$r = -.02$	$r = -.04$
Trail Making Test B Scaled Score	$r = .15$	$r = .19$	$r = .23$
WAIS-III Matrix Reasoning	$r = -.19$	$r = -.06$	$r = -.04$
WAIS-III Letter Number Sequencing	$r = -.07$	$r = .14$	$r = .21$
Ruff 2&7 Total Speed	$r = -.07$	$r = .08$	$r = -.04$
Ruff 2&7 Total Accuracy	$r = -.07$	$r = .05$	$r = .00$

Note: All neuropsychological variables represent the scaled or standardized scores.

Correlations are Pearson Product Moment Correlations. $*p < .05$. $**p < .01$. $***p < .001$.

Table 8. Simple Relationships Between Neuropsychological Predictors (Standardized Scores) and Drug Usage Variables (Past Year)

	<u>Alcohol</u>	<u>Marijuana</u>	<u>Sedatives</u>	<u>Opioids</u>	<u>Stimulants</u>	<u>Hallucinogens</u>	<u>Inhalants</u>
BVRT Recall Total Errors	$r = .27^*$	$r = -.05$	$r = .13$	$r = .05$	$r = .004$	$r = .09$	$r = .07$
CVLT-2 Trial 1 Recall	$r = .16$	$r = -.23$	$r = -.003$	$r = .09$	$r = .08$	$r = -.13$	$r = .08$
CVLT-2 Total Recall	$r = -.09$	$r = .02$	$r = -.19$	$r = -.11$	$r = .06$	$r = -.25^*$	$r = -.06$
CVLT-2 Short Delay Free Recall	$r = -.12$	$r = .05$	$r = -.11$	$r = -.14$	$r = -.17$	$r = -.22$	$r = -.19$
CVLT-2 Long Delay Free Recall	$r = .005$	$r = .07$	$r = -.16$	$r = -.13$	$r = .05$	$r = -.18$	$r = -.04$
CVLT-2 Retention Variable	$r = -.14$	$r = .00$	$r = .10$	$r = .06$	$r = -.12$	$r = .05$	$r = -.16$
CVLT-2 Recognition Discriminability	$r = -.25^*$	$r = -.28^*$	$r = -.11$	$r = -.07$	$r = -.16$	$r = -.24$	$r = -.01$
D-KEFS Inhibition/Switching vs. Color/Naming	$r = .05$	$r = .35^{**}$	$r = .15$	$r = .005$	$r = -.03$	$r = .17$	$r = -.14$
D-KEFS Verbal Fluency FAS	$r = .09$	$r = .16$	$r = .11$	$r = .01$	$r = -.21$	$r = .003$	$r = -.008$
D-KEFS Verbal Fluency Category	$r = -.02$	$r = .03$	$r = -.12$	$r = -.23$	$r = .05$	$r = -.08$	$r = -.03$
D-KEFS Visual Fluency Total Score	$r = -.01$	$r = -.03$	$r = -.004$	$r = .02$	$r = -.18$	$r = -.07$	$r = -.06$
D-KEFS Visual Fluency Accuracy	$r = -.27^*$	$r = .01$	$r = -.02$	$r = -.05$	$r = -.23$	$r = -.05$	$r = -.09$
Trail Making Test B Scaled Score	$r = .14$	$r = .17$	$r = .13$	$r = .03$	$r = .05$	$r = .11$	$r = -.13$
WAIS-III Matrix Reasoning	$r = -.08$	$r = -.14$	$r = -.003$	$r = .04$	$r = -.03$	$r = .005$	$r = .07$
WAIS-III Letter Number Sequencing	$r = -.03$	$r = .04$	$r = -.02$	$r = .04$	$r = .04$	$r = -.11$	$r = -.07$
Ruff 2&7 Total Speed	$r = .05$	$r = .19$	$r = .006$	$r = -.01$	$r = .21$	$r = -.10$	$r = -.17$
Ruff 2&7 Total Accuracy	$r = -.23$	$r = .08$	$r = -.15$	$r = -.32^{**}$	$r = -.07$	$r = -.02$	$r = -.005$

Note: All neuropsychological variables represent the scaled or standardized scores. Correlations are Pearson Product Moment Correlations. * $p < .05$. ** $p < .01$. *** $p < .001$. BVRT = Benton Visual Retention Test. CVLT-2 = California Verbal Learning Test- 2nd edition. D-KEFS = Delis-Kaplan Executive Functioning System.

Table 9. Simple Relationships Between Neuropsychological Predictors (Standardized Scores) and Drug Usage Variables (Lifetime)

	<u>Alcohol</u>	<u>Marijuana</u>	<u>Sedatives</u>	<u>Opioids</u>	<u>Stimulants</u>	<u>Hallucinogens</u>	<u>Inhalants</u>
BVRT Recall Total Errors	$r = .18$	$r = .14$	$r = .16$	$r = .23$	$r = .04$	$r = .16$	$r = .06$
CVLT-2 Trial 1 Recall	$r = .10$	$r = -.08$	$r = .008$	$r = -.04$	$r = .02$	$r = -.11$	$r = .08$
CVLT-2 Total Recall	$r = -.01$	$r = .14$	$r = -.17$	$r = .19$	$r = .08$	$r = -.05$	$r = -.04$
CVLT-2 Short Delay Free Recall	$r = .13$	$r = .26^*$	$r = -.04$	$r = .13$	$r = .02$	$r = .03$	$r = -.34^{**}$
CVLT-2 Long Delay Free Recall	$r = .17$	$r = .26^*$	$r = -.14$	$r = .12$	$r = .19$	$r = .05$	$r = -.11$
CVLT-2 Retention Variable	$r = -.18$	$r = -.18$	$r = .11$	$r = -.001$	$r = -.20$	$r = -.13$	$r = -.05$
CVLT-2 Recognition Discriminability	$r = -.12$	$r = -.05$	$r = -.03$	$r = -.09$	$r = .01$	$r = .06$	$r = -.03$
D-KEFS Inhibition/Switching vs. Color/Naming	$r = .11$	$r = .15$	$r = .11$	$r = .05$	$r = -.04$	$r = .05$	$r = -.10$
D-KEFS Verbal Fluency FAS	$r = -.01$	$r = .06$	$r = .17$	$r = .15$	$r = .01$	$r = .13$	$r = .06$
D-KEFS Verbal Fluency Category	$r = .07$	$r = .03$	$r = -.13$	$r = .03$	$r = .15$	$r = .08$	$r = .18$
D-KEFS Visual Fluency Total Score	$r = .02$	$r = -.05$	$r = .009$	$r = .03$	$r = -.05$	$r = -.20$	$r = -.18$
D-KEFS Visual Fluency Accuracy	$r = -.33^{**}$	$r = -.15$	$r = -.11$	$r = -.20$	$r = -.22$	$r = -.24^*$	$r = -.33^{**}$
Trail Making Test B Scaled Score	$r = .06$	$r = .14$	$r = .05$	$r = .14$	$r = .06$	$r = .28^*$	$r = -.08$
WAIS-III Matrix Reasoning	$r = -.12$	$r = -.14$	$r = -.05$	$r = .003$	$r = -.11$	$r = .08$	$r = .09$
WAIS-III Letter Number Sequencing	$r = -.04$	$r = .04$	$r = -.02$	$r = .25^*$	$r = .18$	$r = .14$	$r = .14$
Ruff 2&7 Total Speed	$r = .18$	$r = .11$	$r = .01$	$r = .14$	$r = .33^{**}$	$r = .17$	$r = -.001$
Ruff 2&7 Total Accuracy	$r = .13$	$r = .10$	$r = -.20$	$r = -.17$	$r = .09$	$r = -.05$	$r = -.13$

Note: All neuropsychological variables represent the scaled or standardized scores. Correlations are Pearson Product Moment Correlations. * $p < .05$. ** $p < .01$. *** $p < .001$. BVRT = Benton Visual Retention Test. CVLT-2 = California Verbal Learning Test- 2nd edition. D-KEFS = Delis-Kaplan Executive Functioning System.

Table 10. Multivariate Relationships Between Neuropsychological Variables and Ecstasy Use Predictors Variables

	<u>Past Year</u>	<u>Lifetime</u>	<u>Max Dose</u>
BVRT Recall Total Errors±	$t = 1.38$	$t = -.31$	$t = .80$
CVLT-2 Total Recall	$t = -2.00^*$	$t = -1.31$	$t = -1.07$
CVLT-2 Short Delay Free Recall	$t = -1.86$	$t = -2.21^*$	$t = -1.07$
CVLT-2 Long Delay Free Recall	$t = -2.79^{**}$	$t = -1.87$	$t = -1.17$
CVLT-2 Retention	$t = 1.13$	$t = .23$	$t = .17$
CVLT-2 Recognition Discriminability	$t = -2.14^*$	$t = -2.30^*$	$t = -1.19$
D-KEFS Inhibition/Switching vs. Color/Naming	$t = .92$	$t = .97$	$t = -1.09$
D-KEFS Verbal Fluency FAS	$t = .83$	$t = 1.58$	$t = .49$
D-KEFS Verbal Fluency Category	$t = .07$	$t = .10$	$t = .79$
D-KEFS Visual Fluency Total Score	$t = .49$	$t = .55$	$t = -1.08$
D-KEFS Visual Fluency Accuracy	$t = -1.21$	$t = .53$	$t = -.21$
Trail Making Test B±	$t = .88$	$t = .59$	$t = .77$
WAIS-III Matrix Reasoning	$t = -.23$	$t = -.69$	$t = -.06$
WAIS-III Letter Number Sequencing	$t = .25$	$t = 1.40$	$t = 2.14^*$
Ruff 2&7 Total Speed	$t = -1.28$	$t = -.20$	$t = -1.02$
Ruff 2&7 Total Accuracy	$t = -.09$	$t = -.17$	$t = 1.12$

Note: ±BVRT recall condition represents the residuals after regressing BVRT copy onto BVRT recall to control for constructional ability. The Trail Making Test (TMT) B also represents the residuals after regressing TMT A onto TMT B to control for simple processing speed. * $p < .05$. ** $p < .01$.

Figure 1: Scatterplot representing the simple relationship between CVLT-2 Total Recall and Past Year Ecstasy Use (“Sunflowers” are shown to demonstrate multiple cases. Each dot and line represent a single case at that data point).

Figure 2: Scatterplot representing the simple relationship between CVLT-2 Long Delay Free Recall and Past Year Ecstasy Use. (“Sunflowers” are shown to demonstrate multiple cases. Each dot and line represent a single case at that data point).

Figure 3: Scatterplot representing the simple relationship between CVLT-2 Recognition Discriminability and Past Year Ecstasy Use. (“Sunflowers” are shown to demonstrate multiple cases. Each dot and line represent a single case at that data point).

Figure 4: Scatterplots Demonstrating Relationships Between CVLT-2 Retention and Past Year Ecstasy Use Among Male Ecstasy Users and Female Ecstasy Users. (“Sunflowers” are shown to demonstrate multiple cases. Each dot and line represent a single case at that data point).

Figure 5: Scatterplots Demonstrating the Relationships Between LNS and Past Year Ecstasy Use Among Male Ecstasy Users and Female Ecstasy Users. (“Sunflowers” are shown to demonstrate multiple cases. Each dot and line represent a single case at that data point).

Figure 6: Scatterplots Demonstrating the Relationships Between D-KEFS Inhibition Task and Past Year Ecstasy Use Among Male Ecstasy Users and Female Ecstasy Users.
("Sunflowers" are shown to demonstrate multiple cases. Each dot and line represent a single case at that data point).