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The effect of concomitant ecstasy-marijuana use on auditory verbal learning and memory performance

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THE EFFECT OF CONCOMITANT ECSTASY-MARIJUANA USE

ON AUDITORY VERBAL LEARNING AND

MEMORY PERFORMANCE

by

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A dissertation submitted in partial fulfillment
of the requirements for the

Doctor of Philosophy Degree in Psychology
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Graduate College
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May 2008

UMI Number: 3319125

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Dissertation Approval
The Graduate College
University of Nevada, Las Vegas

April 18   , 20**08**

The Dissertation prepared by

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Entitled

The Effect of Concomitant Ecstasy-Marijuana Use on

Auditory Verbal Learning and Memory Performance

is approved in partial fulfillment of the requirements for the degree of

Doctor of Philosophy in Psychology

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ABSTRACT

The Effect of Concomitant Ecstasy-Marijuana Use on
Auditory Verbal Learning and
Memory Performance

by

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Previous research indicates that ecstasy users exhibit deficits of verbal learning and memory. This research has not considered polydrug use in ecstasy users, especially marijuana. Marijuana is an important confound because 90 percent of ecstasy users also use marijuana. Several studies have suggested that marijuana use alters verbal memory functioning; consequently, it is difficult to ascertain whether the observed memory deficits in ecstasy users are attributable to ecstasy, marijuana, or other drug use. The present study examined the effects of marijuana and ecstasy on verbal memory function. Marijuana use was accounted for by recruiting concurrent ecstasy-marijuana users' and ecstasy-naïve marijuana-only users. Furthermore, the extent of marijuana use was controlled for in the combined ecstasy-marijuana and marijuana-only groups by assigning marijuana users to either the marijuana light or marijuana heavy experimental groups. Recent animal findings suggest that at low frequencies marijuana may exert neuroprotective effects against ecstasy-induced neurotoxicity. Alternatively, other animal

findings have demonstrated negative synergistic effects between ecstasy and marijuana and working memory performance. Polydrug use was controlled for by restricting other drug use to not more than 15 occasions. Based upon responses to a drug use history questionnaire, 109 students were retrospectively assigned to one of five groups: marijuana-only heavy users, marijuana-only light users, ecstasy-marijuana heavy users, ecstasy-marijuana light users, and non-drug using controls. Participants were matched for age, gender, education, and intelligence as measured by the Wechsler Adult Intelligence Scale, Third Edition. Verbal learning and memory performance was assessed using the Auditory Verbal Learning Test (AVLT) (Rey, 1964; Schmidt, 1996). The Biber Figure Learning Test-Extended version (BFLT-E) was administered during the 20-minute delay of the AVLT. AVLT performance was compared between the two marijuana-only groups and the controls to determine the impact of marijuana use on mnemonic function. The marijuana-only user groups were compared with the ecstasy-marijuana groups to evaluate the effects of ecstasy on verbal memory. Overall, findings in the present study suggest that marijuana use more than ecstasy were associated with AVLT. Additionally, drug use other than ecstasy and marijuana explained some of the impairment observed on the AVLT and even more so for BFLT-E performance

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ACKNOWLEDGEMENTS

The written pages included in this dissertation hold far more than the years of study and work that I have put into this project. This project also reflects the many wonderful relationships that I have formed with those who have become instrumental to the completion of my study.

To my advisor and committee chair, Dr. Douglas Ferraro, thank you for the encouragement and the fact that you never stopped believing in me. Your patience and compassion are deeply appreciated.

To my committee members, Dr. Daniel Allen, Dr. Laurel Pritchard, and Dr. David Beisecker, who were willing to devote their time and attention to my work during many busy semesters.

To my husband, Eric Cramer, who has stood by my side through the many years of frustration, joy, sadness, and happiness that encompass the course of a graduate study.

To my friends, Mike and Helen Montgomery who have shown me the meaning of true friendship and statistical analyses.

To all of my colleagues and professors who believed in me and showed me that through hard work, I will persevere in my goal.

CHAPTER 1

INTRODUCTION

Sought after for its tempered stimulant-hallucinogenic properties and reported

enhancement of social interaction, ecstasy's popularity has risen to make it one of the

four most commonly used illicit drugs in the world (Christophersen, 2000). Ethnographic

data from the National Institute on Drug Abuse (NIDA) (2003) showed that ecstasy use is

spreading from dance parties and raves to high schools, colleges, and other social settings

frequented by adolescents and young adults. This is particularly alarming given that non-

human primate and other animal studies suggest that the main psychoactive ingredient of

ecstasy, namely methylendioxymethamphetamine (MDMA), is neurotoxic upon central

serotonergic systems (e.g., Fischer et al., 1995; Ricaurte et al., 2000).

Taking MDMA leads to an acute massive neuronal release of serotonin, followed by a

period of depletion before levels return to normal. Serotonin is thought to play a

prominent role in memory function and marked toxic effects of MDMA have been

observed in the hippocampus and prefrontal cortex. These areas are crucial to memory

and other cognitive functions (Sabol, Lew, Richards, Vosmer, & Seiden, 1996). This

suggests that MDMA may have long-term effects on memory and cognition.

In laboratory animals, high and repeated doses of MDMA produce widespread

degeneration of serotonergic axon terminals, with a concomitant depletion of serotonin in

brain regions such as the prefrontal cortex and hippocampus (Battaglia, Sharkey, Kuhar,

& de Souza, 1991; Ricaurte, DeLanney, Irwin, & Langston, 1988; Sabol et al., 1996).

The hippocampus and the parahippocampus display relatively low rates of recovery after

abstinence from ecstasy and abnormal patterns of reinnervation are observed in the

hypothalamus and thalamus (Fischer et al., 1995; Hatzidimitriou et al., 1999; Ricaurte,

Martello, Katz, & Martello, 1992).

Corresponding with the animal evidence, neuroimaging studies in human ecstasy

users suggest MDMA use may be associated with structural alterations in serotonergic

functioning and therefore, may be neurotoxic. Functional magnetic resonance imaging

(fMRI), positron emission tomography (PET) and single photon emission tomography

(SPECT) studies have yielded evidence of long-term reductions in serotonergic

transporter densities (SERT) (McCann, Szabo, Scheffel, Dannals, & Ricaurte, 1998;

Reneman et al., 2001; Semple et al., 1999; Thomasius et al., 2003) and in cortical 5-HT_{2A}

serotonergic receptor densities (Reneman, Majoie, Flick, & den Heeten, 2001),

deficiencies in cerebral metabolism (Chang et al., 1999; Chang et al., 2000; Obrocki et

al., 1999) and reduced cerebral spinal fluid (CSF) concentrations of 5-hydroxindoleacetic

acid (5-HIAA) (the major metabolite of serotonin; used as a marker for serotonergic

depletion) (McCann et al., 1999) in recreational ecstasy users. These data have been

interpreted as reflecting cumulative MDMA-induced damage to the serotonergic system,

with recent data pointing to partial recovery after prolonged abstinence (Buchert et al.,

2003; Gouzoulis-Mayfrank et al., 2002; Reneman et al., 2001; Semple et al., 1999;

Thomasius et al., 2003).

It remains unclear how these biological abnormalities might affect long-term

cognitive function since neuropsychological studies of ecstasy users have yielded

inconsistent results. On the one hand, studies indicate that users of ecstasy display residual cognitive deficits, with a selective deficit of verbal learning and memory impairment being most frequently observed in ecstasy users compared to controls on a variety of tasks (i.e., word list learning, prose recall, associative learning) (e.g., Bhattachery & Powell, 2001; Bolla, McCann, & Ricaurte, 1998; Curran & Travill, 1997; Daumann et al., 2004; Fox, Toplis et al., 2001; Gouzoulis-Mayfrank et al., 2000; Gouzoulis-Mayfrank et al., 2003; Krystal et al., 1992; McCann et al., 1999; McCardle et al., 2004; Montgomery, Fisk, & Necombe, 2005; Morgan, 1999; Parrott & Lasky, 1998; Quednow et al., 2006; Reneman et al., 2001; Thomasius et al., 2003; Yip & Lee, 2005). Delayed and immediate measures of recall performance in particular appear to be most adversely affected in ecstasy users (Bhattachery & Powell, 2001; Bolla et al., 1998; Curran & Travill, 1997; Curran & Verheyden, 2003; Fox, Toplis et al., 2001; Gouzoulis-Mayfrank et al., 2000; Krystal & Price, 1992; McCardle et al., 2004; Montgomery, Fisk, & Necombe, 2005; Morgan, 1999; Parrott & Lasky, 1998; Quednow et al., 2006; Reneman et al., 2001; Rodgers, 2000, Thomasius et al., 2003; Yip & Lee, 2005).

Moreover, verbal memory performance in ecstasy users has been found to be negatively associated with cumulative MDMA consumption (e.g., Bhattachary & Powell, 2001; Bolla et al., 1998; Curran & Travill, 1997; Fox, Toplis et al., 2001; Gouzoulis-Mayfrank et al., 2000; Krystal & Price, 1992; Quednow et al., 2006; Thomasius et al., 2003; Yip & Lee, 2005; Zakzanis & Young, 2001), levels of 5-hydroxyindoleacetic acid (5-HIAA) depletion (5-HIAA is the major metabolite of serotonin) (Bolla et al., 1998; McCann et al., 1998) and reduced serotonergic transporter (SERT) binding and availability (Reneman et al., 2001; Semple et al., 1999; Thomasius et al., 2003).

On the other hand, a minority of studies have reported no differences between ecstasy users and controls with regard to verbal memory performance (e.g., Back-Madruga et al., 2003; Croft et al., 2001; Dafters, Hoshi, & Talbot, 2004; Fox, Parrott, & Turner, 2001; Halpern et al., 2004; Lamers et al., 2006; Morgan, 1998; Parrott, 2000; Semple et al., 1999). Some of these studies have compared combined users of ecstasy and marijuana with marijuana-only users and found an association between low memory performance and the concomitant use of marijuana rather than ecstasy (e.g., Croft et al., 2001; Dafters et al., 2004; Gouzoulis-Mayfrank et al., 2000; Lamers et al., 2006; Thomasius et al., 2003). Other studies have failed to find significant differences in verbal memory performance when they compared ecstasy users with polydrug users matched for similar patterns of drug use (Back-Madruga et al., 2003; Fox, Parrott et al., 2001; Halpern et al., 2004; Semple et al., 1999; Simon & Mattick, 2002)

Interpretation of the positive findings of verbal memory deficits are questionable, however, because they are complicated by methodological shortcomings and potentially confounding variables that may have contributed to the deficits observed. First, a number of the earlier memory studies that demonstrate impairment did not adequately match samples of ecstasy users and control participants with regard to pre-morbid cognitive ability, education level, gender and age. More recent studies have attempted to correct for such differences by matching participants. With regard to pre-morbid intellectual ability, researchers have either matched participants or adjusted for some measure of verbal intelligence, since this measure is relatively immune to cortical insults.

Secondly, previous research provides little specific consideration for the concomitant use of other illicit drugs by ecstasy users, especially marijuana (e.g., Bolla et al., 1992;

Curran & Travill, 1997; Krystal et al., 1992; Parrott & Lasky, 1998). Marijuana use is a particular problem for MDMA research because it is common for ecstasy users to consume marijuana to enhance the MDMA-induced euphoria, as well as to mitigate the unpleasant come-down effects that follow when the euphoria begins to diminish (Parrott, 2001). Subsequently, most ecstasy users have used marijuana more or less regularly before they started taking ecstasy and continue using marijuana parallel to their use of ecstasy (Gouzoulis-Mayfrank & Daumann, 2006). Strote et al. (2002) observed that 92 percent of college students who had taken ecstasy also used marijuana. Moreover, a recent survey showed that every novice ecstasy user (cumulative dose one to nine pills) had smoked marijuana at least once during the preceding month and 32 percent had smoked marijuana on five or more occasions during the preceding month. In addition, the more pills these novice users had taken, the more frequently they had smoked marijuana before (Scholey et al., 2004). Previous studies yielded similar results with rates of 90 to 100 percent for co-use of marijuana in ecstasy users (Rodgers, 2000; Schuster et al., 1998; Winstock et al., 2001). Thus, a large number of ecstasy users have also used a substantial quantity of marijuana, making it difficult to recruit ecstasy users who have not also used marijuana.

In addition, a number of neuropsychological studies have reported that habitual use of marijuana may alter cognitive functioning, particularly verbal memory ability (e.g., Block & Gonheim, 1993; Fletcher et al., 1996; Hall & Solowij, 1998; Messinis et al., 2006; Millsaps et al., 1994; Pope et al., 1996; Solowij et al., 2002). Furthermore, the severity of marijuana-induced impairment appears to depend on the duration and the frequency of marijuana use (e.g., Hall & Solowij, 1998; Solowij et al., 2002). To some degree then, the

question remains as to whether cognitive deficits in ecstasy users are attributable to ecstasy itself or to marijuana. Because most studies addressing MDMA neurotoxicity have not controlled for marijuana use, more studies are needed to investigate the separate effects of ecstasy and marijuana on verbal learning and memory performance.

The aim of the proposed study was to assess whether ecstasy users exhibit deficits in explicit long-term verbal memory performance while accounting for concomitant use of marijuana and other illicit drugs, as well as intelligence. To delineate the respective effects of marijuana and ecstasy on memory function, concomitant ecstasy-marijuana users were compared to ecstasy-naïve marijuana-only users approximately matched for age, gender, level of education and intelligence. Furthermore, based on recent animal data illustrating interactive effects of ecstasy and marijuana, the extent of marijuana use was manipulated to examine whether marijuana used in low and high recreational doses with ecstasy exerts additive, supra-additive and/or subtractive effects on verbal memory performance. Other illicit drug and alcohol use was accounted for by instituting strict inclusion criteria.

Explicit Long-Term Verbal Memory Studies in Ecstasy Users

Behavioral studies of ecstasy users have been hampered by the impossibility of using double-blind, placebo-controlled, repeated dose regimens on ethical grounds and by difficulty finding suitable control populations with which to compare ecstasy users (Croft et al., 2001; Dafters et al., 2004). The fact that ecstasy users are usually polydrug users, particularly with a long history of marijuana use has led some researchers to abandon the traditional non-drug using control group, resorting instead to controlling for non-ecstasy

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drug use by statistical adjustments of levels of other drug use (Curran & Verheyden, 2003; Dafters et al., 1999; Fox et al., 2001; Halpern et al., 2004; McCardle et al., 2004; Mongomery et al., 2005; Quednow et al., 2006; Reneman et al., 2001; Simon & Mattick, 2002; Thomasius et al., 2003; Verkes et al., 2001). Others have attempted to compare ecstasy users with ecstasy -naive users with otherwise comparable drug use histories (e.g., Croft et al., 2001; Dafters et al., 2004; Gouzoulis-Mayfrank et al., 2000; Lamers et al., 2006; McCann et al., 1999; Morgan, 1998, 1999; Morgan et al., 2002; Quednow et al., 2006; Rogers, 2000; Thomasius et al., 2003).

Tables 1 and 2 (see Appendix I) summarize previous findings regarding ecstasy-related performance on explicit long-term verbal memory tests. The studies are split into two tables because they vary in the degree of specificity with which any cohort differences can be attributed to ecstasy. With the exception of the ecstasy users recruited by Yip and Lee (2005), Gouzoulis-Mayfrank et al. (2000) and Halpern et al. (2004), the majority of ecstasy users in studies also used a variety of other drugs and alcohol. This is tolerated in this field of research because it is generally considered impractical to obtain samples that do not use alcohol and other drugs. Consequently, evidence with the greatest degree of specificity to ecstasy comes from studies that statistically control for the use of other drugs and/or compare ecstasy users to a control group of individuals who have similar drug use patterns, but have never used ecstasy.

Additionally, studies with a high degree of specificity to the long-term effects of ecstasy control for other potential covariates by excluding individuals with a history of relevant psychiatric conditions and by statistical controlling for and/or matching cohorts on gender, age, estimated pre-morbid intelligence and level of education.

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The studies in Table 1 exercised a relatively higher degree of control over possible confounding variables compared to those in Table 2, namely other illicit drug use and pre-morbid IQ. Thus, the degree of assurance with which one can derive conclusions from these data is greater for the studies reported in Table 1 than in Table 2. Hence, the verbal memory findings reported in Table 2 must be interpreted with caution.

Both tables report the findings of immediate and delayed recall performance and in some cases other measures of memory performance (e.g., recognition). Delayed recall performance is the measure that is most specific to explicit verbal memory and is typically assessed after a 20- or 30-minute delay. Presumably, delayed recall performance represents one's ability to encode, store and retrieve incoming information. A number of studies have examined the impact of recreational ecstasy use on delayed recall performance in ecstasy users. While significant deficits in ecstasy users have been observed using a variety of tests, the results are far from consistent across studies.

Of the studies in Table 1 that assessed delayed memory performance, seven reported a significant deficit in ecstasy users compared to other drug users (except when noted). Despite being statistically significant, the size of the deficit detected in ecstasy users compared to controls was quite small, typically seven percent to 28 percent, such that ecstasy users only recall one or two words less than controls on a list of 15 words (e.g., Curran & Verheyden, 2003; Fox, Toplis et al., 2001; McCardle et al., 2004). Larger deficits in ecstasy users were found by Reneman et al. (2001, 22 percent, ecstasy users = 10.1 words versus polydrug users = 13.1 words on the AVLT), as well as Yip and Lee (2005, 61 percent, ecstasy users = 5.28 words versus non-drug users = 13.52 words on the AVLT).

Yip and Lee's (2005) study deserves particular consideration, not just because large deficits in both immediate and delayed recall performance were observed in ecstasy users, but because a large sample of ecstasy users was tested (N = 100). Moreover, the ecstasy users recruited were unusual in that they were relatively "pure" ecstasy users. They were "pure" in the sense that they did not report any history of substance abuse other than ecstasy use. The authors attributed recruitment of such subjects to the fact that the use of ecstasy had only recently become a popular trend in Hong Kong.

What's more interesting is that Yip and Lee (2005) observed deficits in ecstasy users with relatively low lifetime ecstasy consumption. Ecstasy users had on average consumed 35.8 tablets (range 16 to 60 tablets). The only other study to report significant deficits in ecstasy users with such a low average use of ecstasy was McCardle et al. (2004), but the deficit detected was only seven percent (ecstasy users = 11.18 words versus polydrug users = 12.13 words on the AVLT). In comparison, deficits of 28 percent were obtained by Curran and Verheyden (2003) in users with an average lifetime dose of 707 tablets (ecstasy users = 5.81 words versus polydrug users = 8.06 words on the RBMT-Prose Recall) and Fox, Toplis et al. (2001) in users with an average lifetime dose of 811.5 tablets (ecstasy users = 10.6 words versus polydrug users = 12.7 words on the AVLT).

Others have not found a statistically significant deficit in users who have also used several hundred ecstasy tablets in their lifetime (e.g., Semple et al., 1999; Simon & Mattick, 2002). For example, ecstasy users in Simon and Mattick's (2002) study had consumed a mean lifetime 258 tablets, whereas in Semple et al., (1999) the mean lifetime consumption of ecstasy users was 672 tablets. Although Semple and colleagues (1999) did not find significant differences in delayed recall, they did obtain an association

between lifetime numbers of ecstasy tablets and verbal memory performance. Larger

lifetime doses of ecstasy were associated with reduced verbal memory performance in the

CVLT.

Other evidence for ecstasy-related verbal memory impairment has been provided by

four studies (e.g., Fox, Toplis et al., 2001; Gouzoulis-Mayfrank et al., 2000; Quednow et

al., 2006; Thomasius et al., 2003) that too, observed dose-related impairment between

some measure of ecstasy use and the delayed recall performance. For example,

Gouzoulis-Mayfrank et al. (2000), Quednow et al. (2006) and Thomasius et al. (2003)

observed a negative association between cumulative lifetime consumption and delayed

recall scores as measured by the Auditory Verbal Learning Test (AVLT). That is, heavier

ecstasy use was associated with lower delayed recall scores. With the exception of

Gouzoulis-Mayfrank et al. (2000) (M = 93 tablets), cumulative lifetime consumption of

ecstasy was high (e.g., Fox et al., M = 811 tablets; Quednow et al., M = 457 tablets;

Thomasius et al., M = 1,033 tablets). Fox and colleagues (2001) also found that delayed

recall scores were negatively associated with both the usual and largest number of ecstasy

tablets consumed on any one occasion.

Lifetime consumption of marijuana has also been observed to be associated with

AVLT immediate memory performance (Fox, Toplis et al., 2001; Gouzoulis-Mayfrank et

al., 2000; Morgan, 1999; Quednow et al., 2006; Thomasius et al., 2003). For example, the

extent of marijuana use was associated with performance on AVLT-Trial two in the Fox,

Toplis et al. (2001) study, whereas in Gouzoulis-Mayfrank et al. (2000) younger age of

onset of marijuana use and higher frequency of use were associated with learning

performance or sum of AVLT Trials one through five. Thomasius and colleagues (2003)

found the amount of marijuana smoked in the year prior to testing best predicted AVLT-Trial six performance (immediate recall of interference list B) ($R^2 = 0.05$, $p = 0.023$).

In addition to cumulative lifetime consumption, an association between duration of abstinence from MDMA and delayed recall scores has been observed (Bhattachary & Powell, 2001). This is suggestive of some degree of recovery of function with cessation of ecstasy use. However, studies of ecstasy users who have been abstinent for at least one year have demonstrated persistent mnemonic deficits (Curran & Verheyden, 2003; Reneman et al., 2001). These findings suggest that the after effects of ecstasy use may be long lasting or permanent. A single, small scale longitudinal study of ecstasy users (N = 15) found that continued use of ecstasy over a one-year follow up period was associated with progression of deficits in both immediate and delayed verbal memory (Zakzanis & Young, 2001).

The reported frequency of ecstasy use at baseline ranged from one to 55 tablets (mean = 19 tablets) (Zakzanis & Young, 2001). At the one-year follow-up, this increased from a minimum of three tablets to reportedly as many as 225 tablets (mean = 55 tablets). Average use in the ecstasy users had gone up by an average of 4 tablets per month, but the use of various other illicit drugs also increased over the same period complicating the conclusions about ecstasy's long-term effects on memory. While this study is far from a final say on the matter, its longitudinal design is more convincing than simple comparison group testing.

Like Zakzanis and Young (2001), findings of significant verbal memory deficits in ecstasy users in six other studies in Table 2 are complicated by the absence of statistical evaluation of the potential influence of other drugs (Bhattachery & Powell, 2001; Bolla et

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al., 1998; Krystal et al., 1992; Morgan, 1999; Parrott & Lasky, 1998; Reneman, Majoie et al., 2001). This makes it difficult to identify the relative contribution of these substances to verbal long-term impairment. Consequently, these findings must be treated with more caution because drug use other than ecstasy may have contributed to the observed deficits.

In contrast to the number of significant findings for delayed recall, five of the relatively well controlled studies in Table 1 failed to detect a difference between ecstasy users and controls on delayed verbal memory or detected a difference that failed to remain significant after controlling for other drug use and/or other covariates (Croft et al., 2001; Dafters et al., 2004; Halpern et al., 2004; Lamers et al., 2006; Semple et al., 1999; Simon & Mattick, 2002). For example, Dafters and colleagues (2004) compared the verbal memory performance of subjects who used both ecstasy and marijuana, marijuana-only, and neither drug, on the Rivermead Behavioral Memory Test (RBMT), which involved the recall of an audio taped story after a 30-minute delay. In addition, free recall performance of 30 words (i.e., subjects listen to 30 words and are instructed to recall as many as they can remember) was tested. All the drug user groups displayed significantly impaired memory function compared to the non-drug users. However, there were no significant differences between subjects who used ecstasy-marijuana and those who used only marijuana.

Likewise, Lamers et al. (2006) and Croft et al. (2001) found that combined ecstasy-marijuana users and marijuana-only users did not differ from each other in their delayed recall performance. A variety of tests were used to assess delayed recall performance, including the AVLT (Lamers et al., 2006), Coughlan List Test (Croft et al., 2001) and the

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Weschler Memory Scale III test (WMS-III) (Simon & Mattick, 2002). In addition, the sample sizes of the Lamers et al. (2006) and Croft et al. (2001) studies were relatively small (Lamers et al., 2006, ecstasy-marijuana users N = 11, marijuana-only users N = 15, non-drug users N = 15). The sample size in the Simon and Mattick (2002) study was larger (ecstasy users N = 40, marijuana-only users N = 37). Taken together, these results provide very little support for an effect of ecstasy use on delayed verbal memory performance. These studies suggest that marijuana use, rather than MDMA use, may better account for many of the verbal memory deficits among ecstasy users reported elsewhere in the literature.

The majority of studies in Tables 1 and 2 also assessed immediate recall. Immediate recall performance presumably reflects some combination of long-term memory and working memory performance because there is no inhibition of the use of working memory to retain items between study and test (Fox, Toplis et al., 2001). In the AVLT, for example, the number of words recalled on trial six (the trial immediately following recall of words from interference list B) is typically used to represent participants immediate recall score. However, trials one through five have also been interpreted to reflect immediate recall performance.

Like the delayed recall memory results, there has been a mix of significant and non-significant results across studies with regard to immediate recall performance (e.g., 13 studies have found deficits, whereas 13 studies have not). Yip and Lee (2005) have observed the most profound deficit in ecstasy users immediate recall performance (51 percent). On average, the ecstasy user group recalled 5.20 words whereas the non-users recalled an average of 10.51 words. Mean recognition performance in the ecstasy users

was also significantly impaired relative to non-users (ecstasy users M = 5.64 v. non-users M = 12.80 words) (Yip & Lee, 2005).

Negative correlations between immediate recall scores and patterns of ecstasy use have also been observed. For example, Reneman Lavalaye et al. (2001) found that immediate recall scores on the AVLT were lower in ecstasy users who had reported greater lifetime consumption and/or used higher lifetime doses of ecstasy. Furthermore, Thomasius et al. (2003) showed that immediate recall on the first trial was best predicted by the average number of exposures to ecstasy.

Immediate recall deficits have often been observed in relatively heavy ecstasy users. For example, Quednow and colleagues (2006) demonstrated immediate memory deficits in ecstasy users with more than 450 tablets per lifetime. Studies showing no or only weak impairment in immediate recall (e.g., Back-Madruga et al., 2003; Croft et al., 2001; Gouzoulis-Mayfrank et al., 2000; McCardle et al., 2004; Simon & Mattick, 2002) in ecstasy users examined mostly users with a lifetime dose lower than 100 tablets. However, ecstasy users in the Simon and Mattick (2002) study had consumed a somewhat higher dose of 258 tablets.

Explanations for the Diversity of Findings

Several factors may contribute to the diversity of findings. Among them are failure to comprehensively to assess intelligence and control for IQ differences between groups, lack of a normal control group in some studies, age and/or educational differences between subjects and controls and relatively small sample sizes. One of the most crucial influencing factors to the diversity of finding is the relative use of marijuana and ecstasy.

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Table 3 (see Appendix I) summarizes the mean lifetime consumption of ecstasy users in the verbal memory studies reviewed in Tables 1 and 2. As Table 3 depicts, there is a great deal of variability across studies with regard to cumulative MDMA exposure. Moreover, verbal memory deficits have been detected in ecstasy users who have used a small number of tablets (mean = 20 tablets, Rodgers, 2000), whereas others have failed to find deficits in ecstasy users who have consumed a substantial number of tablets (mean = 672 tablets, Semple et al., 1999). In addition, in some studies the extent of use of marijuana was significantly greater than ecstasy use. For example, in Croft et al. (2001a), the mean lifetime use of marijuana was 10,964 occasions, whereas the use of ecstasy was 41 occasions. Similarly, participants in Simon and Mattick's (2002) study (ecstasy users and marijuana-only users) were also heavy marijuana users, with a mean 67.9 joints smoked per month in the ecstasy user group and a mean 62.6 joints smoked per month in the marijuana-only group, but generally lighter ecstasy users (mean lifetime exposure 258 tablets). It could be posited that the higher use of marijuana may have contributed to these researchers finding that the verbal memory deficits were related to marijuana, rather than ecstasy.

The Marijuana Confound

Marijuana may confound MDMA studies in two ways. First, the main psychoactive constituent of marijuana, delta-9- tetrahydrocannabinol (THC), has been shown to interact with the dopamine system (Tanda et al., 2000) and dopamine has been shown largely to determine MDMA-related serotonin impairment in rats (Aguirre et al., 1998; Sprague et al., 1998; Stone et al., 1989). Thus, marijuana may interact with MDMA in

determining serotonin deficit in recreational users. Second, rat hippocampus is impaired following chronic marijuana administration (Ameri et al., 1999; Scallet, 1991) and as the hippocampus plays a significant role in memory (Sun et al., 1999), marijuana may also impair neurocognitive function.

Brain imaging studies of marijuana users have demonstrated altered function, blood flow, and metabolism in prefrontal and cerebellar regions (Block et al., 1999; Loeber & Yurgelun-Todd, 1999; Lundqvist, 2005). Thus, marijuana produces various metabolic changes in the brain. Long-term marijuana users appear to have lower resting levels of regional cerebral blood flow (rCBF) compared with non-smokers. Marijuana increases rCBF and brain metabolism in experienced users, while it decreases rCBF in non-users. These effects have been particularly apparent in frontal cortical areas. Decreases in rCBF were localized to brain regions that mediate sensory processing and attention.

Studies using a challenge paradigm indicate that even after an extended washout period, specific differential patterns of cortical activation exist in subjects with a history of heavy marijuana use. During a challenge paradigm, smokers who completed a 24-hour washout showed diminished activation in the dorsolateral prefrontal cortex (DLPFC). The effect remained diminished after 28 days of washout, although some increase in the DLPFC activation was noted, relative to the 24-hour time point (Yurgelun-Todd et al., 1999). Memory-related blood flow in frequent marijuana users showed decreases relative to controls in the prefrontal cortex, increases in memory-relevant regions of the cerebellum, and altered lateralization in the hippocampus (Block et al., 2002). The greatest differences between users and controls occurred in brain activity related to episodic memory encoding.

Behavioral studies corroborate the brain imaging data and provide good consensus that heavy marijuana use produces residual deficits on measures such as memory of word lists (Fletcher et al., 1996; Pope & Yurgelun-Todd, 1996; Pope et al., 1995, 2001; Solowij et al., 2002) and complex attention tasks (Fletcher et al., 1996; Pope et al., 2001) that may last for many days after cessation. For example, Pope and colleagues (2001) found persistent deficits among users who commenced marijuana use prior to the age of 17. Bolla et al. (2002) found dose-related decrements in neuropsychological performance after 28 days of abstinence using a very similar neuropsychological test battery. Solowij and colleagues (1995) have observed partial recovery, but with persistence of some selective attention deficits after a mean, abstinence of two years, however, at present, consensus is still lacking on the question of whether increasing duration of marijuana exposure causes increasing cognitive deficits. To date, the results of different studies indicate that marijuana-associated cognitive deficits may be reversible and related to recent marijuana exposure (Pope et al., 2002).

In summary, both neuropsychological assessment studies and studies based on brain imaging techniques indicate that heavy chronic marijuana use may be associated with dysfunction on tests of verbal memory that were found previously to differentiate ecstasy users from controls (e.g., Block & Gonheim, 1993; Bolla et al., 2002; Fletcher et al., 1996; Fried, Watkinson, James, & Gray, 2002; Hall & Solowij, 1998; Messinis et al., 2006; Pope et al., 2001; Solowij et al., 2002). This raises the question of whether the adverse cognitive profiles of ecstasy users who also concomitantly use marijuana, are more closely associated with the extent of marijuana use rather than ecstasy use. To date,

investigations regarding the contribution of marijuana to the long-term memory effects of MDMA have yielded inconsistent findings.

Evidence Demonstrating Interactive Effects of MDMA and Marijuana

The potential mechanism(s) by which MDMA and marijuana interact is not well known. Parrott and colleagues (2004) have suggested that the effects of marijuana and MDMA may interact when taken together. This notion has been partially based on the acute profiles of MDMA and marijuana, which are opposite in certain crucial aspects. For example, MDMA is a powerful central nervous system (CNS) stimulant whereas marijuana has sedative and relaxant properties. MDMA is hyperthermic, whereas marijuana is hypothermic, MDMA increases oxidative stress while cannabinoids are powerful antioxidants (Croxford, 2003). This led Parrott et al. (2004) to generate the tentative hypothesis that when taken together marijuana may act to ameliorate the stimulatory effects of ecstasy. Furthermore, they suggested that if marijuana does reduce the acute neuronal over-stimulation induced by ecstasy, it may then also attenuate MDMA-induced neurotoxicity (Parrott et al., 2004). There is animal evidence which lends support to the notion that marijuana may interact with MDMA to mitigate MDMA-induced neurotoxicity.

Morley and colleagues (2004) found that administration of the main psychoactive constituent of marijuana, delta 9 tetrahydrocannabinol (THC), or the synthetic cannabinoid CP 55940, in male wistar rats attenuated the hyperthermic and serotonin depleting effects of MDMA, which previously have been found to cause neurotoxicity. MDMA alone, THC alone, a combination of MDMA-THC, a synthetic cannabinoid

agonist CP 55940 and a cannabinoid antagonist SR 141716 were administered in repeated injections every four hours for two days. Body temperature, locomotor activity, emergence (a measure of anxiety), social interaction, and neurochemical analyses in the hippocampus, amygdala, and prefrontal cortex (known to be depleted of serotonin when MDMA is taken) were assessed.

With regard to body temperature, MDMA alone caused hyperthermia whereas THC caused modest hypothermia. Interestingly, the co-administration of MDMA-THC induced greater hypothermia than THC given alone, particularly within the first two hours of testing. A similar robust hypothermia was also evident when the effect of synthetic cannabinoid CP 55940 was combined with MDMA. Co-administration of the CB_1 antagonist SR 141716 prevented this hypothermia suggesting the involvement of CB_1 receptors in the effect.

In addition, in the MDMA-THC group, THC at a high dose (2.5 mg/kg every four hours for two days) partially prevented the depletion of serotonin and 5-HIAA in each of the prefrontal cortex, amygdala and hippocampus compared to when MDMA was given alone. Subsequently, the combination of MDMA-THC tended to decrease MDMA-induced hyperactivity and increases in anxiety seen in the emergence test. These findings were taken as evidence that THC when combined with MDMA provided some degree of neuroprotection against MDMA-related neurotoxicity.

Morley and colleagues (2004) have suggested that the mechanism of neuroprotection may be due to THC's antioxidant properties, possibly by counteracting MDMA-induced oxidative stress (Morley et al., 2004). There is evidence which suggests that THC has a structural resemblance to the powerful antioxidant vitamin E (Chen & Buck, 2000).

Furthermore, cannabinoids have been found to exert antioxidant effects in vitro and are neuroprotective in animal models of stroke (Leker et al., 1999; Mishima et al., 2005).

However, Morley and colleagues (2004) caution that their findings do not suggest that human MDMA users should resort to consuming THC to minimize harm. Firstly, the protective doses of THC used in their study were high and these effects are unlikely to be obtained with the relatively small amounts of THC typically consumed during recreational marijuana use. Secondly, the effect of cannabinoids on MDMA-induced neurotoxicity in cannabinoid tolerant animals is not known. Thus, protection from the neurotoxic effects of MDMA may not necessarily be obtained in frequent marijuana users. Finally, the neuroprotective effects of THC were by no means complete and were in fact only partial in all brain regions examined.

Croft et al. (2001) has also suggested that marijuana may exert neuroprotective effects against MDMA-induced neurotoxicity by inducing dopamine down regulation. Marijuana indirectly augments levels of dopamine in the mesocortical pathway (Diana, Melis, & Gessa, 1998). A possible mechanism explaining this increase in dopamine levels is through an indirect excitatory action of marijuana on the ventral tegmental area (VTA) dopaminergic neurons, the main ascending dopaminergic projection to the nucleus accumbens (Cheer et al., 2004). Cannabinoid receptor (CB_1) agonists have been found to enhance the firing rate of dopaminergic neurons (Cheer et al., 2003) via a reduction of afferent GABAergic transmission (Szabo et al., 2002). Marijuana binds to CB_1 receptors located on pre-synaptic glutamatergic neurons that project to the nucleus accumbens, effectively controlling the firing of the nucleus accumbens GABAergic neurons, which in turn inhibit the dopaminergic neurons of the VTA. Via the reduction of excitatory

transmission in the nucleus accumbens, marijuana could disinhibit dopamine cells of the VTA, increase their firing rate, and trigger the release of dopamine in the nucleus accumbens (Robbe et al., 2001).

Long-term over stimulation of dopamine decreases the number of receptors (down regulation) and the remaining receptors become desensitized. Down regulation is thought to be an underlying mechanism for psychodynamic tolerance, where exposure to a drug causes less response than previously obtained.

In contrast to the hypothesis that marijuana attenuates MDMA-induced neurotoxicity, there are other animal data which suggest that ecstasy and marijuana may interact to produce greater impairment than that which is observed when either drug is used alone. Young, McGregor, and Mallet (2005) tested working memory using a double-Y maze task in male wistar rats. The double-Y maze task involved the presentation of two consecutive tasks on each trial: a spatial discrimination task in the first "Y", followed by a delayed alternation task in the second "Y". The spatial discrimination component of the double-Y maze requires the use of reference memory only, whereas the delayed alternation component also requires the use of working memory (Mallet & Beninger, 1993).

Low (THC 0.25 mg/kg and MDMA 1.25 mg/kg), medium (THC 0.5 mg/kg and MDMA 2.5 mg/kg), and high (THC 1.0 mg/kg and MDMA 5.0 mg/kg) drug doses were administered alone and together. At low doses, THC and MDMA alone did not impair memory. Combined however THC and MDMA significantly impaired working memory, which was evidenced by impaired choice accuracy in the delayed alternation component, but no effect in the spatial discrimination component of the maze task. At medium doses,

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the administration of THC or MDMA alone or in combination had no significant effect in the spatial discrimination task of the double-Y maze. THC, but not MDMA significantly impaired choice accuracy in the delayed alternation component. The combined drug treatment led to a further impairment of choice accuracy in the delayed alternation. At high doses, THC and MDMA treatments alone both caused increased errors in the delayed alternation component, with THC causing greater impairment than MDMA. Co-administration of THC and MDMA rendered the rats incapable of completing either maze task. These findings provide strong evidence of a synergistic interaction of THC and MDMA on memory function.

To summarize, Young and colleagues findings revealed that MDMA alone did not significantly affect memory at the low or medium doses tested (which are within a dose range relevant to human consumption), but MDMA at these doses interacted with THC to produce an impairment of memory that was greater than that observed with THC alone. MDMA and THC acted synergistically to impair memory.

Young and colleagues (2005) posited that the neurochemical basis for the observed synergistic effects of THC and MDMA may involve dopamine. THC primarily exerts its effects via activation of cannabinoid CB_1 receptors, which are predominately located on pre-synaptic hippocampal neurons (Tsou et al., 1998). THC is known to increase dopamine production in several areas including prefrontal mesocortical areas, strongly connected with working memory function (Bergson et al., 2003). MDMA has direct action on the serotonin, dopamine, and norepinephrine neurotransmitter systems (Climko et al., 1986), suggesting that an interaction of the two drugs may occur within the dopamine system.

The Proposed Investigation

Most investigations examining explicit long-term verbal memory function in recreational ecstasy users have not controlled for other illicit drug use. Marijuana use is a particular problem for MDMA research because it is common for ecstasy users to consume marijuana to alleviate the residual negative effects that result from taking ecstasy. Thus, a large number of ecstasy users have also used a substantial quantity of marijuana. This is problematic because marijuana use by itself has been associated with deficits on tests of verbal learning and memory previously found to differentiate ecstasy users from controls (e.g., Bolla et al., 2002; Hall & Solowij, 1998; Pope et al., 1996; Solowij et al., 2002). These findings suggest that at least some of the widely reported deficits in memory performance in ecstasy users might be attributable to marijuana rather than ecstasy.

The primary aim of the proposed study was to delineate the respective effects of marijuana and ecstasy on verbal learning and memory performance. The Auditory Verbal Learning Test (AVLT) (Rey, 1964; Schmidt, 1996) was used to assess verbal memory performance. Participants completed a drug use history questionnaire, which explored participants' prior illicit drug use and demographic information.

Illicit drug use beyond ecstasy and marijuana was controlled for by setting strict criteria that limited other drug use to 15 or fewer occasions in a lifetime. Additionally, to control for individual differences participants were matched for age, gender, and level of education. Participants also were matched on intelligence, which was assessed using the vocabulary subtest of the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) (Wechsler, 1997).

Concurrent ecstasy-marijuana users, ecstasy-naïve marijuana-only users and non-drug users were recruited for participation. The extent of marijuana use was controlled for in the drug user groups by classifying marijuana use as either light or heavy. Categorization of marijuana use as light or heavy was based on retrospective examination of participants self-report data collected from the drug use history questionnaire. The marijuana use criterion resembled that used by Fried, Watkinson, James, and Gray (2002). Heavy marijuana use was defined as using marijuana five or more times per week and light marijuana use was defined as using marijuana fewer than five times a week.

Moreover, the comparison of heavy and light marijuana users in the concurrent ecstasy-marijuana and marijuana-only users enabled the assessment of potential interactive effects of combined marijuana and ecstasy use. The rationale for examining the interactive effects of these two drugs is found in recent animal findings. One set of findings has suggested that marijuana at high doses may exert positive neuroprotective effects against MDMA-induced neurotoxicity (Morley et al., 2004). In contrast, another set of animal findings has demonstrated a negative synergistic disruption in working memory performance by co-administration of THC and MDMA (Young et al., 2005).

CHAPTER 2

REVIEW OF RELATED LITERATURE

History of MDMA

The German pharmaceutical company Merck first synthesized MDMA in 1912.

MDMA was incidentally created as a by-product while trying to synthesize a different

drug. For reasons that have been lost over time, Merck did little to explore its properties

as a drug. In fact, there was little interest in MDMA until the 1950s when the U.S. Army

studied it as a potential chemical warfare agent that would temporarily disable enemy

troops. In the 1970s, despite a lack of any meaningful controlled clinical trials, many

psychotherapists used it as a therapeutic agent. The use of MDMA as an adjunct to

therapy was based on the notion that MDMA lowers defensiveness and heightens the

effects of physical contact, which purportedly allows users to achieve important healing

insights about their problems (Rochester & Kirchner, 1999).

In the 1980s, MDMA earned a new nickname, ecstasy (also XTC or E), given to it by

the newest group to experiment with it, our nation's youth. At about the same time that

MDMA first appeared as a so called "party" or "club" drug at raves or all-night dance

parties, evidence was emerging that this compound was not benign, and could cause

damaging effects on serotonergic neurons.

In 1985, MDMA was found to have toxic effects on brain serotonin neurons in

rodents (Ricaurte et al., 1985). Subsequently, the U.S. Drug Enforcement Agency (DEA)

added MDMA to the Schedule I list of drugs having high abuse potential with no accepted medical use. Despite MDMA's classification as a Schedule I drug, it continues to be used illegally.

Neuropharmacology of MDMA

MDMA is a derivative of methamphetamine (known by such street names as "speed," "crystal," and "meth") and its parent compound amphetamine. Ecstasy differs from amphetamine and methamphetamine in that it has a methylenedioxy ($-O-CH_2-O-$) group attached to positions three and four of the aromatic ring of the amphetamine molecule (i.e., it is ring substituted). In this respect, it resembles the structure of the hallucinogenic material mescaline (Nichols, 1986; Shulgin, 1986). As a result, the pharmacological effects of MDMA are a blend of those of the amphetamines and hallucinogenic mescaline. 3,4-methylenedioxyamphetamine (MDA) and methylenedioxiethyl-amphetamine (MDEA) are also amphetamine-mescaline derivatives (i.e., they are similar in chemical structure to MDMA) and therefore, produce pharmacological effects similar to MDMA. This group of substances is frequently referred to as "designer drugs" because when illicit laboratories began to produce them for non-medical use, the blend of amphetamine-like and mescaline-like effects was intentionally sought and could be achieved reliably by the appropriate design of the drug molecule (Kalant, 2001).

MDMA blocks the reuptake of serotonin by binding with a high affinity to the serotonergic transporters (SERTS). This action is similar to serotonin specific reuptake inhibitors (SSRIs), such as anti-depressants like fluoxetine (Prozac), sertraline (Zoloft), and paroxetine (Paxil). Unlike SSRIs, but similar to the action of the amphetamines,

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MDMA appears to enter the nerve terminal itself, either through passive diffusion or directly through the SERT, by exchange diffusion (a concentration gradient that involves the reversal of the normal inward bound direction of serotonin with MDMA) and causes the release of serotonin. This release is calcium-independent (i.e., independent of the firing of the serotonin neuron) and appears to come from cytoplasmic stores rather than from synaptic vesicles. The released serotonin then enters the synaptic cleft through the serotonin transporter, by exchange diffusion with MDMA. MDMA acts on serotonin release in much the same way as amphetamines act on dopamine release.

It is thought that the movement of serotonin into the synaptic cleft, and the subsequent action of serotonin on pre- and post-synaptic binding sites is central to MDMA's neuropharmacology. MDMA has potency for the serotonin $5\text{-}HT_{2A}$, muscarinic M_1, adrenergic alpha ($\alpha\text{-}2$) and histamine H_1 receptors (Nichols et al., 1982; Berger et al., 1992b). Animal studies indicate that $5\text{-}HT_2$ receptors might be involved in MDMA's effects because $5\text{-}HT_2$ antagonists reduced several effects of MDMA, such as MDMA-induced serotonergic neurotoxicity, acute hyperthermia and disruption of sensorimotor gating (Schmidt et al. 1990). $5\text{-}HT_{2A}$ receptors have been implicated in the hallucinogenic effects of classic psychedelic drugs such as LSD (Vollenweider et al. 1998). It is possible that some of MDMA's psychedelic effects occur because of interactions with this receptor. The $\alpha\text{-}2$ adrenergic receptor also may be associated with some of the cardiovascular effects of MDMA (Berger et al., 1992).

MDMA also triggers the releases of dopamine, which may be central to both its psychological action and to its neurotoxicity in animal studies (Johnson et al., 1991). In mice, MDMA produces a selective long-term loss of dopamine nerve endings (Miller &

O'Callaghan, 1994). Pre-treatment of an animal with a drug that blocks dopamine release, appears to block MDMA neurotoxicity (Colado, O' Shea, & Green, 2004). Also, serotonin specific releasing agents, which are non-dopaminergic have been synthesized and been found to be devoid of MDMA's neurotoxicity and psychological effects in animals. MDMA tends to indirectly inhibit the firing and release of dopamine in nigrostriatal dopamine neurons (i.e., neurons projecting from the substantia nigra to the striatum) due to local serotonin release (Colado, O' Shea, & Green, 2004).

In summary, MDMA affects serotonin similarly to the way that amphetamines affect dopamine, by inhibiting the reuptake and causing the release of serotonin. This effect is somewhat similar to the effect that SSRI antidepressant drugs have. Subsequently, MDMA influences the 5-HT_{2A} (psychedelic) and $\alpha\text{-}2$ adrenergic (cardiovascular) receptor sites. MDMA's effects on dopamine appear, at this point, to be involved both with its neurotoxicity and psychological effects.

The Serotonin System

Serotonin, also called 5-hydroxytryptamine or 5-HT is found in mast cells, blood platelets, intestinal tissue, and especially in the brain. In the brain, serotonin acts as a primary neurotransmitter. It is synthesized from tryptophan through the intermediate 5-hydroxytryptophan in the axon terminals of serotonin neurons. After serotonin is manufactured, it is stored in sacks called synaptic vesicles located in the 5-HT axon terminals. These vesicles release their serotonin into the synaptic cleft via exocytosis (the excretion of neurotransmitter through the membrane of a pre-synaptic terminal and into the synaptic cleft), in response to the firing of the serotonin neurons.

In the synaptic cleft, the serotonin neurotransmitter exerts its action on both pre-synaptic and post-synaptic receptor sites (sites on the serotonin neuron itself and on the neuron with which it is communicating). Serotonin is then taken back into the pre-synaptic serotonin neuron (from the synaptic cleft) via a reuptake pump referred to as the synaptic membrane serotonin transporter (SERT). Thus, the concentration of serotonin in the synaptic cleft is controlled directly by its reuptake into the pre-synaptic terminal. Serotonin that is reclaimed is again stored in the vesicles or metabolized by monoamine oxidase (MAO-A) into 5-hydroxyindileacetic acid (5-HIAA).

Serotonergic Neuron Distribution and Pathways

Serotonergic neurons are widely distributed in pathways throughout the CNS. As Figure 1 depicts, the largest group of serotonergic neurons is B7, which is continuous with a smaller group of serotonergic cells, B6. Groups B6 and B7 often are considered together as the dorsal raphe nucleus, with B6 being its caudal (tail or hind end) extension. Another prominent serotonergic cell body group is B8, which corresponds to the median raphe nucleus. Group B9, part of the ventrolateral tegmentum of the pons and midbrain, forms a lateral extension of the median raphe and therefore is not considered one of the midline raphe nuclei. Ascending serotonergic projections innervating the cerebral cortex and other regions of the forebrain arise primarily from the dorsal raphe, median raphe and B9 cell group.
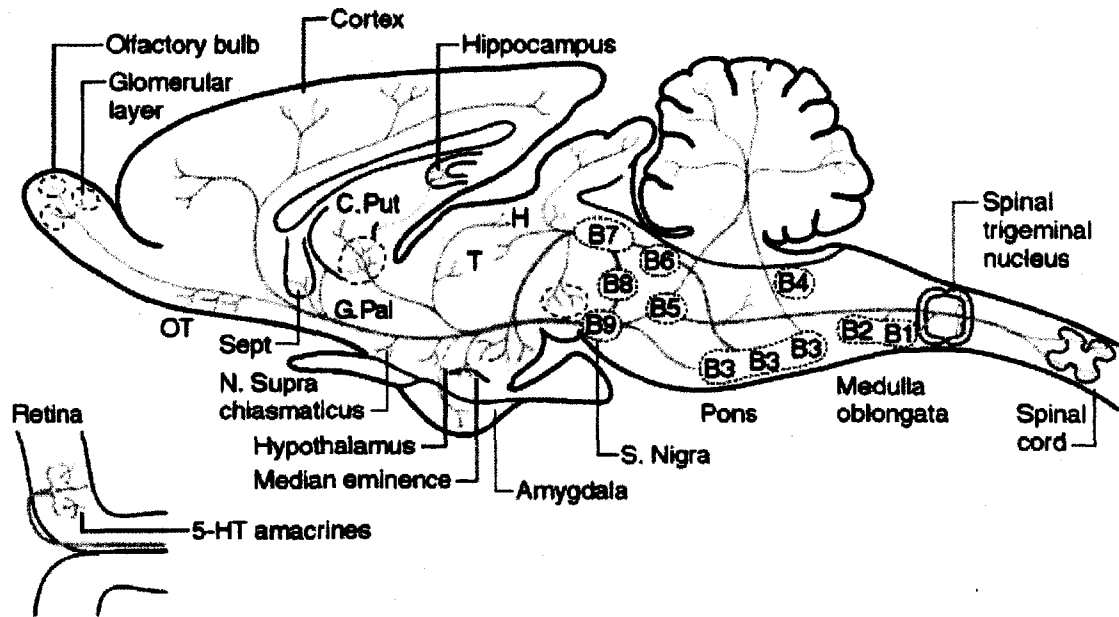
Figure 1.   Schematic drawing depicting the location of the serotonergic cell body groups in a sagittal section of the rat central nervous system and their major projections. Serotonergic cell bodies are located within the B cell groups of Dahlstrom and Fuxe (1964), from which they project caudally to the spinal cord and rostrally to many forebrain structures. OT, olfactory tuberculum; Sept, septum; C. Put, nucleus caudate-putamen; G. Pal, globus pallidus; T, thalamus; H, habenula; S. Nigra, substantia nigra. (Modified from Consolazione & Cuello, 1982).

Two distinct ascending projections arise from the rostral (head or front end)

serotonergic system. The two main ascending serotonergic pathways emerging from the

midbrain raphe nuclei to the forebrain are the dorsal periventricular path and the ventral

tegmental radiations. Both pathways converge in the caudal hypothalamus, where they

join the medial forebrain bundle. Axons of both dopaminergic and noradrenergic neurons

run through the medial forebrain bundle as well.

Ascending projections from the raphe nuclei to forebrain structures are organized in a

topographical manner. The dorsal and median raphe nuclei give rise to distinct

projections to forebrain regions. The median raphe projects heavily to the hippocampus,

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septum and hypothalamus, whereas the striatum is innervated predominantly by the dorsal raphe nuclei. The dorsal and median raphe nuclei send overlapping neuronal projections to the neocortex.

Within the dorsal and median raphe, cells are organized in particular zones or groups that send axons to specific areas of the brain. For example, the frontal cortex receives heavy innervation from the rostral and lateral sub-regions of the dorsal raphe nucleus. Raphe neurons send collateral axons to areas of the brain that are related in function, such as the amygdala and hippocampus or the substantia nigra and caudate putamen. The specific and highly organized innervation of forebrain structures by raphe neurons implies independent functions of sets of serotonergic neurons dependent on their origin and terminal projections, as opposed to a nonselective or general role for serotonin in the CNS.

The existence of specific pathways projecting from the raphé nuclei to the forebrain and the density of serotonin receptors in these and other areas, such as the hippocampus, amygdala and cortex, supports the growing body of evidence implicating serotonin in the processes of learning and memory (Buhot, 1997; Buhot, Martin, & Segu, 2000). Spoont (1992) has proposed that serotonin may play a role in cognition and that extreme deviations of serotonin activity can result in biases in cognitive processing. There is also evidence that suggests that serotonin is particularly likely to be involved in learning (e.g., Hunter, 1988), visuospatial memory (Wenk, 1997), visual discrimination, associative functions and aspects of planning (Park et al., 1994), and general memory consolidation and retrieval (Meneses & Hong, 1994).

Serotonin has been also implicated in the regulation of mood, anxiety, aggression, impulsiveness, sexual activity, appetite, sleep, pain, circadian and seasonal rhythms, motor activity, and body temperature (Morgan, 2000). Transient reductions in serotonin activity, induced by tryptophan depletion have been reported to produce a rapid lowering of mood in normal males (Young et al., 1985) and relapse in recently remitted depressed patients (Delgado et al., 1990). Furthermore, there is evidence that disorders of central serotonergic neurotransmission, as reflected by low levels 5-HIAA (the major metabolite of serotonin) are associated with anxiety disorders (e.g., Garvey et al., 1995) and impulsive and aggressive personality traits (e.g., Linnoila et al., 1993).

Serotonergic Receptors

Over the past decade, more than 14 different serotonin receptors have been located in the central and peripheral nervous system (CNS/PNS) (see Table 4). Researchers have also cloned serotonin receptors through molecular biological techniques, which has facilitated the identification of new therapeutic targets and aided an understanding of the multiple roles played by 5-HT in the brain.

Table 4   Different serotonin (5-HT) receptor subtypes

$5\text{-}HT_1$	$5\text{-}HT_2$	$5\text{-}HT_3$	$5\text{-}HT_4$	$5\text{-}HT_5$	$5\text{-}HT_6$
$5\text{-}HT_{1A}$	$5\text{-}HT_{2A}$	$5\text{-}HT_{3A}$		$5\text{-}HT_{5A}$	
$5\text{-}HT_{1B}$	$5\text{-}HT_{2B}$	$5\text{-}HT_{3B}$		$5\text{-}HT_{5B}$	
$5\text{-}HT_{1D}$	$5\text{-}HT_{2C}$				
$5\text{-}HT_{1E}$					
$5\text{-}HT_{1F}$					

Serotonergic receptors are divided into seven distinct classes based on their structural and operational characteristics. With the exception of the $5-HT_3$ receptor, a ligand gated ion channel, all other 5-HT receptors are G-protein coupled seven transmembrane (or heptahelical) receptors that activate an intracellular second messenger cascade. Binding of serotonin to the receptor causes a conformational change in the intracellular domain of the receptor, which then affects its interaction with the GTP-binding G-protein on the cytosolic side of the plasma membrane. The occupied receptor causes replacement of the GDP bound to the alpha subunit of the G-protein by GTP, activating the G-protein. This activated G- protein regulates an enzyme which generates an intracellular second messenger. If the G- protein is a stimulatory G-protein, it acts on the membrane bound enzyme to increase the concentration of the intracellular second messenger, while an inhibitory G-protein acts to decrease the second messenger concentration (e.g., Linnoila et al., 1993).

At least five receptor subtypes have been classified within the family of $5-HT_1$ receptors ($5-HT_{1A}$, $5-HT_{1B}$, $5-HT_{1D}$, $5-HT_{1E}$, $5-HT_{1F}$). They exhibit high affinity for serotonin and cause the cell membrane to hyperpolarize, which keeps the neuron from firing(Barnes & Sharp, 1999). Selective agonist (a drug that binds to a receptor of a cell and triggers a response by the cell) for $5-HT_1$ receptors include 8-hydroxy-2-di-n-propylamino-tetralin (8-OH-DPAT), which modulate adenylyl cyclase activity in the hippocampus. $5-HT_{1A}$ receptors are found in the hippocampus, cerebral cortex, raphe nuclei, thalamus and amygdala.

The cell body of $5-HT_{1A}$ receptor functions as an autoreceptor sensing the extracellular serotonin concentration and modulating the firing rate of the neurons of the

raphe nuclei (Hamon et al, 1999). When activated, $5\text{-}HT_{1A}$ autoreceptors inhibit firing and consequently inhibit subsequent release of serotonin from distal axon terminals.

$5\text{-}HT_{1A}$ ligands with agonist activity seem to possess anti-anxiety, anti-depressant, anti-aggressive, as well as anti-craving, anti-cataleptic, anti-emetic and neuroprotective properties. For example, Buspirone is a $5\text{-}HT_{1A}$ agonist that is useful in the management of anxiety. The main therapeutic potential of $5\text{-}HT_{1A}$ receptors has been in the treatment of anxiety and depression. Work with $5\text{-}HT_{1A}$ (partial) agonists indicates that the anti-anxiety actions of $5\text{-}HT_{1A}$ may involve primarily pre-synaptic somatodendritic $5\text{-}HT_{1A}$ receptors (leading to reduced release of 5-HT in terminal areas), whereas the anti-depressant action of $5\text{-}HT_{1A}$ agents may primarily involve post-synaptic $5\text{-}HT_{1A}$ receptors. $5\text{-}HT_{1A}$ receptors also may be involved in obsessive-compulsive disorders, impulsivity, sexual behavior, appetite control, thermoregulation, and cardiovascular function.

$5\text{-}HT_{1B}$ receptors were one of the first $5\text{-}HT_1$-like receptors to be described. It was later shown that the distribution and second messenger coupling of $5\text{-}HT_{1B}$ receptors in rodent brain was similar to that of $5\text{-}HT_{1D}$ receptors in mammalian brain, leading to speculation that $5\text{-}HT_{1B}$ and $5\text{-}HT_{1D}$ receptors might constitute species variants of the same receptor. $5\text{-}HT_{1B}$ receptors are located pre-synaptically where they control the release of 5-HT and post-synaptically where the highest density of $5\text{-}HT_{1B}$ receptors in rat and mouse brain is found in the substantia nigra, globus pallidus, and dorsal subiculum. $5\text{-}HT_{1B}$ receptors are negatively coupled to adenylate cyclase.

Rodent $5\text{-}HT_{1B}$ receptors play a role in thermoregulation, respiration, appetite control, sexual behavior, aggression, and anxiety (Liechti et al., 2000). Past studies, however,

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utilized agents that are now recognized as lacking selectivity for 5-HT$_{1B}$ receptors. In addition, the possible existence of multiple populations of 5-HT$_{1B}$ receptors and the relationship between 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors has raised new questions. Nonetheless, recent studies support a role for 5-HT$_{1B}$ receptors in the regulation of sleep, sensorimotor inhibition, and to some extent, locomotor activity (Vollenweider et al., 1998).

Another method for obtaining information about 5-HT$_{1B}$ receptors is by use of 5-HT$_{1B}$ receptor knock-out mice (Schmidt et al., 1990). Such mutant mice failed to display any obvious developmental or behavioral deficit but supported earlier suggestions that 5-HT$_{1B}$ receptors might be involved in locomotor activity and aggressive behavior.

5-HT$_{1D}$ receptors are widely distributed throughout the CNS (Liechti et al., 2000) and are negatively coupled to inhibit adenylate cyclase activity. The clinical significance of 5-HT$_{1D}$ receptors remains largely unknown. There has been speculation that these receptors might be involved in anxiety, depression, and other neuropsychiatric disorders, but this remains for the most part to be substantiated. With the availability of the 5-HT$_{1D}$ antagonists, it has been shown for example that GR127935 blocks the effect of anti-depressants in the mouse tail suspension test. Further, the localization of 5-HT$_{1D}$ receptors in human brain is thought to be consistent with potential involvement in Huntington's disease (Slassi et al., 2004). The causes of migraine headaches are unknown, but appear to include dilation of the cerebral blood vessels. Both 5-HT$_{1B}$ and 5-HT$_{1D}$ receptors mediate vasoconstriction, and 5-HT$_{1D}$ agonists (e.g., sumatriptan) are useful in the treatment of migraine headaches (Whale et al., 2000). Sumatriptan also

called Imitrix is effective after the onset of migraine headaches, yet is not as effective in preventing migraines.

The $5-HT_2$ receptor family consists of three specific receptor subtypes ($5-HT_{2A}$, $5-HT_{2B}$, and $5-HT_{2C}$). $5-HT_{2A}$ receptors (originally referred to as $5-HT_2$ receptors) were among the first 5-HT receptors to be identified. The $5-HT_2$ receptor family stimulates phosphoinositide-specific phospholipase C. $5-HT_{2A}$ receptors are widely distributed at varying densities throughout the brain, with the highest density is in the neocortex. Relative to $5-HT_1$ receptors, $5-HT_2$ receptors exhibit slightly lower affinity for serotonin. In the CNS, the $5-HT_{2A}$ receptors function to suppress cell firing, as well as inhibit neurotransmitter release (e.g., dopamine, acetylcholine, noradrenaline).

$5-HT_{2A}$ receptors display a high homology with $5-HT_{2C}$ receptors. Moreover, recent evidence suggests some of the roles attributed to the $5-HT_{2A}$ receptors may in fact be mediated by $5-HT_{2C}$ receptors. This suggestion was partly based on the finding that $5-HT_{2A}$ ligands bind nearly equally well at both types of receptors. Nevertheless, $5-HT_{2A}$ receptors are believed to play a role in appetite control, thermoregulation, and sleep. They are also involved, along with various other 5-HT receptor populations, in cardiovascular function and muscle contraction.

In addition, $5-HT_{2A}$ receptors have also received considerable attention from a neuropsychiatric standpoint. Various anti-psychotic agents and anti-depressants bind with relatively high affinity at $5-HT_{2A}$ receptors (Vollenweider et al., 1998). Although there is no direct correlation between their receptor affinities and clinically effective doses, evidence is strong that these disorders involve, at least to some extent, $5-HT_{2A}$ (or perhaps $5-HT_{2C}$) receptors (Liechti et al., 2000). For example, chronic administration of

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5-HT$_{2A}$ antagonists results in a paradoxical down-regulation of 5-HT$_{2A}$ receptors, such a down-regulation would be of benefit in the treatment of depression. There also are indications that 5-HT$_{2A}$ antagonists (a drug that blocks an action) possess anxiolytic properties. For example, ritanserin produced anti-anxiety effect in humans. 5-HT$_{2A}$ receptors are also involved in the actions of the classical hallucinogens (e.g., LSD, mescaline, MDMA) (Sanders-Bush, Burries, & Knoth, 1988).

5-HT$_{2C}$ receptors (once referred to as 5-HT$_{2A}$) have been found in low densities in various brain regions of different animal species. 5-HT$_{2C}$ receptors may play a greater role than 5-HT$_{2A}$ receptors in migraine (Liechti et al., 2000). On the basis of a significant correlation between migraine prophylactic activity and binding affinity, 5-HT$_{2C}$ receptors may be involved in the initiation of migraine attacks (Whale et al., 2001). For the most part, the specific role of 5-HT$_{2B}$ receptors is unknown.

The 5-HT$_3$ receptors are different from the other serotonin receptors in that they are non-selective sodium-potassium ion channel receptors, which allow them to alter fast synaptic transmission. They are found in both the PNS and CNS. In the CNS, 5-HT$_3$ receptors are localized in the entorhinal cortex, frontal cortex, and hippocampus.

5-HT$_3$ antagonists (e.g., ondansetron, granisetron, tropisetron) have proven clinically effective for the treatment of chemotherapy-induced or radiation-induced nausea and vomiting. Preclinical studies suggest that 5-HT$_3$ antagonists may enhance memory and be of benefit in the treatment of anxiety, depression, pain, and dementia. In addition, 5-HT$_3$ receptors can control dopamine release and may also be involved in acetylcholine release and control of the GABAergic system. Dopamine itself acts as a 5-HT$_3$ partial agonist.

5-HT$_4$ receptors are localized on neurons and may mediate slow excitatory responses to serotonin. It has been suggested that 5-HT$_4$ agonists may restore deficits in cognitive function and may be useful as anxiolytics or in the treatment of dopamine-related disorders. The marked decrease in 5-HT$_4$ receptors in patients with Alzheimer's disease suggests the 5-HT$_4$ receptors may be involved in memory and learning (Peroutka, Newman, & Harris, 1988). A high density of 5-HT$_4$ receptors in the nucleus accumbens has led some researchers to speculate that these receptors may be involved in the reward system and may influence self-administration behavior (e.g., Geyer, 1994).

The 5-HT$_5$ class of serotonin receptors has been found to not have a high efficiency of coupling to G-proteins. This suggests these may in fact be coupled to ion channels. The pharmacological function of 5-HT$_5$ receptors is currently unknown. It has been speculated that on the basis of their localization they may be involved in motor control, feeding, anxiety, depression, learning, memory consolidation, adaptive behavior, and brain development (Liechti & Vollenweider, 2000). 5-HT$_{5A}$ receptors may also be involved in a neuronally-driven mechanism for regulating astrocyte physiology, with relevance to gliosis (Liechti et al., 2000). Disruption of 5-HT neuron-glial interactions (i.e., gliosis) may be involved in the development of certain CNS pathologies, including Alzheimer's disease, Down's syndrome, and some drug-induced developmental deficits (Liechti et al., 2000).

5-HT$_6$ receptors are found primarily in the CNS and recent evidence suggests that these play a role in many neuropsychiatric disorders (Vollenweider et al., 1999). This is because numerous anti-depressants (clomipramine, amitriptylamine) and antipsychotic

agents (rilapine, clozapine, olanzapine) bind with a high affinity for these type of receptors acting as antagonists (Glennon, Dukat, & Westkaemper, 1999).

The newest classes of 5-HT receptors (5-HT$_{7A}$ and 5-HT$_{7B}$) are thought to be involved in both mood and learning, as well as in neuroendocrine and vegetative behaviors. It has recently been found that these two receptors also have a high affinity for many anti-depressants and anti-psychotic agents (Naughton, Mulrooney, & Leonard, 2000).

MDMA and Serotonin Receptors

MDMA causes a profound release of serotonin by binding with high affinity to the serotonin transporter (SERT). The binding of MDMA to the SERT inhibits the reuptake of serotonin into the serotonin neurons, consequently flooding the brain with serotonin. Recent studies suggest that the body responds to these extraordinarily high levels of serotonin by decreasing the amount of serotonin receptors in the brain. When serotonin levels return to normal, but there are less 5-HT receptors in the brain this may lead to changes in behavior (Rutty & Milroy, 1998).

Indeed, the major effect associated with the long-term abuse of the drug ecstasy has been the development of clinical depression in frequent users (e.g. Parrott, 2004; Thomasius et al., 2003). As MDMA affects serotonin release, and since serotonin has long been known to be linked to depression, it was assumed that MDMA eventually caused a lower production in the amount of serotonin released. If this were true, then treatment with anti-depressants should have fixed the problem.

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Most anti-depressants are known as SSRI's, or selective serotonin reuptake inhibitors. This class of drugs works in that they inhibit the reuptake of serotonin back into the nerve terminal, therefore increasing the amount of available synaptic 5-HT, and thus, reversing depression (Connor et al, 2001). However, in ecstasy users, the administration of SSRI's had no effect, suggesting that the problem was not in the serotonin levels after all, as the increased serotonin levels did not provide the expected results.

After studies found that even high levels of SSRI administration didn't work to decrease depression, it was then postulated that the problem wasn't in the levels of serotonin, but in the 5-HT receptors. Autopsy observations on humans who have died from complications of ecstasy use (heart failure, heat stroke, seizures) found that their serotonin levels were normal (as measured by high performance liquid chromatography or HPLC), further suggesting that the problem was in the serotonin receptors. However, it still wasn't known if the 5-HT receptors were merely dysfunctional or if they had actually been completely depleted. However, evidence now exists that it is actually in the number of receptors, as studies in rodents have found a reduction in post-synaptic 5-HT receptors following MDMA dosage (e.g., Battaglia et al., 1991).

The depletion of serotonin receptors is much like Type II Diabetes Mellitus, in that the ligand is present in normal amounts, but the low concentration of receptors is what causes the problems. Therefore, anti-depressants show no effect, as the increased levels of serotonin aren't any help because the receptors aren't present to take up the ligand (Colado et al., 2004).

The mild hallucinogen-like perceptual effects of MDMA appear to be due to serotonergic $5-HT_{2A}$ receptor stimulation whereas MDMA-induced hyperactivity is

mediated in part by $5\text{-}HT_{1B}$ and $5\text{-}HT_{2A}$ receptors. In contrast, the stimulation of $5\text{-}HT_{2C}$ receptors results in inhibition of the expression of MDMA-stimulated hyperactivity (Liechti & Vollenweider, 2000).

The positive mood effects of MDMA may be related in part to dopaminergic D_2 receptor stimulation. Serotonin neurons innervate dopamine nigrostriatal and mesocorticolimbic circuits, including the projection from dopamine cell bodies in the substantia nigra (SN) and ventral tegmental area (VTA) to the dorsal striatum and nucleus accumbens. These pathways are known to be critical in mediating the behavioral effects of psychostimulants.

The $5\text{-}HT_{1B}$, $5\text{-}HT_{2A}$, and $5\text{-}HT_{2C}$ are among the 5-HT receptors that have been suggested to control brain dopamine function and also play a role in the behavioral effects of MDMA. The $5\text{-}HT_{1B}$ and its homolog, $5\text{-}HT_{1D}$ function pre-synaptically as an inhibitory autoreceptor (a receptor located on pre-synaptic nerve cell terminals and serves as a part of a feedback loop in signal transduction; it is sensitive only to those neurotransmitters or hormones that are released by the neuron in whose membrane the autoreceptor sits) and post-synaptically as an inhibitory heteroreceptor (a receptor regulating the synthesis and/or the release of neurotransmitter(s) other than its own ligand) to control release of neurotransmitters (Barnes & Sharp, 1999). Localization and lesion studies support the hypothesis that $5\text{-}HT_{1B}$ are localized on the axon terminals of γ-aminobutyric acid (GABA) efferents projecting from the striatum and nucleus accumbens. $5\text{-}HT_{1B}$ receptors provide inhibitory feedback to the origins of nigrostriatal and mesoaccumbens dopamine pathways (e.g., Brocke et al., 2000).

Stimulation of 5-HT$_{1B}$ by direct (5-HT) or indirect agonists (e.g., cocaine) has been shown to inhibit GABA release from terminals that innervate dopamine neurons in the substantia nigra (Johnson et al., 1998) and VTA suggesting an important role for the 5-HT$_{1B}$ in the control of dopamine function. In support of this hypothesis, microdialysis studies have shown that 5-HT$_{1B}$ agonists facilitate release of dopamine in the nucleus accumbens (Parsons et al., 1999) and striatum (Ng et al., 1993).

Neuropsychopharmacological Effects of MDMA in Experimental Animals

The effect of MDMA on brain concentrations of serotonin is biphasic in the rodent brain, and can be divided into acute and long-lasting phases. An acute, reversible phase of serotonin depletion occurs within three to six hours after drug administration, after which serotonin concentrations return to normal values (Schmidt, 1987). A long-lasting depletion of serotonin occurs two to three days after drug treatment, and this depletion of serotonin is evident in most brain regions containing serotonin terminals (Sabol et al., 1996). There is only a partial recovery to control concentrations of serotonin after depletion produced by MDMA. Serotonin concentrations remain depleted in most brain regions up to one year following MDMA administration (Lew et al., 1996; Sabol et al., 1996).

MDMA administration in rats also results in hyperthermia or an increase in core body temperature (Colado et al., 1993; Dafters, 1994; Gordon, Wilkinson, O'Callaghan, & Miller, 1991). Hyperthermia is related to the ambient temperature. Both Gordon et al. (1991) and Dafters (1994) showed that at normal (24°C) and high (30°C) ambient temperatures, MDMA administration resulted in an increase in temperature of

approximately 2.0°C, whereas administering the drug to animals that had been kept at low ambient temperature (11 °C) for 24-hours before injection resulted in a fall in temperature. Transferring the rats to a low temperature room 30-minutes after drug administration attenuated the temperature rise (Dafters, 1994).

Hyperthermia that follows MDMA administration was once thought to be serotonin receptor-mediated, however, more recent data suggests that it is a consequence of dopamine release (Mechan et al., 2002a; Sugimoto et al., 2001). Support for this proposal comes from findings that show that selective serotonin receptor antagonists do not block MDMA-induced hyperthermia (Mechan et al., 2002a). In addition, it has been shown that the administration of Prozac almost totally inhibited the increase in extracellular serotonin levels, but had no effect on the hyperthermic response in the same animals (Berger et al., 1992; Malberg et al., 1996; Schmidt et al., 1990). What is more, Mechan and colleagues (2002a) observed that a dopamine D_1 receptor antagonist (SCH 23390), dose-dependently inhibited MDMA-induced hyperthermia. These researchers postulated that MDMA might be producing hyperthermia, by enhancing the release of dopamine, which then acts on dopamine D_1 receptors.

Another major consequence of MDMA administration in rats is the appearance of hyperactivity and the "serotonin behavioral syndrome" (Grahame-Smith, 1971a; Colado et al., 1993; Slikker et al., 1989). The syndrome consists of hyperactivity accompanied by, head-weaving, piloerection, fore-paw treading, penile erection, ejaculation, and salivation (Green et al., 2003). Callaway et al. (1990) reported that MDMA produced a dose-related increase in locomotor activity that was prevented by pretreatment with Prozac. This finding shows that serotonin release plays a key role in the behavioral

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effects of MDMA. In addition, Kehne et al. (1996a) demonstrated a reduction of the MDMA-induced locomotor response following pretreatment with a serotonin 5-HT$_{2A}$ receptor antagonist, indicating the importance of 5-HT$_{2A}$ receptors in the expression of MDMA-induced locomotor responses.

Acute Subjective Effects of MDMA in Humans

Commonly consumed in oral tablet form, the average recreational dose of ecstasy is between one and two tablets, each containing approximately 60 - 120 milligrams (mg) of MDMA (Morgan, 2000). Most individuals use the drug on weekends, once a week or less because tolerance to its positive effects develops rapidly (Peroutka, Newman, & Harris, 1988; Solowij, Hall, & Lee, 1992).

Recreational users typically describe a range of positive moods while on MDMA, including euphoria, feelings of intimacy and closeness to others, heightened arousal, self-confidence, increased sensory sensitivity, increased depth of emotion, and decreased appetite (Curran & Travill, 1997; Davison & Parrott, 1997; Parrott, 1997; Peroutka et al., 1988). The commonly reported acute adverse physiological side effects include increased heart rate, jaw clenching, bruxism (tooth grinding), pupil dilation, gait instability, and nausea (Davison & Parrott, 1997; Petroutka et al., 1988).

Long-Lasting Subjective Effects of Ecstasy in Humans

Following the acute subjective effects, ecstasy users generally report a 24- to 48-hour period characterized by the persistence of an array of negative moods, such as feelings of lethargy, irritability, aggression, and depression. The negative moods presumably

develop as a consequence of central serotonergic depletion. This cycle of positive moods while on the drug and negative moods afterward was confirmed in a prospective study by Curran and Travill (1997). Twelve recreational MDMA users were compared with 12 alcohol users (controls), at a Saturday night dance club, over a period of four days following consumption. MDMA users reported comparatively better moods on the Saturday night (i.e., day one), and worse moods in the days afterwards, at which point some participants scored within the range of clinical depression. In contrast, alcohol users showed less pronounced changes, which followed a U-shaped curve, with the lowest point being day two.

Mechanisms of MDMA-Induced Neurotoxicity

MDMA predominately causes serotonin to be released from its storage sites in neurons, thereby, dramatically increasing brain activity. An acute dose of MDMA can release around 80 percent of central serotonin stores within four hours of administration (Green, Cross, & Goodwin, 1995). Through the release of large amounts of serotonin, MDMA causes a significant depletion of central serotonin stores, which can take two weeks or longer to replenish (Green et al., 2003).

Neurotoxicity appears to develop because MDMA interferes with the synthesis of serotonin neurons. That is, MDMA triggers both oxidative and metabolic stress in serotonergic neurons, which adversely affects the ability of these neurons to produce serotonin. For example, Stone, Johnson, Hanson, and Gibb (1989) found that MDMA-induced oxidation rapidly destroyed tryptophan hydroxylase (an enzyme essential for the synthesis of serotonin), which causes a long-term depletion of serotonin in affected

neurons, and eventual cell death, particularly in the striatum and the cortex (Ricaurte et al., 1985).

It appears that oxidation is triggered by MDMA binding to the serotonin transporter and by MDMA-induced release of dopamine. Researchers have discovered that blocking either dopamine release or MDMA binding to the serotonin transporter blocks the production of free radicals (a usually short-lived, highly reactive molecular fragment that contained one or more unpaired electrons) and the destruction of tryptophan hydroxylase. In addition, investigators have shown that the formation of reactive oxygen triggered by MDMA and other amphetamine derivatives increases with body temperature, which explains observations that hyperthermia increases MDMA-induced toxicity.

Other evidence that MDMA induces oxidative stress comes from studies that have measured the levels of the major metabolite of serotonin, 5-HIAA, and the serotonin transporter. These studies have observed that 5-HIAA and the serotonin transporter levels decrease markedly after MDMA administration and appear to remain low for months after exposure. For example, in a study of rhesus monkeys, Taffe and colleagues (2001) found that a four-day course of twice daily injections of a moderate dose of MDMA produced four-to-five fold reductions in cortical serotonin levels 17 months after exposure.

MDMA may also produce neurotoxicity by triggering the production of hydroxl radicals, which cause an acute depletion of brain serotonin. Shankaran, Yamamoto, and Gudelsky (1999) measured the production of hydroxl radicals within the brains of rats given MDMA. These investigators found that following MDMA injection, there was an immediate rise in hydroxl radicals, in serotonergic neurons in the striatum.

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What is more, MDMA leads to a reduction in antioxidant (enzymes that prevent the formation of hydroxl radicals) levels. For example, experimenters found decreased levels of the antioxidants ascorbic acid (vitamin C) and vitamin E in the striatum of rat brains following MDMA administration. Subsequent studies, however, have found that artificially boosting the levels of antioxidant enzymes may reduce MDMA's damaging effects on serotonergic and also dopaminergic neurons (e.g., Cadet & Thiriet, 2001). It also appears that drugs, such as Prozac, which inhibits the serotonin transporter specifically, may decrease the number of free radicals produced by MDMA use. For example, in the Shankaran et al. (1999) study mentioned above, researchers administered Prozac an hour prior to MDMA injection and observed a dramatic reduction in hydroxl radical formation and in the amount of serotonin released in the striatum. MDMA-induced dopamine release in the striatum was also suppressed. The same effect was seen even when Prozac was administered four hours after MDMA. This finding suggests that these neurotoxic effects involve MDMA's actions at the serotonin transporter.

Histological studies have provided more dramatic evidence for the serotonin neurotoxicity produced by MDMA. Two weeks after receiving 20 mg/km of MDMA, twice daily for four days, tissue taken from rat brains showed a substantial decrease in neurons containing serotonin. Furthermore, the axons of these neurons appeared to be missing. More recently, investigators observed similar findings in squirrel monkeys showing that the loss of serotonin axons from four-day exposure to MDMA was severe 18 months after exposure and persisted seven years later (Hatzidimitriou, McCann, & Ricaurte, 1999).

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Further examination of this structural damage suggests that MDMA "prunes" or reduces in number serotonin axons and axon terminals in some brain regions, like the striatum, while sparing others, such as the amygdala (Ricaurte, 2001). This pattern is a hallmark of axon pruning, since neurons will often grow replacement axon terminals upstream of the damaged terminals. Taken together, these results provide evidence not only of MDMA's neurotoxicity but of the brain attempting to rewire the serotonin system after damage.

Finally, the regulation of serotonin receptors may also be involved in the mechanism of neurotoxicity. During the acute action of MDMA, there is an adaptive down regulation of serotonin receptors in the cerebral cortex (Sprague, Everman, & Nichols, 1998). This may lead to many of the conditions associated with low serotonin levels, primarily depression, even after brain serotonin levels have been restored, due to the inability of serotonin to bind to its down regulated receptors (Morgan, 2000). In contrast, in long-term users, in the drug-free state, there is upregulation of receptors (an adaptive response to the decrease in serotonin release) (Reneman et al., 2000).

Although it was initially thought that the development of toxicity required multiple exposures to relatively high doses of MDMA, studies in rats (Cami et al., 2000) have shown that even a single exposure can produce some neuronal damage. Neurotoxic effects found in non-human primates are long lasting and possibly permanent. Monkeys, for example, have shown decrements in serotonin levels for as long as 18 months after MDMA intake (Ricaurte et al., 1992). Repeated exposures to MDMA increase the behavioral and biochemical responses of the animals to the drug and sensitization seems to occur after repeated exposure to low doses (Rodgers, 2000).

Evidence of the Neurotoxic Effects of MDMA in Animals

In animals, there is extensive evidence that MDMA causes dose-related reductions of

brain serotonin and 5-HIAA concentrations, the density of serotonin uptake sites, and the

activity of tryptophan hydroxylase. These neurochemical deficits, which last well beyond

the period of drug administration, have been correlated with the disappearance of

serotonin axons, suggesting that they are related to axonal damage. Moreover, it appears

that MDMA damages only those serotonergic axons in the cortical region of the brain, in

particular, those that arise from the dorsal raphe nucleus (Green et al., 2003).

The profile of neurodegenerative changes produced by MDMA is remarkably

consistent across a variety of species, including rats, mice, guinea pigs, and non-human

primates. Mice appear to be less sensitive to MDMA neurotoxicity, whereas non-human

primates show more MDMA-induced serotonergic damage.

The magnitude and duration of MDMA's effects are dependent on the dose and the

number of injections given. Single doses (20 mg/kg or more) or several more moderate

doses, typically 5 mg/kg twice daily for four consecutive days (Battaglia et al., 1988;

Colado et al., 1993; O'Shea et al., 1998; Ricaurte et al., 1992) produce marked depletion

of serotonin and 5-HIAA. The neurotoxic effects are evident for up to one year after drug

administration in rats (Battaglia et al., 1987), and have been observed up to seven years

after drug administration in non-human primates (Hatzidimitriou et al., 1999). The lowest

MDMA dose that elicited long-term structural damage in non-human primates was

5mg/kg twice daily, for four consecutive days (Ricaurte et al., 1992). This is higher and

more frequent dosing than is typical in human recreational users. However, principles of

interspecies scaling suggest that a dose of 5 mg/kg of MDMA, in a squirrel monkey, is

equivalent to 1.4 mg/kg in humans (Ricaurte et al., 2000). Furthermore, it has been reported that up to one third of recreational users "binge" by taking several tablets at once or over a period of hours to days (Topp et al., 1999).

With regard to regional brain sensitivity to the neurotoxic effects of MDMA, areas rich in serotonin terminals, such as the cerebral cortex, show more severe deficits than brain regions containing fibers of passage (e.g., hypothalamus) or cell bodies (brain stem) (Commins et al., 1987; Steele et al., 1994). In particular, repeated administration of MDMA has been found to produce especially long-lasting degeneration of serotonin axons and decreases in brain serotonin and 5-HIAA concentrations in many regions of the forebrain. These include the neocortex (prefrontal cortex), hippocampus, caudate nucleus, putamen, and many thalamic nuclei (Hatzidimitriou et al., 1999; Ricaurte et al., 1992).

Following MDMA injury, there is evidence of a lasting reorganization of ascending serotonin axon projections. Projections to distant forebrain sites like the dorsal prefrontal cortex, exhibit little or no evidence of recovery, while projections to more proximal targets, such as the hypothalamus, recover fully, and in excess (Fischer et al., 1995). Moreover, Fischer and colleagues (1995) reported that altered reinnervation patterns develop much more frequently in MDMA-treated primates than in MDMA-treated rodents.

Similar evidence has also been obtained using positron emission tomography (PET). Scheffel and colleagues (1998) utilized a radioligand (a radio active chemical marker which binds to certain cells and is used to allow areas inside the brain to be mapped or measured) that selectively labels the serotonin transporter to investigate the long-term

neurotoxic effects in a baboon that had been administered 5 mg/kg MDMA, twice daily

for four consecutive days. In agreement with the results of Fischer et al. (1995), PET

scans nine and thirteen months post-MDMA showed regional differences in the recovery

of serotonin transporters. For example, an increase in transporters was observed in the

hypothalamus whereas a persistent decrease in transporters occurred in the prefrontal

cortex.

Taken together, the available animal evidence, which focus on the neurotoxic effects

of MDMA, suggests that repeated administration of high oral doses of MDMA may

produce long-term reductions in serotonin activity and degeneration of serotonin axons.

In particular, non-human primates show increased sensitivity to such effects, with a lesser

tendency for reinnervation to occur in cortical serotonin systems.

Evidence of Neurotoxic Effects of MDMA in Humans

The neurotoxic dose of MDMA in non-human primates approaches the dose of

MDMA typically taken by recreational users (Ricaurte & McCann, 1992). This raises the

concern that human MDMA users might also incur MDMA-induced serotonin damage.

Since there are no currently available methods for directly evaluating the status of

serotonin neurons in living humans, studies of MDMA's neurotoxic potential in humans

rely on indirect methods. These methods include measurements of the concentration of 5-

HIAA in cerebral spinal fluid (CSF) (levels of serotonin metabolites in the CSF reflect

the amount of release during neuronal activity in the brain), quantification of serotonin

transporter density, neuroendocrine challenge (the administration of drugs that stimulate

serotonergic pathways, and a variety of neuroimaging techniques.

The earliest study to measure 5-HIAA concentrations in CSF failed to find evidence of reduced levels of 5-HIAA in recreational users (Peroutka et al., 1987). More recent data, however, has reported significantly lower levels of CSF 5-HIAA in recreational ecstasy users compared to polydrug users who had never used ecstasy (e.g., Bolla et al., 1998; McCann et al., 1994; 1999; Ricaurte et al., 1990).

In addition to a marked reduction in 5-HIAA levels, investigators have consistently observed decreases in the number of serotonin transporters in MDMA users. Serotonin transporters are sites on the pre-synaptic axons and axon terminals of serotonin neurons that reabsorb serotonin from the synapse. They are considered to be a reliable marker of serotonin neurotoxic changes (Renenman et al., 2001). Thomasius and colleagues (2003) utilized single photon emission computed tomography (SPECT) to measure serotonin transporter densities in 30 current and 31 ex-MDMA users (with MDMA abstinence of at least five months), and 29 polydrug and 30 drug naïve controls. Current ecstasy users showed significantly reduced distribution volume ratios of serotonin transporter availability in the mesencephalon and caudate nucleus. Furthermore, regression analyses indicated that the number of ecstasy tablets taken, best-predicted serotonergic alterations.

Similarly, Reneman et al. (2001) compared serotonin transporter densities in 22 recent MDMA users, 16 ex-MDMA users (individuals who had stopped using MDMA for more than one year), and 13 drug naive controls. These investigators found that recent MDMA users showed global decreases in cortical serotonin transporter densities (nine percent reduction), whereas ex-MDMA users densities did not differ from those of controls. Semple, Ebmeier, Glabus, O'Carroll, and Johnstone (1999) also reported a ten percent reduction in serotonin transporter densities in the occipital cortex of recent

MDMA users. In addition, recent MDMA users showed a widespread reduction of cortical serotonin transporter binding. What is more, decrease correlated with the extent of previous use. Semple and colleagues (1999) observation of reduced transporter binding corroborate earlier PET findings (McCann et al., 1998).

There is also evidence that brain atrophy might occur in association with chronic ecstasy use. Magnetic resonance spectroscopy (MRS) has been used to investigate myo-inositol concentrations, a specific marker of glial cell density and neuronal damage. Increases in the number of glial cells are indicative of brain injury (Kalant, 2001). Chang et al. (2001) reported that myo-inositol concentrations were elevated in the parietal white matter of heavy ecstasy users compared to that of drug naïve subjects. A significant effect of the cumulative lifetime ecstasy dose on the parietal white matter and in the occipital cortex was also observed. Similarly, the duration of MDMA use was related to myo-inositol in the parietal white matter, as well as in the frontal cortex.

There is also neuroimaging evidence that the hippocampus, amygdala, and frontal region of the cortex may be particularly affected by extensive exposure to ecstasy. Obrocki et al. (1999) employed positron emission tomography (PET) to investigate regional brain glucose metabolism in seven heavy ecstasy users, who had used between 12 and 840 single doses and had remained drug free for 2 – 16 months. The ecstasy users exhibited bilaterally reduced glucose metabolic uptake in the hippocampus, amygdala, and cingulate cortex. Moreover, glucose metabolism was significantly more affected in MDMA users who began taking the drug before age 18.

Other evidence of potential MDMA-induced brain alterations is provided by functional magnetic resonance imaging (fMRI) and evoked potential studies. For

example, Cowan and colleagues (2001) found that MDMA users showed less brain activity in the visual cortex following a light flash than did drug-naïve control subjects. Subsequently, a comparison of the auditory evoked potentials of heavy ecstasy users with those of two matched control groups, a non-user and a marijuana-user group found that ecstasy users demonstrated altered patterns of cortical brain activation relative to both control groups (Tuchtenhagen et al., 2000). Specifically, ecstasy users (who had been drug free for seven days to a year) exhibited an increase in the amplitude of the tangential N1/P2 source activity, with higher stimulus intensities. High intensity dependence of the tangential N1/P2 source activity has been associated with low levels of serotonergic neurotransmission in humans (Hergerl & Juckel, 1993).

A major limitation of these studies is that, even if they demonstrate decreased numbers of serotonin cells and reduced serotonin system function in the brains of MDMA users, they cannot prove that the MDMA use necessarily caused the changes. The alterations in serotonin function may have been present before the drug use began or, alternatively, they may have contributed to the initiation of drug use (Kalant, 2001). However, several studies have shown that the degree of change in serotonin function is proportional to the duration and intensity of the preceding use of MDMA. This finding is more compatible with the MDMA use being the cause rather than the consequence of impaired serotonin function.

Although none of the studies whether animal or human have proven without a doubt that MDMA is exerting long-term or permanent neurotoxic effects on serotonergic neurons, all of the experimental results presented above appear to converge on that notion. Evidence from both animal and human studies strongly suggest that MDMA

produces a lasting decrease in serotonergic activity by permanently disrupting its neuron terminals. The animal and human MDMA studies carried out thus far have made a great deal of progress toward clarifying MDMA's neurotoxic effects. However, much more still needs to be done in order to elucidate the whole MDMA picture, including its exact neurotoxic effects and the dosages, which bring about those effects. Nevertheless, the fuzzy MDMA picture painted so far is enough to raise real concerns over the escalating MDMA usage seen in the 1990's and 2000's. In conclusion, individuals who use MDMA as a recreational drug may be putting themselves at risk of developing permanent brain serotonergic system injuries.

Evidence that MDMA Induces Residual Effects on Cognition

If MDMA induces neurotoxic effects in serotonergic neurons, functional changes can be expected in psychological functions that are related to serotonergic processes. Learning and memory are two such processes. There is some evidence that repeated treatment of rats with high doses of MDMA produces persistent impairments in learning and memory. For instance, MDMA-induced 73 percent depletion of neocortical serotonin, which resulted in a mild impairment of the ability to develop an efficient search strategy in a place-navigation task (Robinson et al., 1993). Furthermore, a selective, delay-dependent deficit in delayed non-match to place performance developed 12 days after rats were exposed to high doses of MDMA for three days (Marston et al., 1999).

There is evidence that suggests human recreational MDMA users may display residual cognitive dysfunction. Some studies have observed that recreational ecstasy

users perform more poorly than other drug users and non-drug users on tests of visual-spatial and verbal working memory, as well as executive function (e.g., Fox et al., 2002; Gouzoulis-Mayfrank et al., 2000; Montgomery et al., 2005; Morgan, 2002; von Gesuau et al., 2004; Wareing et al., 2004; Wareing et al., 2000; Zakzanis & Young, 2001). However, the most robust finding in the MDMA literature is that recreational ecstasy users exhibit a selective deficit in verbal learning and memory performance (e.g., Bhattachery & Powell, 2001; Bolla et al., 1998; Curran & Verheyden, 2003; Fox et al., 2001; Gouzoulis-Mayfrank et al., 2000; Krystal et al., 1992; McCann et al., 2001; McCardle et al., 2004; Morgan, 1999; Parrott & Lasky, 1998; Parrott et al., 1998; Quednow et al., 2006; Reneman et al., 2001; Rodgers, 2000; Verkes et al., 2001; Yip & Lee, 2005; Zakzanis & Young, 2001). Moreover, there appears to be a dose-dependent relationship between memory problems and extent of ecstasy use, such that higher cumulative lifetime dose of ecstasy is associated with lower memory scores.

Bolla et al. (1998) compared 24 abstinent MDMA users who had used MDMA on at least 25 occasions (and had abstained from use for >2 weeks) and 24 control subjects matched for age, gender, level of education, vocabulary score, and prior drug use (had no self-reported prior use of MDMA, but other drugs were used). Subjects were assessed on the Rey-Auditory Verbal Learning Test (AVLT), the Wechsler Memory Scale-Revised (WMS-R) and the Rey-Osterrieth Complex Figure (RCF) tasks. Bolla and colleagues (1998) found that greater use of MDMA (in terms of total mg/per month) was associated with greater impairments in immediate verbal memory and delayed visual memory. The relation among CSF 5-HIAA, average total MDMA per dose per month, and memory function were also analyzed. The mean concentration of 5-HIAA in the CSF was lower in

the MDMA users compared to control subjects and CSF 5-HIAA levels decreased with increasing MDMA dose. Furthermore, the lower CSF 5-HIAA concentrations resulted in worse memory performance. These data suggest that MDMA-induced brain serotonin neurotoxicity might account for the observed memory deficits.

Morgan (1999) utilized subtests of the Rivermead Behavioral Memory Test (RBMT), to investigate immediate and delayed recall. He asked MDMA users and controls to listen to a brief, audio-taped news story of five sentences and 65 words and then write down as much of what they had heard as possible, immediately after the story and again 40 minutes later. Members of the MDMA group, all of whom had taken the drug on at least 20 occasions, but were abstinent from all psychoactive drugs on the day of the study, scored substantially lower than either the polydrug group or non-drug group on both immediate and delayed recall. Though the analysis found that there was no correlation between the amount of MDMA taken over an individual's lifetime and memory performance, there was a trend suggesting that the immediate recall abilities might be related to the average dose taken per occasion.

Other neuropsychological test batteries yield similar findings with regard to cognitive function. For example, McCann et al. (1999) assessed cognitive performance in 22 MDMA users (who had used MDMA on at least 25 separate occasions) and 23 control subjects (who had never used MDMA) using a computerized version of the Walter Reed Army Institute of Research Performance Assessment Battery (WRAIR PAB).

The test battery consisted of seven tests designed to assess a variety of psychomotor and cognitive functions, including the Time Wall task, the Serial Add and Subtract test, the Logical Reasoning Task, the Manikin task, Code Substitution, the Matching to

Sample task, and the Delayed Recall test. CSF 5-HIAA measures were also obtained.

Compared to control subjects, MDMA users who had abstained from drug use for at least

three weeks had impaired performance deficits on four of seven cognitive tests in the

WRAIR PAB. Specifically, performance deficits were found on a sustained attention task

requiring arithmetic calculations, a task requiring visual discrimination and working

memory, a short-term memory task, and a task of semantic recognition and verbal

reasoning. Performance deficits on the working memory task were directly associated

with the extent of prior MDMA use. Significant reductions in CSF 5-HIAA (the major

metabolite of 5-HT) concentrations were also observed in ecstasy users relative to

controls. McCann et al.'s (1999) findings extend those from previous investigations

demonstrating deficits in verbal and visual memory in MDMA users to include a variety

of different psychomotor, perceptive and cognitive tasks (e.g., Curran & Travill, 1997;

Parrott et al., 1998).

The evidence that impaired serotonergic function may be associated with memory

deficits in recreational ecstasy users is further extended by correlations between

alterations in cortical serotonin $5\text{-}HT_{2A}$ receptor binding (Reneman et al., 2000), altered

D-fenfluramine-induced cortisol responses (Verkes et al., 2001), altered tryptophan

metabolism (Curran & Verheyden, 2003), and memory deficits. For example, Reneman

et al. (2000) demonstrated higher overall serotonin $5\text{-}HT_{2A}$ receptor binding ratios in the

brains of an ecstasy user group compared to control subjects. These differences reached

statistical significance in the occipital cortex, and the authors suggested that the increased

binding was due to MDMA-induced serotonin depletion resulting in an upregulation of

serotonin $5\text{-}HT_{2A}$ receptors. The ecstasy users also demonstrated a significant impairment

in delayed recall as measured by the AVLT, which directly correlated with the increase in serotonin 5-HT$_{2A}$ receptor binding ratios (Reneman et al., 2000). Verkes et al. (2001) demonstrated a significantly reduced cortisol response to D-fenfluramine in ecstasy users compared to control subjects. In addition, ecstasy users also had significantly longer reaction times to visual and auditory stimuli, lower visual recall, and lower working memory scores. The reduced cortisol response was demonstrated to correlate significantly with visual recall scores, indicating a significant association between chronic ecstasy use, diminished memory performance, and serotonergic neuroendocrine functional deficits (Verkes et al., 2001).

Furthermore, Curran and Verheyden (2003) observed increased plasma tryptophan levels following a tryptophan challenge (an indirect method of assessing the integrity of serotonin function) in ex-ecstasy users (ex-users had stopped using ecstasy for at least a year and on average, 2.4 years), which correlated very highly with ex-users poorer immediate and delayed prose recall. Elevated plasma levels of tryptophan may imply there is a disruption in tryptophan metabolism in ex-ecstasy users. If tryptophan is not metabolized into serotonin, then the concentration of tryptophan in the brain will increase, thereby reducing the transport gradient between the brain and plasma resulting in elevated levels of plasma tryptophan (Curran & Verheyden, 2003). This decreased metabolism may, therefore, reflect alterations in serotonin function in ex-users. In conjunction with findings from non-human primates (Hatzidimitriou et al., 1999), it is possible that this relates to degeneration of serotonin axonal terminals.

Other memory investigations have attempted to assess whether long-term ecstasy use or long-term marijuana use is responsible for the memory impairment often observed in

recreational ecstasy users (e.g., Croft et al., 2001; Dafters et al., 2004; Gouzoulis-Mayfrank et al., 2000; Halpern et al., 2004; Lamers et al., 2006; Quednow et al., 2006; Rodgers, 2000; Simon & Mattick, 2002). For example, in a well-controlled study, Gouzoulis-Mayfrank et al. (2000) compared three groups of 28 subjects: ecstasy users (average lifetime dose of 93 tablets), marijuana users, and non-drug users. The marijuana group had the same exposure to marijuana as the ecstasy group, but no other regular drug use. The groups were well-matched for age, sex and education (with slightly lower education in ecstasy users).

A cognitive test battery was administered. Memory was assessed using a German version of the AVLT (delayed recall was not assessed), the digit span forward/backward task to tap working memory and a visual memory task. Test scores in all three groups were within the normal range. Ecstasy users scored significantly lower than non-drug controls in immediate verbal and visual recall and in working memory (digit span backward), and required more repetitions to learn the AVLT word list. Subsequently, the ecstasy group also performed worse than the marijuana users in immediate visual recall and required more repetitions to learn the word list. Ecstasy users further showed poorer performance than the other two groups in tests of selective attention, logical thinking, problem solving and general knowledge. Decreasing immediate verbal recall and working memory performance correlated with increasing lifetime doses of ecstasy. An increasing frequency of marijuana use correlated with an increasing number of repetitions required to learn the word list. Taken together, theses findings indicate that poorer memory performance in ecstasy users may not be solely accounted for by concomitant marijuana use.

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Like Gouzoulis-Mayfrank et al. (2001), findings from Rodgers (2000) study suggest that marijuana use may be responsible for some proportion of the impairment seen in ecstasy users verbal memory performance. Three groups of 15 subjects were recruited: ecstasy users (mean ecstasy use of 20 tablets), exclusive marijuana users, and non-drug users. All groups were matched for age, sex and education. Marijuana and ecstasy users were matched for their marijuana use. The marijuana users had consumed marijuana four days a week for about 11 years and the ecstasy users had consumed marijuana for about ten years. With regard to drugs other than ecstasy and marijuana, the ecstasy group was not matched to the other groups.

Memory was assessed with the Wechsler Memory Scale (WMS), which includes measures for verbal and visual memory (both immediate and delayed). A further series of tasks assessed basic and complex reaction time. Ecstasy users scored lower than controls in one test of immediate verbal recall, which required them to retell brief stories from memory, but not in another one that required memorizing associated word pairs. Marijuana users showed the same pattern of significantly lower scores in the former, but not the latter test for immediate verbal recall. Ecstasy users were also substantially worse than controls and marijuana users in tests of verbal and visual delayed recall. In the delayed story recall condition, both ecstasy and marijuana users scored significantly worse than controls. No group differences were found in tests of immediate visual memory, attention, and basic and complex reaction time.

One major concern with this study is in the extent of use of marijuana and ecstasy in the ecstasy users. The ecstasy users were very light users of ecstasy (mean = 20 tablets), but very heavy users of marijuana. It seems more appropriate to say that this study tested

regular marijuana users with an occasional use of ecstasy, then to speak of ecstasy users with concomitant marijuana use. From this perspective, the fact that the additional light ecstasy use in one of the marijuana groups was associated with lower scores in delayed memory performance above those seen in exclusive marijuana users seems remarkable. The main suggestion offered by this work is that marijuana use could be responsible for some proportion of the lowered memory scores (particularly in immediate verbal recall), but that additional, even moderate ecstasy use, can extend the impact on memory to include delayed memory performance.

This view is in partial agreement with Gouzoulis-Mayfrank et al. (2000) who reported that marijuana use is likely to have affected cognition and to have contributed to some extent to the poorer performance of ecstasy users. However, in the Gouzoulis-Mayfrank et al. study, marijuana users did not perform significantly worse than non-drug controls. The reason for this may be that their use of marijuana, although comparable in frequency to the marijuana users in Rodgers' (2000) study had spanned only three years compared to 11 years.

Croft et al. (2001) compared the cognitive performance of 11 ecstasy users with concomitant marijuana use with 18 ecstasy-naïve marijuana users and 31 non-drug user controls. Ecstasy and marijuana users had both used a substantial amount of marijuana (10,965 v. 7,762 lifetime joints). Long-term memory performance was assessed using the Coughlin List and Design Learning Test and a facial recognition test. Other cognitive tests were included in the test battery (forward/backward digit span, verbal fluency, spatial associative learning, the Stroop test, a pegboard test). The only difference between ecstasy users and marijuana users were higher scores in design learning and the pegboard

test in the ecstasy group. The pooled ecstasy and marijuana groups performed worse than the non-drug controls in tests for auditory verbal learning, immediate and delayed recall, forward and backward digit span, face recognition, as well as in non-memory tests including spatial associative learning, verbal fluency, and the Stroop test for speed of processing.

Most interestingly, when statistically removing the effect of marijuana use none of the significant differences remained except for in the Stroop test for speed of processing. This means all but one difference in cognitive test performance between the drug using subjects and the controls could be statistically accounted for by marijuana use, while ecstasy use only accounted for the difference in the Stroop test. This finding suggests that concomitant marijuana use may be responsible for much, if not all of the cognitive differences between ecstasy users and control subjects that have been reported thus far. However, an alternative explanation for this result is that MDMA did cause cognitive impairment, but the lack of difference between the MDMA-marijuana and marijuana-only group was due to some interaction between the drugs. Croft et al. (2001) have suggested that marijuana might attenuate the effects of ecstasy through marijuana-related dopamine down regulation thereby exerting neuroprotection against MDMA-induced serotonergic deficits.

Nevertheless, the Croft et al. (2001) study clearly shows the need to adequately control for marijuana use in future studies. In that respect it adds to the studies of Rodgers (2000) and Gouzoulis-Mayfrank et al. (2000) that already demonstrated an involvement of marijuana in verbal memory deficits found in ecstasy users. However, an important difference with the latter studies is that Croft et al. (2001) found no relative

impairment of the ecstasy users compared to the marijuana users, while Gouzoulis-Mayfrank et al. (2000) and Rodgers (2000) found poorer verbal learning and recall, as well as visual recall in ecstasy plus marijuana users compared to marijuana but not ecstasy users. Thus, although the jury is still out on this, it seems that the putative effects of ecstasy use on cognitive performance can extend beyond those of marijuana use (given the particularly careful methodology of the Gouzoulis-Mayfrank et al. (2000) study). However, this does not preclude the possibility that a substantial part of the observed cognitive differences may be the consequence of regular marijuana use.

Other, more recent investigations corroborate Croft et al.'s (2001) finding of no significant differences between ecstasy and marijuana users verbal memory performance, after controlling for marijuana use (e.g., Dafters et al., 2004; Halpern et al., 2004; Lamers et al., 2006; Simon & Mattick, 2002). These investigations have found that marijuana users, whether or not they also used ecstasy, exhibit significant impairment in memory function when compared to the non-drug user controls. However, there is no significant difference between the ecstasy and marijuana users.

There are, of course well-designed investigations that have controlled for marijuana use and demonstrated verbal memory deficits are more closely associated with ecstasy use, rather than marijuana. For example, Yip and Lee (2005) observed large deficits in both immediate and delayed recall performance on a Chinese version of the AVLT, in a large sample of ecstasy users (N = 100). Moreover, these researchers were able to recruit exclusive ecstasy users (no other illicit drug use) because ecstasy use had only recently become a popular trend in Hong Kong.

What's more interesting is that Yip and Lee (2005) observed deficits in ecstasy users with relatively low lifetime ecstasy consumption. Ecstasy users had on average consumed 35.8 tablets (range 16 to 60 tablets). The only other study to report significant deficits in ecstasy users with such a low average use of ecstasy was McCardle et al. (2004), but the deficit detected was only 7 percent (ecstasy users = 11.18 words versus polydrug users = 12.13 words on the AVLT).

Like Yip and Lee (2005), Quednow et al. (2006) conducted a well-designed study that supports the claim that deficits in delayed recall performance in recreational ecstasy users are attributable to ecstasy use instead of marijuana. Quednow and colleagues (2006) examined AVLT performance in three groups of 19 male participants: abstinent ecstasy users, abstinent marijuana users and non-drug users. The comparison with a control group of marijuana users allowed these researchers to estimate the influence of concomitant marijuana use in ecstasy users.

Ecstasy users showed widespread marked verbal deficits compared to non-drug user controls, as well as compared to marijuana users, whereas marijuana users' memory performance did not differ from controls subjects. Ecstasy users revealed impairments in learning, consolidation, recall and recognition. In addition to that, they have also displayed a worse organization of memory information which is reflected in a high inconsistency of recall and a diminished retroactive interference, which is expressed by a high loss after interference. The ecstasy users also did show slightly worse performance in the supraspan (AVLT-trial 1), which may indicate a moderate deficit in working memory. These results remained significant after statistically covarying for marijuana use and verbal IQ.

Taken together, the findings are mixed with regard to whether long-term ecstasy use or long-term marijuana use is responsible for the changes sometimes observed in ecstasy users. Interpretation of the positive findings of verbal memory deficits are questionable, however, because they are complicated by methodological shortcomings and potentially confounding variables that may have contributed to the deficits observed. For instance, a number of the earlier memory studies that demonstrated impairment did not adequately match samples of ecstasy users and control participants with regard to pre-morbid intellectual function, education level, gender and age. More recent studies have attempted to correct for such differences by matching participants.

In addition, much of the earlier research provides little specific consideration for the concomitant use of other illicit drugs by ecstasy users, especially marijuana. A large number of ecstasy users have also used a substantial quantity of marijuana. Neuropsychological studies have reported that the heavy chronic use of marijuana may produce subtle deficits in attention and verbal learning and memory (e.g., Block & Gonheim, 1993; Fletcher et al., 1996; Hall & Solowij, 1998; Messinis et al., 2005; Millsaps et al., 1994; Pope et al., 1996; Solowij et al., 2002). The severity of marijuana-induced impairment appears to depend on the duration and the frequency of marijuana use (e.g., Bolla et al., 1998; Hall & Solowij, 1998; Solowij et al., 2002). To some degree then, the question remains as to whether cognitive deficits in ecstasy users are attributable to ecstasy itself or to marijuana.

Alternatively, recent work with male wistar rats suggests that MDMA and THC (the main psychoactive component in marijuana) may interact synergistically, such that the combined effect of MDMA and THC is greater than the sum of their individual effects

(Morley et al., 2004; Young et al., 2005). For instance, Young and colleagues (2005) observed a greater acute impairment in working memory performance in rats that were co-administered both MDMA and THC relative to rats that received either drug alone.

In contrast, Morley et al.'s (2004) findings revealed positive synergistic effects of MDMA and THC. When THC was administered with MDMA, THC at high doses attenuated the typical negative effects associated with MDMA up to six weeks following drug administration. For example, Morley et al. (2004) found that THC reduced body temperature, serotonin depletion in the hippocampus, amygdala and prefrontal cortex, as well as reduced anxiety.

Executive Function

Executive functions are general-purpose control mechanisms that modulate the operation of various cognitive subprocesses and thereby regulate the dynamics of human cognition (Miyake, Friedman, Emerson, Witzki, & Howerter, 2000). It is proposed that these functions make possible the anticipation of and establishment of goals, the designing of plans, the self-regulation and monitoring of tasks, the appropriate selection of, organization and sequencing of behaviors in space and time, the monitoring of behavior with regard to affective and motivational states, adaptive decision-making, and effective execution and feedback (Damasio, 1994).

Executive functions have been neuroanatomically associated with different neural interaction pathways involving the prefrontal cortex (Roberts, Robbins, & Weiskrantz, 1998). In particular, the dorsolateral portion of the prefrontal cortex (DLPFC) is the area that seems to be involved in executive function. Moreover, the psychopharmacological

literature suggests that DLPFC function is underpinned by dopaminergic systems, which are in turn modulated by serotonin activity. Given that MDMA affects serotonin activity, this raises the possibility that MDMA disrupts the modulating role of serotonin in the DLPFC.

Indeed, there is evidence, which suggests that MDMA use may be associated with selective impairments in executive function, and like the findings on memory performance, it appears that increases in MDMA consumption might relate to more pronounced impairment in executive function. For example, in their assessment of 26 MDMA users (a minimum consumption of 10 ecstasy tablets was required with at least one occasion in the most recent year) and 33 non-users, von Geusau et al. (2004) found that MDMA users performed significantly worse on tasks that tapped cognitive flexibility (i.e., Dots-Triangles test and Local-Global test). Moreover, male MDMA users performed poorly on the cognitive flexibility task and made more perseverative errors whereas no significant difference were found in female MDMA users relative to control subjects. Significant differences between male MDMA users and controls were also found on the complex executive function tasks (i.e., WCST and Tower of London (TOL)). In the WCST, users performed worse on virtually all the dependent measures (e.g., total number of correct responses, number of perseverative errors). This finding is consistent with those reported by Fox et al. (2001), who also observed more errors of perseveration in MDMA users on the TOL task.

Verdejo-Garcia et al. (2005) analyzed the relationship between severity of consumption of different drugs and performance on tasks sensitive to impairment in the executive subprocesses of working memory, response inhibition, cognitive flexibility,

and abstract reasoning in a sample of 38 detoxified polydrug abusers. A significant effect of MDMA was found on the working memory and analogical reasoning components of executive function.

In another study, Zakzanis and Young (2002) observed that MDMA users scored appreciably lower on the Behavioral Assessment of Dysexecutive Syndrome, a test designed to measure mental organization, planning strategies, thinking ahead, mental rule formation, and the estimation of temporal activities. In addition, several significant product moment correlations were found suggesting that increases in MDMA consumption may relate to more pronounced impairment in executive function. Similarly, Semple et al. (1999), using the Spatial Working Memory subtest of the Cambridge Neuropsychological Test Automated Battery (CANTAB), Trail Making Test (Part B), phonemic word fluency, and the Stroop task to examine executive function in abstinent ecstasy users found that larger lifetime doses of MDMA were associated with more errors on the Spatial Working Memory test.

Wareing and colleagues (2000; 2004), utilizing a random letter-generating task sensitive to the central executive of working memory, also showed that recreational users of MDMA generated fewer letters and exhibited a greater degree of redundancy and a greater number of intrusions. Subsequently, Gouzoulis-Mayfrank et al. (2000), employing a digit span backward task demonstrated impairments that persisted for at least six months after abstinence in ecstasy users.

In contrast to the above-mentioned findings, other researchers have failed to observe impairments in executive function in MDMA users. For instance, Fox et al. (2002) examined the neuropsychological performance of 20 MDMA polydrug abusers and 20

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non-MDMA polydrug abusers who had never taken ecstasy, on a computer-assisted neuropsychological battery designed to assess memory and executive functioning. Both groups had remained abstinent for a minimum period of two weeks. Their results showed significant differences in performance of the polydrug ecstasy abusers on tasks of visual short-term memory, working memory, and verbal fluency. Although working memory and fluency processes have been associated with prefrontal executive deficits, the polydrug ecstasy group did not show significant impairments on other tasks designed to evaluate planning, impulse control, or decision-making abilities. The authors interpreted their results in terms of a selective profile of temporal dysfunction.

Subsequently, Gouzoulis-Mayfrank et al. (2003) compared the performance of 60 abstinent MDMA users (30 heavy users and 30 moderate users) and 30 non-user controls on tests aimed to judge general intelligence, memory, working memory, and executive control processes. They reported that heavy ecstasy users were significantly impaired compared to moderate users and healthy controls, in the general intelligence and memory domains whereas these users did not show significant impairments on tests of planning, impulse control, and working memory. However, memory deficits were still significant when general intelligence was included as a covariate and they were significantly related to a measure of frequency of MDMA use.

Likewise, Thomasius et al. (2003) compared a group of 31 former ecstasy users who quit using ecstasy at least 20 weeks before the study, a group of 29 polydrug users who had never taken ecstasy and were asked to abstain from consumption for at least six days and a group of 30 healthy controls on neuropsychological tests of intelligence, learning, and memory, divided attention, impulse control, and mental flexibility. Results showed

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that former ecstasy abusers were significantly more impaired in memory functions and that polydrug, non-MDMA users made significantly more preservative errors on the WCST. Finally, no significant group differences were detected on premorbid intelligence and complex attention. Finally, Simon and Mattick (2002) did not detect significant differences between 40 ecstasy users asked to abstain for a minimum of 24-hours and a group of 37 controls and novice ecstasy users on the Wechsler Memory Scale-III (WSM-III).

Taken together, the available evidence seems to suggest that sustained MDMA consumption incurs a selective impairment on the cognitive flexibility component of executive function (as shown by performance on switch tasks and the WCST). Moreover, heavy ecstasy users appear to exhibit greater impairment, relative to moderate users and drug naive controls. Thus, the recreational use of ecstasy may result in deficiencies in the adaptive ability to adjust behavior in response to changing environmental demands.

Methodological Challenges

While the neuropsychological data strongly suggests that MDMA damages the central serotonergic system and produces long-lasting behavioral deficits, there are a number of methodological challenges. These challenges are not unique to MDMA investigations but are common problems in all drug research involving human subjects. Nevertheless, this makes it difficult to unequivocally prove a cause and effect relationship between MDMA use and specific psychological damage in humans.

A fundamental difficulty in such research is knowing how to interpret the causality of associations between outcome measures and recreational use of MDMA. Any differences

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between MDMA users and nonusers could indicate either a persistent effect of exposure to the drug or pre-existing differences between the two groups. It is possible that there is a biologically vulnerable set of individuals whose use of MDMA and other psychoactive substances reflects preexisting predispositions to such use. High levels of impulsivity and other related personality traits could be a predisposing factor. Individuals with low serotonergic function may be more impulsive and thus more predisposed to using MDMA and other drugs (Ricaurte et al., 2000). In fact, they may be equally depressed and predisposed to using drugs (Reneman et al., 2000). Furthermore, differences in memory function and indirect measures of serotonin activity (e.g., 5-HIAA levels in CSF and serotonin transporter density) between MDMA users and non-users may also have existed before the onset of substance use. For example, individuals with low 5-HIAA levels may both have memory problems and be predisposed to MDMA use (McGuie, Cope, & Fahy, 1994).

Another major concern is that few clinically based controlled prospective studies have been performed. Most of the controlled studies have been conducted, retrospectively, on small numbers of subjects, who have consumed widely varying amounts of MDMA tablets. Given that there is little quality control of street drugs, most investigations provide only an estimate at best when calculating each subjects MDMA intake. Thus, there has been no control over MDMA administration nor has there been confirmation of the dose or purity of MDMA consumed. Published reports (e.g., Schifano et al., 1998; Wolff, Hay, Sherlock, & Conner, 1995), however do suggest that the majority of tablets sold as "ecstasy" in fact contain MDMA.

The method of self-report, which relies on the drug user's recollection of prior drug experience, is also an issue. Self-report of drug taking behavior in drug users is notoriously unreliable (Parrott, 2000). Memory for how much and how often MDMA is actually consumed over many years is likely to be undependable.

Most ecstasy users are polydrug users, which raises the possibility that one or several of these other drugs are responsible for decrements in performance. MDMA users have a tendency to use a variety of illicit substances, including amphetamine, cocaine, ketamine, LSD, sedatives (e.g., opiates), and especially, marijuana (Fox et al., 2001; Milani et al., 2000). Preliminary investigations of recreational MDMA users did not collect data on other illicit substances (e.g., Curran & Travill, 1997; Parrott, 1997). Researchers have since refined their methodology to control for the problem of polydrug use by using a control group comprising individuals who have never used MDMA, but who otherwise have closely matched histories of using other drugs of abuse.

The recruitment of subjects is another methodological concern. MDMA users tend to be exclusively recruited through targeted sampling techniques, by advertising for volunteers or through word of mouth. This is problematic because it introduces an unknown bias into each study, since it is possible that these self-referred individuals are not representative of MDMA users as a whole. Ideally, researchers would like to be able to study MDMA's effects in drug naïve individuals, but, given the ethical issues involved in conducting such studies, there is little likelihood of studying MDMA's effects on substantial numbers of volunteers.

Finally, the applicability of the animal neurotoxicity evidence to human subjects has been contested, largely because the dosage used in animal experiments is perceived to be

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much higher than that taken by humans (Ricaurte et al., 2000). The lowest MDMA dose reported to elicit long-term structural damage in serotonergic neurons of non-human primates is 10 mg/kg subcutaneously daily for four days (Gouzoulis-Mayfrank et al., 2000). According to principles of interspecies scaling, this is equivalent to 1.4 mg/kg in humans (Ricaurte et al., 2000), an amount similar to that used for recreational purposes (Burgess, O'Donohue, & Gill, 2000).

Despite the many methodological concerns, the pattern of cognitive dysfunction seen in the frontal cortex (i.e., impulsivity and impaired higher executive processing) and the hippocampus (i.e., memory deficits) in human MDMA users is consistent with damage that has been found in animals exposed to MDMA (Volkow et al., 2001).

Directions for Future Research

All of the methodological shortcomings with the previous research, outlined earlier, should be addressed in future studies. It might be possible, in the future, to randomly select a large sample of individuals with different patterns of drug use and then investigate the persistent psychological consequences of a variety of different illicit drugs simultaneously. Researchers should also attempt to corroborate self-reported current drug use and prior drug use with urine and hair analysis. If it is not possible to recruit exclusive ecstasy users, investigators should consider employing a design that facilitates the statistical control of previous use of other illicit drugs (e.g., Morgan, 1999).

A prospective, randomized study of the chronic effects of pharmaceutical MDMA would be necessary to definitively determine its persistent effects on human behavior, but ethical and legal constraints prevent such a study, at least in the United States. It may be

possible in the future, however, to conduct a prospective study on the long-term psychological consequences of recreational MDMA use. For example, it might be possible to assess a large sample of adolescents before they have taken ecstasy and then again at subsequent time points, on the assumption that some proportion will go on to experiment with the drug. However, this type of study is not without ethical issues.

Future research should also explicitly investigate which aspect of recreational ecstasy use plays the most significant role in determining subsequent persistent psychological problems. The results of some of the studies reviewed earlier suggest that a gross estimate of lifelong exposure to ecstasy can predict the risk of future persistent psychological problems. But it is likely that the pattern of use also plays a significant role. For example, Topp et al. (1999) have reported that young, female polydrug users, and those who have binged on ecstasy for 48 hours or more, appeared most at risk for experiencing harm that they attributed to their ecstasy use. Thus, it was useful to further investigate the relationship between ecstasy exposure variables, (for example, total past ecstasy dose, average monthly dose, frequency of use, and bingeing) and cognitive dysfunction and determine if risk factors for the development of ecstasy-related cognitive deficits can be identified (for example, gender, IQ, and psychiatric history).

There is also a pressing need for more information concerning the longevity of the psychological impairments exhibited by heavy ecstasy users. Clearly, longitudinal studies designed to follow ecstasy users, both as they continue to use the drug and after they have stopped using it are needed. Such studies would give important insight into how age and length of use affect ecstasy's acute and long-term neurochemical toxicity. In addition, such studies would allow researchers to determine if deficits appear later in life, long

after use stops, or if adverse effects diminish over time. Such studies, if designed with regular assessment intervals, might also allow researchers to develop better measures of MDMA toxicity, and to more accurately determine how much drug is used and in what circumstances.

In addition, little is presently known about the decline of serotonergic function in humans over the life span. One possible direction for future research would be to compare markers of serotonin transporter binding in healthy young individuals with those of healthy older individuals with SPECT or PET. Finally, other neuroimaging techniques, such as fMRI and EEG are required to investigate the effects of experimentally manipulated serotonin neurotransmission on brain activity and cognitive function in ecstasy users.

Summary and Conclusions

Since the late 1980s recreational use of ecstasy has become increasingly popular. We now know much about the pharmacology of this drug in experimental animals, both in terms of its acute actions and its longer-term neurotoxic effects. In general, MDMA's effects are consistent across species, with the exception of the mouse. Importantly, its acute effects in humans are also very similar to those seen in experimental animals. What is uncertain is whether the clear and consistent long-term neurotoxic effects seen in animals can and do occur in humans. There are data suggesting that damage may occur in the human brain and this should be cause for concern. It appears that adverse effects (both acute and long-term) are related to both dose and frequency of administration.

The major problems in investigating the effects of MDMA are the facts that prospective studies are generally unethical, so retrospective studies must be performed, the purity of the ingested drug, the doses taken, and frequency of administration are unknown, and many of the subjects are polydrug users either by choice or unknowingly because of the impure nature of the tablets ingested.

Marijuana

Marijuana or marijuana has been used for centuries, for its medicinal and euphoric properties, and its fibers, to make hemp cloth and paper. Medicinally, between 1850 and 1942, it was prescribed in the United States Pharmacopeia as a remedy for a variety of ailments including gout, tetanus, depression, and cramps (Farthing, 1992). Today, it is used for reducing intraocular pressure due to glaucoma, as an anti-emetic to relieve nausea associated with chemotherapy and as an appetite stimulant for AIDS patients. Recreationally, marijuana is the most widely used illicit drug, especially among young adults (Chan, Hinds, Impey, & Storm, 1998). According to the 2003 National Survey on Drug Use and Health (NSDUH), more than 94 million Americans (40 percent) age 12 and older have tried marijuana at least once.

Marijuana contains chemicals called cannabinoids, including cannabinol, cannabidiol, cannabinolidic acids, cannabigerol, cannabichromene, and several isomers of delta 9 tetrahydrocannabinol (THC). One of these isomers, delta 9-THC is believed to be responsible for most of the characteristic psychoactive effects of marijuana.

Marijuana refers to the leaves and flowering tops of the marijuana plant. The buds of the marijuana plant are often preferred because of their higher THC content. Hashish

consists of the THC-rich resinous secretions of the plant, which are collected, dried, compressed and smoked. Hashish oil is produced by extracting the cannabinoids from plant material with a solvent. In the U.S., marijuana, hashish and hashish oil are Schedule I controlled substances.

Smoking remains the most efficient means of delivering THC and experienced users can titrate the dose by adjusting the frequency and depth of inhalation. A typical joint contains between 0.5 grams and one gram of marijuana. As little as two to three milligrams of available THC will produce a "high" in occasional users, but regular users may smoke five or more joints a day (Iversen, 2003). THC or marijuana extracts may also be taken orally in fat-containing foods (e.g., brownies), but marijuana is mostly smoked because this is the easiest way to achieve the desired psychoactive effects.

Metabolism of Cannabinoids

Different methods of using marijuana lead to differing absorption, metabolism and excretion of THC. When smoked, THC is absorbed from the lungs into the bloodstream within minutes. It is first metabolized in the lungs, and then in the liver where it is transformed into a number of metabolites. THC rapidly disappears from the blood plasma and is taken up in fat where it remains with a half life decay rate of five to seven days. This means that after a single dose of THC, less than one percent of the primary active ingredient remains in fatty tissue after approximately 35 to 50 days (Nahas, 1984). When swallowed, THC takes one to three hours to enter the bloodstream delaying the onset of psychoactive effects (Tart, 1970).

THC and its metabolites account for most of the psychological effects of marijuana. Peak blood levels of THC are usually reached within ten minutes of smoking and decline to about five to ten percent of their initial level within an hour. This rate of decline reflects the rapid conversion of THC to its metabolites and the distribution of THC to fatty tissues including the brain. THC and its metabolites are lipophilic or highly fat soluble and readily cross the blood-brain barrier. They may remain in the fatty tissues of the body for long periods of time. THC and its metabolites accumulate in the body because of their slow rate of clearance. Thus, they may be detected in the blood for several days and traces may persist for several weeks.

The acute toxicity of cannabinoids is very low. There are no confirmed published cases worldwide of human deaths from marijuana poisoning, and the dose of THC required to produce 50 percent mortality in rodents is extremely high compared with other commonly used drugs (Degenhardt, Hall, & Lynskey, 2003).

Cannabinoid Receptors

Two types of G-protein-linked cannabinoid receptors (CB_1 and CB_2) have been identified. CB_1 receptors are expressed predominantly in neurons of the CNS, while CB_2 peripheral cannabinoid receptors appear to play an important immunomodulatory role the PNS.

Cannabinoid receptor activation is linked to inhibition of adenylate cyclase activity (Howlett et al., 1991). Advances in cannabinoid pharmacology have generated a number of selective agonists and antagonists for these receptor subtypes (Pertwee, 1997). One of these compounds rimonabant (SR141716A), which acts selectively to block CB_1

receptors has been widely used in studies of the actions of cannabinoids in the CNS (Rinaldi-Carmona et al., 1998).

The distribution of cannabinoid receptors was first mapped in the rat brain by Herkenham et al. (1991). The mapping studies in the rat brain showed that CB_1 receptors are mainly localized to axons and nerve terminals in the CNS and are largely absent from the neuronal soma and dendrites. Consequently, cannabinoid receptors are predominantly pre-synaptic rather than post-synaptic.

In both animals and humans, there are high densities of CB_1 receptors in the frontal regions of the cerebral cortex, the basal ganglia and in the cerebellum. A high density of cannabinoid receptors in the caudate nucleus and the cerebellum are consistent with the marked effects of cannabinoids on motor behavior. In addition, CB_1 receptors are found in particularly high densities in the limbic forebrain, including in the hypothalamus, the anterior cingulate cortex and the hippocampus (Herkenham et al., 1991). CB_1 receptor density is highest in the hippocampus, the brain structure known to be involved in human memory processes (Pertwee, 1999).

Within the hippocampus, CB_1 receptors are expressed at especially high densities in the dentate gyrus, CA1, and CA3 regions (Herkenham et al., 1991; Matsuda et al., 1990; Tsou et al., 1998). Furthermore, immunohistological staining has demonstrated that CB_1 receptors are found primarily on hippocampal GABAergic interneurons (Katona et al., 1999; Marciano & Lutz, 1999; Tsou et al., 1999). High densities of CB_1 receptors in limbic brain regions correlate with cannabinoids effects on perception, cognition, memory, learning, endocrine function, food intake, and regulation of body temperature

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(Hall & Pacula, 2003). CB_2 receptors have been localized in the spleen, thymus and tonsils and on mast cells and plasmocytes (Matsuda et al., 1990).

In addition to cannabinoid receptors, the brain produces its own cannabinoid substances called endocannabinoids. Endocannabinoids are neurotransmitters that bind to the same receptors as marijuana, however, these compounds act with much shorter duration compared to marijuana because they are rapidly degraded by specific enzymes in the brain cells. Two endocannabinoid ligands, anandamide and 2-arachidonylglycerol (2-AG) have been identified suggesting the existence of a cannabinoid neuromodulatory system. Together with the cannabinoid receptors, this cannabimimetic system is thought to have a widespread role in fine-tuning a variety of brain functions, including nociception, control of movement, memory and neuroendocrine regulation (Iversen, 2003).

It is noteworthy that the highest levels of anandamide are expressed in the hippocampus (Felder et al., 1996). Interestingly, Tomaso and colleagues (1996) have speculated that part of the pleasure of chocolate comes from anandamide. These researchers discovered three compounds in dark chocolate strongly resemble anandamide.

Mechanisms of Action

Marijuana exerts its effects in the CNS by binding to the CB_1 receptor. The CB_1 receptor modifies the activity of several intracellular enzymes, particularly cyclic AMP (cAMP) whose activity is reduced. Less cAMP means less protein kinase A and the reduced activity of this enzyme affects the potassium and calcium channels, so as to

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reduce the amount of neurotransmitters released. Consequently, the general excitability of the brain's neural networks is reduced.

However, in the reward circuit just as in the case of other drugs more dopamine is released. The reward circuit includes the ventral tegmental area (VTA), which is connected to the nucleus accumbens and the prefrontal cortex in the pathway where they communicate through neurons. The paradoxical increase in dopamine is explained by the fact that the dopaminergic neurons in this circuit do not have CB_1 receptors, but are normally inhibited by GABA neurons that do have them. Marijuana removes this inhibition by the GABAergic neurons and thereby activates the dopamine neurons.

Does Marijuana Produce Dependence, Tolerance and Withdrawal?

Animals develop tolerance to the effects of repeated doses of THC (Compton et al., 1991) and studies suggest that cannabinoids may affect the same reward system as alcohol, cocaine and opioids (Wickelgreen, 1998). Heavy smokers of marijuana also develop tolerance to its subjective and cardiovascular effects (Compton et al., 1991) and some report withdrawal symptoms on the abrupt cessation of marijuana use (Compton et al., 1991; Weisbeck et al., 1996). Studies in clinical and non-clinical samples of long-term marijuana users have reported withdrawal symptoms, such as anxiety, insomnia, appetite disturbance and depression (e.g., Copeland, Swift, & Rees, 2001; Stephens, Roffman, & Simpson, 1994).

Also, there is evidence that a marijuana dependence syndrome occurs with heavy chronic use in individuals who report problems in controlling their use and who continue to use the drug despite experiencing adverse personal consequences (Hall, Solowij, &

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Lemon, 1994). Marijuana dependence is the most common form of drug dependence after

alcohol and tobacco in the U.S (NIDA, 2006). About one in ten of those who ever use

marijuana become dependent on it at some time during their four or five years of heaviest

use (Anthony, Warner, & Kessler, 1994). This risk is more like the equivalent risk for

alcohol (15 percent) than for nicotine (32 percent) or opioids (23 percent).

Acute Physiological Effects of Marijuana

The most immediate physiological effect of smoking marijuana is an increase in heart

rate by 20 to 50 percent within a few minutes to a quarter of an hour of smoking (Chesher

& Hall, 1999). Changes in blood pressure also occur. These depend upon posture, that is,

blood pressure is increased while the person is sitting and decreases while they are

standing. A sudden change from lying down to standing up may produce postural

hypotension and a feeling of lightheadedness and faintness that is often the earliest

indication of intoxication in naïve users (Maykut, 1984).

Marijuana reliably induces a swelling of the minor conjunctival blood vessels in the

membranes around the eye, producing a slight "blood-shot" appearance, termed

conjunctival congestion. This is similar to that seen with alcohol. A reduction in

intraocular (within the eye) fluid pressure has also been reported with marijuana and may

have therapeutic significance (Adler & Geller, 1986).

Acute Psychological Effects of Marijuana

A variety of psychological effects are produced by marijuana. At low doses,

marijuana typically induces euphoria and relaxation, perceptual alterations, time

distortion, and the intensification of ordinary experiences, such as eating, watching films, and listening to music (Jaffe, 1985). However, at high doses marijuana use often results in confusion, amnesia, delusions, hallucinations, anxiety and agitation, especially by users who are unfamiliar with the effects of marijuana (Jaffe, 1985; Hall & Solowij, 1998).

Psychotic symptoms, such as delusions and hallucinations, are very rare experiences that may occur at very high doses of THC and in susceptible individuals at lower doses (Thomas, 1993). More experienced users may report these effects after swallowing marijuana because its effects may be more pronounced and of longer duration than they usually experience after smoking (Hall & Pacula, 2003).

Appetite, Noiception and Anti-Emetic Acute Effects of Marijuana

Marijuana intoxication produces an increase in appetite that results in increased food intake, with a preference for sweet foods, even in subjects who were previously satiated (Hubbard, Franco, & Onaivi, 1999). This effect has been confirmed under labortatory conditions (e.g., Hollister & Gillespie, 1970; Mattes et al., 1994). For example, controlled clinical trials in patients suffering from AIDS-related wasting syndrome showed that THC (dronabinol) had significant beneficial effects on counteracting appetite loss and reductions in body weight in (Beal et al., 1995).

Anti-nausea and anti-emetic effects of THC and other cannabinoids also have been well demonstrated (e.g., Zimmerman, 1998). Studies in experimental animals have confirmed that the anti-emetic effects of cannabinoids are mediated through CB_1 receptors (Darmani, 2002).

In addition to its effects on appetite, marijuana intoxication diminishes pain perception and increases pain tolerance. These analgesic effects involve actions at a number of different levels, including peripheral sensory neurons (Lynch & Taylor, 2005), spinal cord (Neeleman, 2000) and central pathways (Cichewicz, Martin, Smith, & Welch, 1999). In the brain and spinal cord, a cannabinoid interaction with the opioidergic system may act to modulate the perception of painful stimuli (Pertwee, 2001). Cannabinoids ameliorate pain by modulating rostral ventromedial medulla (RVM) neuron activity in the brainstem in a manner similar to morphine (Meng et al., 1998). Cannabinoids also inhibit synaptic transmission in the midbrain. This area forms part of a descending antinociceptive pathway that via the RVM modulates nociceptive transmission at the level of the spinal cord (Fields, Heinricher, & Mason, 1991).

Acute Cognitive Effects of Marijuana

Attention and Perception

Marijuana intoxication produces minor distortions in sensory awareness, including some reports of heightened sensory perception (Hollister, 1986). In monkeys, acute marijuana exposure had no serious deleterious effects on simple visual discrimination tasks (Schwartz et al., 1989). However, there are reports of significant effects of cannabinoids on attention processes in both humans and animals.

THC produced dose-dependent effects on both the accuracy and latency of responses to differential tone discrimination (e.g., Campbell et al., 1986) and on signal detection performance in rats (e.g., Heyser, Hampson, & Deadwyler, 1993). The performance of monkeys trained to respond in a choice reaction time task was significantly disrupted by

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acute exposure to marijuana smoke (Paule et al., 1992). In humans, marijuana intoxication produced detrimental effects on both attention span and divided attention tasks (e.g., Chait & Pierre, 1992; Hall & Solowij, 1998; Solowij et al., 2002).

These data suggest that cannabinoid receptor activation does not appear to affect the performance of tasks that do not require focused attention or persistent detailed perception. On the other hand, discriminatory processes may become susceptible to the influence of cannabinoid agonists when more sustained or divided attention is necessary. In general, in animal models the outcome of cannabinoid receptor activation on attention or perception tasks is thought to resemble that of hippocampal lesions (Irving et al., 2000).

Learning and Memory

The main acute effects of cannabinoids on cognition in humans relate to the disruption of short-term memory (Chait & Pierri, 1992; Miller & Branconnier, 1983). Marijuana produces dose-related memory impairment in the ability to freely recall words from a list. Free recall is impaired both immediately after list presentation (immediate recall) and 20 or 30 minutes following list presentation (delayed recall). In the case of immediate free recall, words presented at the end of a list are more likely to be recalled than those presented earlier in the list, suggesting that some aspect of memory storage has been disrupted (Chait & Pierre, 1992). This pattern of memory deficits seen following marijuana intoxication is similar to that seen in patients with hippocampal dysfunction induced by encephalitis, Korsakoff's syndrome, or Alzheimer's disease (Miller & Branconnier, 1983).

Experiments in animals also demonstrate cannabinoid-mediated memory deficits and these are related to impairment of the function of the hippocampus, a structure that is intimately involved in the processes that underlie learning and memory (Sullivan, 2000). Studies have shown that activation of cannabinoid receptors produces memory deficits similar to those produced by neurochemical lesions of the hippocampus (Hampson & Deadwyler, 1999). Such lesions impair performance in short-term spatial memory tasks learned prior to the lesion.

In rats, THC reduced exploratory parameters and motor activity and caused more errors in maze tests and problems with information retention (Sullivan, 2000). In monkeys, the administration of THC prior to testing impairs performance on delayed non-match-to-sample memory task, in which the animal must identify which of a presented pair of objects was displayed 15-minutes earlier (Aigner, 1988). In contrast, cannabinoids have no effect on concurrent discrimination learning, during which the drugged animal must learn over several sessions separated by 24-hours, to identify which of two objects is always paired with food. This differential effect of THC on delayed non-match-to-sample performance and concurrent discrimination learning is similar to the pattern of deficits seen after amygdalo-hippocampal lesions in monkeys (Aigner, 1988).

Most behavioral and physiological effects of THC return to baseline levels within three to six hours after exposure (Chait & Pierri, 1992; Hollister, 1986), although, some investigators have demonstrated residual effects in specific behaviors up to 24-hoursafter drug (Leirer, Yesavage, & Morrow, 1991). More research is needed to define the onset, magnitude, and duration of marijuana's behavioral effects, especially following long-term, frequent use of the drug.

Long-term Residual Effects of Marijuana Use on Neuropsychological Functioning

Findings in Brain Imaging Studies

Neuroimaging studies illustrate that differential patterns of cortical activation exist in chronic marijuana users. Two types of paradigms have been employed in the neuroimaging studies. These include the resting paradigm and the cognitive challenge paradigm. In the resting condition, the subject is instructed to lie down, relax and not to think whereas, in the challenge condition, the subject is engaged with a task.

Resting paradigm studies employing different techniques (e.g., regional cerebral blood flow (rCBF), positron emission tomography (PET), single photon emission computed tomography (SPECT), functional magnetic resonance imaging (fMRI)), have shown subnormal cerebral blood flow (Mathew et al., 1998; Tunving et al., 1986) or lower cerebellar metabolism (Amen & Waugh, 1998; Volkow et al., 1996) in long-term marijuana users who were assessed within one week of cessation of use. For example, Lundqvist et al. (2001) measured brain blood flow levels after cessation of marijuana use (mean 1.6 days). The findings showed significantly lower mean hemispheric blood flow values and significantly lower frontal values in the marijuana subjects compared to normal controls. Block et al. (2000) found that after 26 hours of controlled abstinence, young frequent marijuana users showed hypoactivity relative to controls in a large region of the bilateral posterior cerebellar hemispheres, vermis and in the left and right ventral prefrontal cortex (Brodmann's area 11). Compared with average whole brain activity in controls, marijuana users showed nine percent lower values. Block et al. (2000) also used magnetic resonance imaging (MRI) to investigate brain structures in young currently

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frequent marijuana users. The users showed no evidence of cerebral atrophy or global or regional changes in tissue volumes compared to controls.

Cognition in an everyday situation demands cognitive effort. It is therefore necessary to involve studies, which have a challenge within their paradigm. Yurgelun-Todd et al. (1999) assessed chronic marijuana smokers twice with fMRI after 24-hours and 28 days of abstinence, on a visual working memory task. The control subjects produced significant activation in the dorsolateral prefrontal cortex (DLPFC) during the task. Marijuana smokers who completed 24-hours of washout showed diminished activation in this region. The effect remained diminished after 28 days of washout, although some increase in the DLPFC activation was noted relative to the 24-hour time point. In contrast, smokers produced increased activation in the cingulate during both washout conditions, whereas controls did not. These results indicate that even after an extended washout period, specific differential patterns of cortical activation exist in subjects with a history of heavy marijuana use.

Block et al. (2002) measured cerebral blood flow during the performance of verbal memory recall tasks and during a selective attention task. Memory-related blood flow in frequent marijuana users showed decreases relative to controls in prefrontal cortex, increases in memory-relevant regions of the cerebellum, and altered lateralization in the hippocampus. The greatest differences between users and controls occurred in brain activity related to episodic memory encoding.

Eldreth and colleagues (2004) used PET imaging and a modified version of the Stroop task to determine if 25 day abstinent heavy marijuana users have persistent deficits in executive function and brain activity. The 25 day abstinent marijuana users

showed no deficits in performance on the modified version of the Stroop task when compared to the comparison group. Despite the lack of performance differences, the marijuana users showed hypoactivity in the left anterior cingulate cortex and the left lateral prefrontal cortex and hyperactivity in the hippocampus bilaterally, when compared to the comparison group. Eldreth and colleagues (2004) results suggest that marijuana users display persistent metabolic alterations in brain regions responsible for executive function. They have suggested that it may be that marijuana users recruit an alternative neural network as a compensatory mechanism during performance on a modified version of the Stroop task.

Kanayama et al. (2004) found in an fMRI study that heavy long-term marijuana abusers displayed greater and more widespread brain activation than normal subjects attempting to perform a spatial working memory task. This observation suggests that heavy long-term marijuana abusers may experience subtle neurophysiological deficits and that they compensate for these deficits by "working harder," that is, calling upon additional brain regions to meet the demands of the task.

Behavioral Findings Related to the Residual Effects of Marijuana

Research into the neuropsychological impairments associated with the use of marijuana developed a growing literature during the 1960s and 1970s, although these first studies produced contradictory results. From the 1980s onwards, the increase in methodological control and the progressive refinement of the experimental designs provided a much more exact delimitation of the possible neuropsychological deficits that may result from the use of marijuana (Pope et al., 1995).

Of the studies conducted in the 1970s and at the beginning of the 1980s, none of those that used controlled doses managed to detect significant differences between users and non-users of marijuana (e.g., Barrat et al., 1972; Cohen et al., 1976; Dornbush et al., 1972; Frank et al., 1976; Jones & Benowitz, 1976), whereas the assessment studies of recreational users have yielded about the same number of positive results (e.g., Mendihiratta et al., 1978, Souief, 1976; Wig & Varma, 1977) as negative ones (e.g., Culver & King, 1974; Grant et al., 1976; Mendelson et al., 1976). Carlin and Trupin (1977) and Schaefer et al. (1981) even documented superior neuropsychological performance among marijuana users.

During the 1980s, probably because of the progressive increase in methodological control, including supervised abstinence periods and matched control groups, several studies began to detect neuropsychological deficits associated with the effects of marijuana. Varma et al. (1988) conducted a study that supervised a 12-hour controlled abstinence period prior to the neuropsychological evaluation. They detected deficits on two of the tests used (Pencil Tapping, estimation of size and time). Page et al. (1988) carried out a study in Costa Rica with subjects who had consumed marijuana for more than 25 years and with a non-supervised abstinence interval of between 12- and 24-hours. They observed significantly impaired performance in the marijuana users on information processing, attention and memory compared to a control group.

This same sample of Costa Rican marijuana users was the object of a large prospective study, which included different groups of young and adult users (Fletcher et al., 1996). Fletcher and colleagues (1996) detected memory deficits on free recall tasks and on learning lists of words, as well as on selective and divided attention tasks. Their

results suggested deterioration in functions like attention or memory could be more lasting over time than those in more basic functions.

Solowij and colleagues (1993; 1992) assessed the relationships between degree of impairment and the frequency and duration of marijuana use. Thirty-two marijuana users were divided into four groups of equal size (N = 8) defined by frequency (light: two or fewer times per week versus heavy: more than three times per week) and duration (short: four or fewer years of use versus long: five or more years of marijuana use). Subjects were matched to a group of nonuser controls (N = 16). The marijuana users performed worse than the controls and the greatest impairment was in the heavy user group. The long duration user group found it harder to ignore irrelevant stimuli than the short duration users and controls that did not differ. This impairment increased with the number of years of use but it was not related to frequency of use. There were no differences between groups defined on frequency of use on this measure. Speed of information processing was related to frequency of marijuana use but not to duration of use.

Solowij et al. (2002) conducted a multi-site cross sectional study in the U.S. between 1997 and 2000 among 102 near daily marijuana users, 51 long-term users (mean = 23.9 years of use), 51 shorter-term users (mean = 10.2 years) and 33 non-users. They assessed attention, memory, and executive function from nine standard neuropsychological tests prior to users' entry into a treatment program and following a median 17 hour abstinence period. Solowij and colleagues (2002) found that long-term marijuana users displayed memory impairment, as measured by performance on the AVLT. Specifically, they recalled fewer words and showed impaired learning, retention, and retrieval compared

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with controls and shorter-term users. Moreover, performance measures correlated significantly with the duration of marijuana use being worse with increasing years of regular marijuana use.

Similarly, Bolla and colleagues (2002) found as joints smoked per week increased, performance decreased on tests measuring memory (AVLT) and executive function (Wisconsin Card Sorting Test (WCST)) in 28 day abstinent heavy marijuana users. There is also event related potential (ERP) data that shows that the degree of impairment increases with the length of marijuana use. For instance, Solowij (1995) assessed whether these ERP changes in long-term marijuana users persisted after extended abstinence from marijuana. She studied 32 former users who had used marijuana for a mean of nine years and who had been abstinent for a mean of two years. Some partial recovery of functioning was found, that is, the speed of information processing was not reduced in the ex-users but their ability to ignore irrelevant stimuli remained impaired. These findings corroborate earlier evidence provided by a NIDA-funded study by Struve et al. (1993). These researchers observed larger changes in electroencephalogram (EEG) frequency, primarily in the frontal-central cortex, in daily marijuana users of up to 30 years duration compared to shorter-term users and nonusers.

Similarly, Pope and Yurgelun-Todd (1996) compared heavy marijuana users (N = 65) cognitive functioning to that of a comparison group of light users (N = 64). Subjects in both groups had smoked marijuana for at least two years and none had smoked regularly for more than a decade. To ensure that the subjects did not smoke marijuana or use other illicit drugs or alcohol during the study, researchers monitored them for 19- to 24-hours. Then the subjects performed a battery of standard tests designed to assess their ability to

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pay attention, learn, and recall new information. The tests indicated that heavy marijuana

users had more difficulty than light users in sustaining and shifting attention and hence in

registering, organizing, and using information. Heavy users exhibited these cognitive

deficits by being less able than light users to learn word lists, by making a greater number

of errors in sorting cards by different characteristics, such as by color or shape, and by

making more errors when the rules for sorting the cards were changed without warning.

Men in the heavy users group showed somewhat greater impairment than women in the

same group.

More recently, Ehrenreich and co-workers (1999) administered a computer-assisted

battery for the assessment of a wide spectrum of attentional functions to a sample of 99

pure marijuana users and 49 healthy controls. They reported on the relationship between

impairments in visual-attentional processing and the early use of marijuana (before 16

years of age). Divided attention was also impaired in marijuana users, but not related to

earlier onset of abuse, whereas flexibility and working memory functions were not

impaired in these users.

Croft et al. (2001) compared the performance of 18 pure marijuana users, 11 MDMA-

marijuana users and 31 normal controls on neuropsychological tests of memory,

attention, and executive and motor functions. They showed that impairments in memory

and verbal fluency were more related to marijuana consumption in concurrent ecstasy

users. Tapert et al. (2002), in a follow-up study that administered an extensive

neuropsychological battery to a sample of 65 adolescent abusers and 40 community youth

controls showed cumulative marijuana use was related to attentional functioning

impairments.

Nevertheless, recent studies have suggested that the marijuana-related

neuropsychological impairments may be largely due to the residual effects of the

substance, rather than to long-term effects. In this sense, Pope et al. (2001) compared the

neuropsychological performance of a group of 45 former heavy users and a group of 63

current users who were asked to abstain over a period of 28 days, with 72 normal controls

on a neuropsychological battery designed to assess general intelligence, memory,

attention and executive function. Results showed subtle impairments in several cognitive

domains of the current marijuana user group during the first week of abstinence, which

were related to the urinary concentrations of the THC metabolite. However, at the end of

the 28-day abstinence period, neuropsychological performance of current users was

indistinguishable from former long-term users or normal controls.

A recent meta-analytic study (Grant et al., 2003), which included most of the studies

mentioned above has also failed to find a significant detrimental effect of marijuana use

on several neuropsychological functions. These researchers calculated effect sizes for

each neuropsychological test administered within the 11 studies that were analyzed. Then

within each of the studies, the individual effect sizes were linearly combined by subsets

into one of eight neurocognitive ability domains. These domains were simple reaction

time, attention (e.g., WAIS-R Digit Span, Digit Vigilance), verbal/language (e.g., WAIS-

R Vocabulary, Verbal Fluency), abstraction/executive function (e.g., WCST, Raven's

Progressive Matrices), perceptual motor (e.g., WAIS-R Block Design, WAIS-R Object

Assembly), simple motor (e.g., Grooved Pegboard, Finger Tapping), learning (CVLT-

Learning Trials, AVLT-Learning Trials), and forgetting/retrieval (e.g., CVLT-Recall,

AVLT-Delayed Recall). The only significant effect of long-term heavy marijuana use was subtle selective memory impairment for learning and forgetting.

In summary, it appears that the long-term heavy use of marijuana does not produce severe, grossly debilitating impairment in cognitive function that is found for example with chronic, heavy alcohol use. Electrophysiological and neuropsychological studies show that marijuana produces subtle impairments in attention, executive function, and memory performance.

The longer marijuana has been used, the more pronounced the cognitive impairment. The impairments are subtle, so it remains unclear how important they are for everyday functioning and whether they are reversed after an extended period of abstinence. Early studies that suggested gross structural brain damage with heavy use have not been supported by better controlled studies with better methods.

Is Marijuana Neurotoxic?

Although there have been claims that chronic marijuana use may permanently damage the brain, there is little scientific evidence to support these claims (e.g., Hollister, 1998; Zimmer & Morgan, 1997). As mentioned earlier, some studies have revealed a modestly impaired ability to focus attention and filter out irrelevant information, as well as an impairment in learning and remembering in ex-marijuana users (e.g., Bolla et al., 2002; Solowij et al., 2002; Solowij et al., 1998), while others have failed to find impairments in cognitive function (e.g., Pope et al., 2001).

Animal studies have yielded conflicting results. Treatment of rats with high doses of THC given orally for three months (Scallet et al., 1991) or subcutaneously for eight

months (Landfield et al., 1988) were reported to lead to neural damage in the hippocampal CA3 zone, with shrunken neurons, reduced synaptic density and loss of cells. However, in another study the potent synthetic cannabinoid WIN 552122 was administered twice daily (2 mg/kg) to rats and led to an apparent increase in hippocampal granule cell density and increased dendritic length in the CA3 zone. In perhaps, the most severe test of all, rats and mice were treated with THC five days each week for two years and no histopathological changes were observed in brain tissue, even after administration of large doses THC (50 mg/kg/day in rats and 250 mg/kg/day in mice) (Chan et al., 1996). Although claims were made that exposure of marijuana smoke in a small number of rhesus monkeys led to structural changes in the septum and the hippocampus (Heath et al., 1980), subsequent larger scale studies failed to show any marijuana-induced histopathology in the monkey brain (Scallet et al., 1991).

Studies of the effects of cannabinoids on neurons in vitro have also yielded inconsistent results as well. Exposure of rat cortical neurons to THC was reported to decrease their survival, with twice as many cells dead after two hours of exposure to 5 μM THC than in control cultures (Downer et al., 2001). Significant effects were also demonstrated with low concentrations of THC (0.1 μM). The effects of THC were accompanied by release of cytochrome C, activation of caspase-3 and DNA fragmentation, suggesting an apoptotic mechanism. All of the effects of THC could be blocked by the synthetic cannabinoid antagonist AM-251 or by pertussis toxin, suggesting that they were mediated through CB_1 receptors.

Toxic effects of THC have also been reported on hippocampal neurons in culture, with 50 percent of cell death after two hours of exposure to 10 μM THC or after five days

exposure to 1 μM THC drug (Chan et al., 1998). THC caused the shrinkage of cell bodies and nuclei of neurons and also caused genomic DNA strands to break. The synthetic cannabinoid antagonist rimonabant blocked these effects, but not pertussis toxin. Chan et al. (1998) proposed a toxic mechanism involving arachidonic acid release and formation of free radicals. However, other authors failed to observe any damage in rat cortical neurons exposed for up to 15 days to 1 μM THC (e.g., Sanchez et al., 1998).

In a remarkable study, injections of THC into solid tumors of C6 glioma in rodent brain led to increased survival times and a complete eradication of the tumors was evident in 20 to 35 percent of the treated animals (Galve-Roperh et al., 2000). The anti-proliferative effects of cannabinoids suggest a potential utility for use in cancer treatment (Guzman et al., 2001).

Other studies have reported neuroprotective actions of cannabinoids. For example, administration of WIN 552122 was found in vivo to reduce neuronal damage in the rat hippocampus and cerebral cortex following global ischemia or focal ischemia (Nagayama et al., 1999). Subsequently, Panikashvili and colleagues (2001) found the endocannabinoid 2-AG protected against damage elicited by closed head injury in the mouse brain. Van der Stelt et al. (2001) observed THC had a similar effect in vivo in protecting against damage elicited by ouabain (ouabain is a poisonous cardiac molecule that is used by researchers for in vitro studies to block the sodium-potassium pump). Furthermore, rat hippocampal neurons in tissue culture were protected against glutamate-mediated damage by low concentrations of WIN 552122 or CP 55940 and these effects were mediated through CB_1 receptors (Shen & Thayer, 1998).

Not all of the neuroprotective effects seem to require mediation via cannabinoid receptors. For example, Zhuang and colleagues (2005) findings suggest that cannabinoids prevent cell death by initiating a time and dose dependent inhibition of adenylyl cyclase, which outlasts direct action at the CB_1 receptor. Also, Nagayama et al. (1999) reported protective effects of WIN 552122 that did not require either cannabinoid receptor in cortical neurons exposed to hypoxia. Similar findings were reported for the protective actions of anandamide and 2-AG in cortical neuron cultures (Sinor et al., 2000). Subsequently, both THC and cannabidiol, which is not active on cannabinoid receptors protected rat cortical neurons against glutamate toxicity (Hampson et al., 1998). The authors suggested that the protective effects of THC in their studies might be due to the antioxidant properties of these polyphenolic molecules, which have redox potentials higher than those of known antioxidants (e.g., vitamins C and E).

Further support for the antioxidant properties of cannabinoids is provided in a recent study by Morley et al. (2004). These researchers investigated whether co-administered cannabinoids and MDMA affected the long-term neurotoxic properties of MDMA in rats. They found that co-administration of THC or CP 55940 (synthetic cannabinoid) prevented hyperthermia. Hyperthermia has been found to induce oxidative stress which results in excessive free radical formation and abnormal free radical reactions (Green et al., 2003).

In addition to reversing hyperthermia, Morley et al. (2004) found that THC partially attenuated the long-term serotonin depletion produced by MDMA. Rats given either THC or the higher dose of CP 55940 in conjunction with MDMA displayed serotonin and 5-HIAA levels in the hippocampus, prefrontal cortex and amygdala that were intermediate

between MDMA treated rats. The lower co-administered dose of THC and CP 55940 (0.1 mg/kg) was largely ineffective in preventing MDMA-induced serotonin depletion, suggesting that the protective effect of cannabinoids requires relatively large co-administered doses.

Morley et al. (2004) attributed the underlying protective effects of cannabinoids to their antioxidant properties. This conclusion was based on the finding that the selective antagonist SR 141716, while reversing the cannabinoid agonist effects on MDMA-induced hyperthermia did not change the partial protection against serotonin depletion. This finding indicated a CB_1-independent mechanism was responsible for the neuroprotection.

Morley and colleagues (2004) posited that the cannabinoids (THC and CP 55,940) acted as antioxidants and may have counteracted the oxidative stress produced by MDMA. Cannabinoids contain a phenolic structure typical of many antioxidants isolated from plants. In contrast, the synthetic cannabinoid WIN 552122 lacks the structural moieties that chemically define the antioxidative activity (Chen & Buck, 2000).

Summary

The neurocognitive changes that may be attributed to chronic marijuana use are subtle and may depend on prolonged and heavy levels of consumption. That is, marijuana does not produce severe impairment of cognitive function like that observed with heavy alcohol use. Daily marijuana use over many years may produce subtle impairments in learning and memory, attention and executive function. Impairment seems to be reversed by an extended period of abstinence.

Moreover, well-controlled studies, using sophisticated methods of investigation (e.g., fMRI, PET) have failed to demonstrate gross structural change in the brains of heavy, long term marijuana users. These negative results are consistent with the evidence that cognitive effects of chronic marijuana use are subtle, and hence unlikely to be manifest as gross structural changes in the brain.

CHAPTER 3

METHOD

Aim of the Proposed Study

As concomitant marijuana and other polydrug use have been deemed a possible confound in previous ecstasy research, the primary aim of this study was to evaluate auditory verbal learning and memory performance, as measured by the Auditory Verbal Learning Test (AVLT) (Rey, 1964; Schmidt, 1996), in ecstasy users while controlling for the extent of marijuana and other illicit drug use. Marijuana use was controlled for by enrolling marijuana-only users and, subsequently, by specifying the extent of marijuana use, in both the ecstasy and marijuana-only user groups. Marijuana use was categorized as either heavy or light, with heavy use defined as using marijuana five or more times per week and light marijuana use defined as using marijuana less frequently than five times a week.

To minimize polydrug use among the user groups, the apriori exclusionary criteria established for other illicit drug use stated that the frequency of other illicit drug use (except alcohol and nicotine) was not to exceed more than ten occasions in a participant's lifetime. This criterion was relaxed post-hoc to not more than 15 lifetime uses for each of the drugs inventoried in this study. This was done in order to include a few participants who reported greater than 10 lifetime uses of one or two of the multiple drugs surveyed.

Moreover, this had the advantage of increasing the power of the statistical analyses by increasing the number of participants in the drug user groups.

Additionally, alcohol use was accounted for by not including participants who reported regular heavy alcohol use. Regular heavy alcohol use was defined as severe drunkenness occurring at a frequency of at least twice a month over six months or longer within the last two years.

Participants

One hundred and nine undergraduate university students ages 18 years and older with a history of ecstasy and/or marijuana use were recruited from introductory psychology courses via an announcement placed in the psychology department subject pool, Experimetrix. Students without a regular history of drug use were also recruited to participate. All groups were matched for age, education level, and verbal intellectual ability. While there were not an equal number of females and males in the groups, there was not a statistically significant difference in the gender ratio among the groups.

To optimize data collection and reduce participant attrition rates, experimental testing was conducted over one session, under laboratory conditions. Consequently, participants were notified via the Experimetrix recruitment announcement to abstain from all illicit drug use for at least 24-hours prior to reporting for experimental testing. This measure was necessary to ensure that participants were free of acute residual drug effects.

Written informed consent was obtained to ask participants about their drug use within the last 24-hours. Participants that provided verbal confirmation of adherence to the 24-hour abstinence period were permitted to begin experimental testing. Alternatively,

participants that reported they had not adhered to the 24-hour abstinence criterion were given the option of either receiving half a research credit and no longer being eligible for future participation in the study, or reporting back for testing at a later date when they were able to meet the abstinence criterion and be eligible to receive full credit for completion of the entire experimental protocol.

Once it had been established that a participant was eligible for experimental testing, written informed consent was obtained for the experimental protocol. The experimental testing session was comprised of two parts: neuropsychological assessment and completion of the drug use history questionnaire.

Neuropsychological testing was conducted first and began with the evaluation of verbal learning and memory performance using the AVLT (Rey, 1964; Schmidt, 1996). The first portion of the BFLT-E was administered during the AVLT 20-minute delay (i.e., learning trials 1 through 5, interference List B, recall of List B designs, immediate recall of List A designs). The remaining trials on the BFLT-E (delayed recall after a 20-minute delay and recognition), were administered following completion of the 20-minute delay. Intellectual function (IQ) was assessed within the BFLT-E 20-minute delay and immediately after AVLT testing was complete. The verbal subtest of the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) was used to infer verbal intellectual functioning (Wechsler, 1997).

In the second part of the experimental testing session, participants were asked to complete a drug use history questionnaire, in which prior levels of drug use for the previous week, month, year, and lifetime were recorded (see Appendix E). The drug use questionnaire data were used retrospectively to assign participants to one of five

experimental groups. Data collected on participants who did not meet the inclusion criteria were not included in any of the statistical analyses.

Experimental Groups

Marijuana-Only Users. Marijuana-only users were separated into two groups. The only difference between the two marijuana-only user groups was the extent of marijuana use. The groups were labeled marijuana-only light users (M_L) and marijuana-only heavy users (M_H). Categorization of marijuana users as light or heavy was based on the self-report data collected from the drug use history questionnaire and resembled the criterion used by Fried, Watkinson, James, and Gray (2002). Specifically, heavy marijuana use was defined as using marijuana five or more times per week and light marijuana use was defined as using marijuana fewer than five times a week.

Additional inclusion criteria for the marijuana-only user groups included: (1) consistent use of marijuana over the past year, (2) no prior use of ecstasy, (3) no current or prior history of regular illicit drug use other than marijuana (the frequency of using other illicit drugs could not exceed more than 15 occasions in the participant's lifetime), and (4) no regular heavy alcohol use (defined as severe drunkenness occurring at a frequency of at least twice a month over six months or longer within the last two years) (Daumann et al., 2003; Gouzoulis-Mayfrank et al., 2000; Gouzoulis-Mayfrank et al., 2003; Yip & Lee, 2005).

Fifty participants met these criteria and were retrospectively assigned to either the M_L user group or M_H user group. The M_L user group was comprised of 28 participants, 12

females and 16 males, while 22 participants, 8 females and 14 males, were assigned to the M_H user group.

Ecstasy-Marijuana Users. Like the marijuana-only users, there were two concomitant ecstasy-marijuana user groups. One group of ecstasy users was classified as ecstasy-marijuana light users ($E+M_L$) if they reported using marijuana fewer than five times per week, while the other ecstasy user group was defined as concurrent heavy marijuana users ($E+M_H$) if they used marijuana five or more times per week. In accordance with other ecstasy investigations (e.g., Von Geusau et al., 2004; Bedi & Redman, 2006; Lamers et al., 2006; Parrott et al., 1998; Rizzo et al., 2005), participants were eligible for inclusion into the ecstasy user groups if they had used ecstasy on a minimum of at least 10 occasions, with at least one occasion in the most recent year.

Based on these criteria, 34 participants were assigned to either the $E+M_L$ user group or the $E+M_H$ user group. Fifteen participants, 8 females and 7 males, were assigned to the $E+M_L$ user group and 19 participants, 6 females and 13 males, were assigned to the $E+M_H$ user group.

While the issue of impurity in illicit ecstasy tablets was a problem for researchers in the early 1990s (Spruit, 2001), impurity is far less of an issue now (Parrott, 2006). For instance, during the late 1990s, the proportion of ecstasy tablets containing MDMA increased to around 80 to 90 percent. The latest reports suggest that non-MDMA tablets are very infrequent, with purity levels between 90 and 100 percent being the norm (Parrott, 2004a). Moreover, many of the psychological effects reported by illicit ecstasy users is similar to those reported by participants in clinical MDMA studies (Cami et al. 2000; Grob et al. 1996; Vollenweider et al., 1998a). Increases in positive mood, energy,

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difficulty concentrating, and alterations in perception have been documented in both retrospective and clinical studies. Taken together, these findings suggest that the recreational ecstasy user is probably consuming MDMA and so using data from recreational ecstasy users to estimate the human neuropsychological consequences of repeated MDMA exposure is considered herein to be reasonable.

Like the criterion for the marijuana-only user groups, participants were not included in the combined ecstasy and marijuana user groups if their frequency of other illicit drug use exceeded more than 15 occasions in their lifetime and/or they reported regular, heavy alcohol use.

Non-Drug Using Controls. The fifth group of participants consisted of non-drug using controls. The inclusion criteria for assignment to this group included: (1) no prior use of ecstasy, (2A) no previous use of marijuana, (2B) no previous or current history of other illicit drug use, such as hallucinogens, cocaine, stimulants, or opiates (the frequency of using other illicit drugs should not exceed more than 15 occasions in the participant's lifetime), and (3) no regular heavy alcohol use (defined as severe drunkenness occurring at a frequency of at least twice a month over six months or longer within the last two years). The control group (C) consisted of 25 participants, 15 females and 10 males. The only drug use reported by the C group was alcohol and nicotine.

Similar to many of the well-controlled ecstasy studies (e.g., Croft et al., 2001; Curran & Verheyden, 2003; Fox et al., 2001; Gouzoulis-Mayfrank et al., 2000; Gouzoulis-Mayfrank et al., 2003; Lamers et al., 2006; McCardle et al., 2004; Quednow et al., 2006; Reneman et al., 2001; Reay et al., 2006; Rizzo et al., 2005; Semple et al., 1999; Simon & Mattick, 2002; Thomasius et al., 2003), participants in each group were not included if

they had: (1) a current or previous history of an Axis I psychiatric disorder (except for drug abuse in the user groups), (2) any organic brain disorder, (3) a history of head injury with loss of consciousness requiring hospitalization, (4) a medical or neurological condition that might affect cognitive function, or (5) regularly used legal or illegal psychotropic drugs such as opiates or benzodiazepines (the frequency of using other psychotropic drugs should not exceed more than 15 occasions in the participant's lifetime).

Dependent Measures

Verbal Learning and Memory. The AVLT (Rey, 1964; Schmidt, 1996) was used to evaluate auditory verbal learning and memory performance. The AVLT is a standard neuropsychological test of explicit memory that measures delayed recall performance for lists of unrelated words. Explicit long-term memory tasks have been shown to rely critically on the hippocampus. This is supported by a review of 147 case studies of amnesia patients involving hippocampal damage, which found that all cases showed severe deficits in conscious retrieval (i.e., explicit memory), but intact non-conscious retrieval (i.e., implicit memory) (Spiers, Maguire, & Burgess, 2001). Also, in functional magnetic resonance imaging (fMRI) studies, explicit memory has been found to be associated with neural activation of the hippocampus, as well as activation of sensory areas of the cortex (Thiel, 2003).

Explicit memory tests, such as the AVLT, are particularly sensitive to hippocampal functioning because the filled delay prohibits the retention of words in working memory between study and test. In addition, memory for unrelated words involves less elaborative

and/or associative processing than other memory tasks, such as the verbal paired-associates task. The elaborative and/or associative processing of words has been shown in functional neuroimaging studies to activate specific parts of the prefrontal cortex in addition to the hippocampus (Posner, Peterson, Fox, & Raichle, 1988; Roskies, Fiez, Balota, Raichle, & Peterson, 2001; Schreckenberger et al., 1998). This distinction served as the basis for selection of the verbal learning memory task used in this investigation.

Additionally, the AVLT has been utilized in several ecstasy and marijuana investigations (e.g., Bolla et al., 1998; Curran et al., 2003; Fox, Toplis, et al., 2001; Gouzoulis-Mayfrank et al., 2000; Lamers et al., 2006; McCardle et al., 2004; Quednow et al., 2006; Reneman et al., 2000; Solowij et al., 2002; Thomasius et al., 2003; Yip & Lee, 2005) and was selected so that direct comparisons could be made between the findings in these previous studies and those obtained in this study.

The QPSS computerized version of the AVLT-AB was used to enable real-time recording and scoring of the test (Poreh, 2004). The QPSS software utilizes the same set of standardized instructions and is administered in the same manner as the paper and pencil version of the AVLT.

The software was installed on two laptop computers. The experimenter was seated in front of the computer and controlled the presentation of the instructions and the stimuli. Additionally, the experimenter was responsible for recording participants' responses. All instructions and stimuli (i.e., words) were read by a pre-recorded voice on the computer.

On each trial, a configuration of buttons that correspond to the AVLT words was displayed on the computer screen. Once the participant started to verbalize a response (i.e., recall a word from the word list), the experimenter used the mouse to click on the

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corresponding word-picture button. If the participant responded with a word that did not appear in the list, the experimenter recorded the word as either a confabulation or as an association. Error confabulations were defined as words unrelated to those in the stimulus list, whereas error associations were defined as words that were semantically or phonemically related to those in the stimulus list.

For the recognition trial on the AVLT, a word appeared one at a time on the computer screen. The experimenter saw the word, while the participant heard it played by the computer. Participants' were asked to verbally answer either "yes" if the word they just heard was from List A or "no" if it was not. The experimenter clicked on the "yes" button if the participant answered yes or on the "no" button if the participant responded no. There was an undo function, in the event the experimenter clicked on the wrong word-picture, yes-no button, or incorrectly typed in a word that was not on the stimulus list.

The AVLT required participants to learn a list of 15 words (List A) across five successive trials (trials 1 through 5). All words from the list were concrete nouns and were presented at the rate of one word every two seconds (inter-trial interval = 20 seconds). The order of word presentation was the same on each trial and the same for all participants. At the end of each trial, participants were required to recall as many words from the list as possible. Additionally, participants were instructed that the order in which they recalled the words did not matter.

Following the fifth learning trial, a second list of 15 unrelated words from List B was presented to participants across a single trial (trial B). After recall of the interference list, participants were asked to recall the List A words (trial 6). This trial represented participants' short-delay or immediate recall performance. Following a 20-minute delay,

participants were asked again to recall the List A words (trial 7). This trial represented participants' long-delay or delayed recall performance.

A recognition test followed the 20-minute delayed recall trial. Participants were asked to identify as many words as possible from the first list (List A) when presented with a list of 50 words containing items from both Lists A and B, as well as words that were semantically related or phonemically similar to words on Lists A and/or B. Participants heard each word one at a time and were asked to verbalize a response of "yes" if the word was from List A or "no" if the word was not from List A.

Memory scores were calculated for each individual trial and reflected the number of words correctly recalled. The number of words recalled after the first presentation of List A was defined as immediate word span or supraspan. Supraspan reflects attentional processes related to the acquisition of information prior to storage (Fox, Toplis et al., 2001; Lezak, 2004).

Like trial 1 of List A, the interference trial (List B) involved initial mnemonic processes on a new word list. However, unlike trial 1, the interference trial assessed participants' supraspan ability immediately following learning.

A score for total acquisition was calculated by summing the number of words recalled on trials 1 through 5. Error confabulations (words unrelated to those in the stimulus list) and error associations (words semantically and phonemically linked to those in the stimulus list) were recorded along with intrusion errors from List A to B and vice versa. A high number of intrusion errors is usually associated with confabulation, which is often interpreted as an inability to accurately evaluate any retrieved information (Burgess & Shallice, 1996). High levels of confabulation errors are predominantly

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reported in patients who have frontal cortical lesions (Mayers & Daum, 1997). In contrast, an increase of association errors is indicative of retrieval problems, such as the "tip-of-the-tongue" syndrome, where participants reveal that they know the correct word but are unable to actually recall it (Brown & McNeill, 1966).

Non-Verbal Distracter Task. The Biber Figure Learning Test-Extended (BFLT-E) is patterned after the AVLT (Glosser, Cole, et al., 2002). The paper-pencil version of the BFLT-E was employed as a distracter task and was administered during the 20-minute delay of the AVLT. The basis for selection of this distracter task was that it takes sufficient concentration to effectively to prohibit the continuous rehearsal of words between the study- test phases of the AVLT. Also, the use of non-verbal stimuli was intended to minimize the opportunity for interference between the distracter task and the AVLT stimuli.

In the BFLT-E, participants completed five trials in which 15 designs from List A were presented at a rate of one every three seconds. After each trial, participants were asked to recall as many of the 15 designs as they could in any order by drawing the designs. Following figure recall on the fifth trial, a second set of designs was presented from List B (interference trial). After the recall of List B designs and without additional exposure, participants were asked to draw the original 15 designs from List A (immediate recall).

Following a 20-minute delay, recall and recognition memory were tested. For the recall portion, participants were asked to reproduce the designs presented in List A. The recognition trial consisted of 45 designs, the original 15 designs seven designs from the distracter list (List B) and 23 foils (i.e., designs that had not been presented before). The

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45 designs were shown one at a time. Participants were asked to verbalize a response of "yes" if the design was from List A or "no" if the design was not from List A.

Memory scores were calculated for each individual trial and consisted of the number of designs correctly recalled. The number of designs recalled after the first presentation of List A will specifically be defined as immediate span or supraspan. Similar to trial 1 of List A, List B also involved initial mnemonic processes on a new word list. However, unlike trial 1, List B assessed participants supraspan ability immediately following learning. The number of designs recalled on trial 6 (the trial immediately following recall of designs from interference List B) represented participants immediate recall scores, while the number of designs recalled on trial 7 (after a 20-minute delay) was referred to as participants' delayed recall scores. Also, the number of designs correctly identified on the recognition trial was calculated and scores for total acquisition were calculated by summing the number of designs recalled on trials 1 through 5.

Verbal Intelligence (IQ). To control for pre-existing differences in general cognitive capacity among groups, IQ was assessed from performance on the vocabulary subtest of the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) (Wechsler, 1997). In order to permit time for neuropsychological testing, an estimate of Full Scale IQ (FSIQ) was derived from the vocabulary subtest.

Sattler (2001) maintains that the vocabulary short form has been substantiated statistically, as this subtest has a moderate correlation with FSIQ ($r = .80$) and high reliability ($r = .93$) (The Psychological Corporation, 1997). Ringe, Saine, and Cullum (1999) provide further evidence supporting the use of the vocabulary subtest as an estimate of FSIQ. These researchers observed an excellent correlation ($r = .94$) between

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estimated IQ from the vocabulary subtest and FSIQ in a population of mixed neurological and psychiatric patients (n = 63). Moreover, they conducted multiple regression analyses which demonstrated that the vocabulary subtest accounted for 90 percent of the variance in FSIQ scores among the sample. The internal consistency reliability for the vocabulary subtest was high (r = .93) (The Psychological Corporation, 1997).

The WAIS-III vocabulary subtest assesses word knowledge by requiring the subject to verbally provide a dictionary style definition for 33 words that increase in order of difficulty. The examiner read the question, "What does ____ mean?" The easiest word in the test is "bed," but administration began with the fourth word, "winter," which is the normal procedure (Lezak, 2004). The test continued until the participant failed six words consecutively or until the list was exhausted. The most difficult word on the WAIS-III is "tirade." A score of either zero, one, or two points was given depending on the accuracy, precision, and aptness of each definition. This measure is heavily influenced by formal education and literacy, as well as age and gender. The vocabulary test took approximately 15- to 20-minutes to administer.

Vocabulary subtest raw scores were converted to age-corrected standard scaled scores based on normative data provided in the WAIS-III manual. The age-corrected scaled scores were then summed and converted into an estimated FSIQ based on the method and tables established by Sattler (2001).

Drug Use History Questionnaire. All participants completed the drug use history questionnaire (see Appendix II). The questionnaire consisted of two parts. The first part consisted of items pertaining to demographic and health information. Details of age,

gender, level of education, past or present history of a medical illness, and prior diagnosis of a major psychiatric (Axis I) disorder were obtained.

The second part of the questionnaire was composed of items that probed for previous patterns of drug use. Specifically, the questionnaire was used to evaluate the age of onset, frequency (consumption episodes in a given week, month, and year), and duration of use of a number of often abused psychoactive drugs. For every substance a participant had actually consumed, the following information was requested: (1) the total lifetime consumption of each drug, (2) the frequency of consumption episodes per week and month, (3) the age of onset of use, and (4) the number of years that have elapsed since the onset of use. In addition to these items, participants who reported ecstasy use were asked to provide information regarding (1) the average number of pills used in each episode and (2) the largest number of pills ingested in an episode of use.

Procedure

No biological screening for drug use was carried out. However, it was requested that participants abstain from using ecstasy and other drugs for at least 24-hours prior to testing. Notice to abstain from all drug use was specified in the study advertisement placed in Experimetrix. Individuals who reported for testing that had not met this requirement were not allowed to participate at that time.

It was emphasized in the informed consent form that neither the experimenter nor the University condoned illicit drug use. Additionally, it was emphasized that this investigation should not be seen as approval or encouragement for the use of ecstasy and marijuana or other illegal drugs, particularly since they could have serious side effects. It

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was also stated in the informed consent form that taking part in this study was voluntary and that a participant could withdraw from the study at anytime without giving a reason.

Participants were informed that the data would be treated as strictly confidential. A participant's name never appeared on the drug history questionnaire nor was it used to code files associated with the experimental tests. Rather, a six digit numerical code created by the random number generator function in Microsoft Excel was assigned to each participant following completion of the informed consent form. The master list of participant names and the numerical code assigned to each of them was deleted promptly after credit was assigned to the participant, which occurred immediately following the completion of the protocol. This was done in order to ensure that there was no record which could link data to a particular participant. Furthermore, electronic data obtained from the computerized version of the AVLT and the drug use history questionnaire were promptly removed from the hard drive and stored on a master disk which was locked in a filing cabinet along with the other participant data.

All neuropsychological testing and completion of the drug history questionnaire were administered under laboratory conditions, in one experimental session. Experimental testing lasted approximately two hours. Data collected on participants who completed testing but did not meet the study's inclusion criteria were not included in any of the statistical analyses. Participants received one research credit for each hour they participated in the experiment. All participants ran through the entire experimental protocol and, consequently, received two credits for participation.

Participants reported one at a time to the UNLV Psychopharmacology Laboratory and experimental testing was conducted in a quiet room, by either the primary investigator or

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an undergraduate research assistant. The research assistants received extensive training on administration of the experimental protocol by the principal investigator. Training included verbal explanations and hands-on familiarization with the administration of the neuropsychological tests (WAIS-III vocabulary subtest, AVLT, BFLT-E), drug use history questionnaire, informed consent forms and information or debriefing sheet. Moreover, a written set of instructions regarding the protocol administration was provided. Each research assistant was evaluated by the principal investigator prior to conducting experimental testing and periodically throughout data collection to ensure reliability.

Predictions

Additive Effects. One possible outcome hypothesized in this study was that combined use of ecstasy and marijuana would have negative additive effects on AVLT word recall performance. Additive effects are the simplest case of combined drug action and indicate that each drug acts independently to produce its own effects. The effects of the drugs simply summate, that is, the combined effect of the two drugs equals the sum of their individual effects in isolation.

Figure 2 provides an example of possible negative additive effects of both ecstasy and marijuana use on AVLT recall performance. In the example, examination of the difference between marijuana-only users and the combined ecstasy-marijuana users, at each level of marijuana use should reveal that the addition of ecstasy decreased word recall by two units $[(M_L - E+M_L) = (10 - 8) = 2 = (M_H - E+M_H) = (6 - 4) = 2]$.

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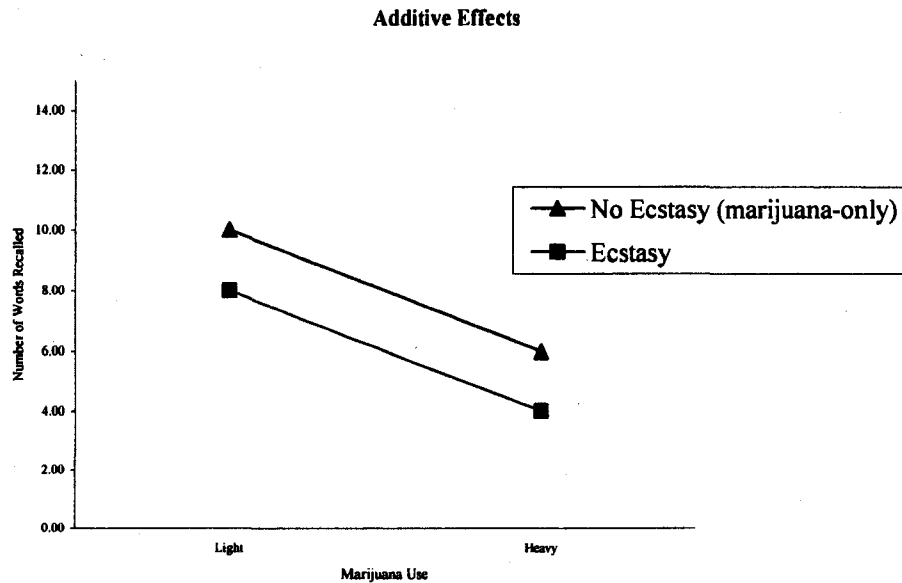
Additive Effects

Figure 2.   Predictions for additive effects of ecstasy and marijuana use on the number of words recalled on the AVLT. The effect of marijuana is independent of the effect of ecstasy. The differences between marijuana only light users and ecstasy-marijuana light users $(10 - 8 = 2)$ and the marijuana-only heavy users with ecstasy-marijuana heavy users $(6 - 4 = 2)$ is equal.

Positive Synergistic Effects (Neuroprotection). Another possible outcome observed in

this study is that marijuana interacts with ecstasy in such a way that marijuana reduces

the impact of ecstasy's effects on verbal learning and memory performance. The extent to

which marijuana minimizes the reduction of recall scores will depend upon the extent of

marijuana use. This prediction is based on Morley and colleagues (2004) findings in rats,

which suggest that cannabinoids attenuate the long-term neurotoxic effects caused by the

addition of MDMA, especially at high doses of marijuana. If Morley et al.'s (2004)

animal findings are applicable to human verbal learning and memory performance then

marijuana use in the combined user groups should reduce the rate of decline in the

number of words recalled on the AVLT, with the greatest minimization of deficits

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occurring in the heavier marijuana users. Moreover, heavy marijuana use will attenuate

the effect of ecstasy, making it comparable to the performance of the marijuana-only

users. Figure 3 provides an example of positive neuroprotective effects of marijuana on

ecstasy. From this example, the difference between the marijuana light groups is greater

than the marijuana heavy groups $[(M_L - E+M_L) = (10 - 9) = 1 > (M_H - E+M_H) = (6 - 6) =$

0].

Positive Synergistic Effects-Neuroprotection
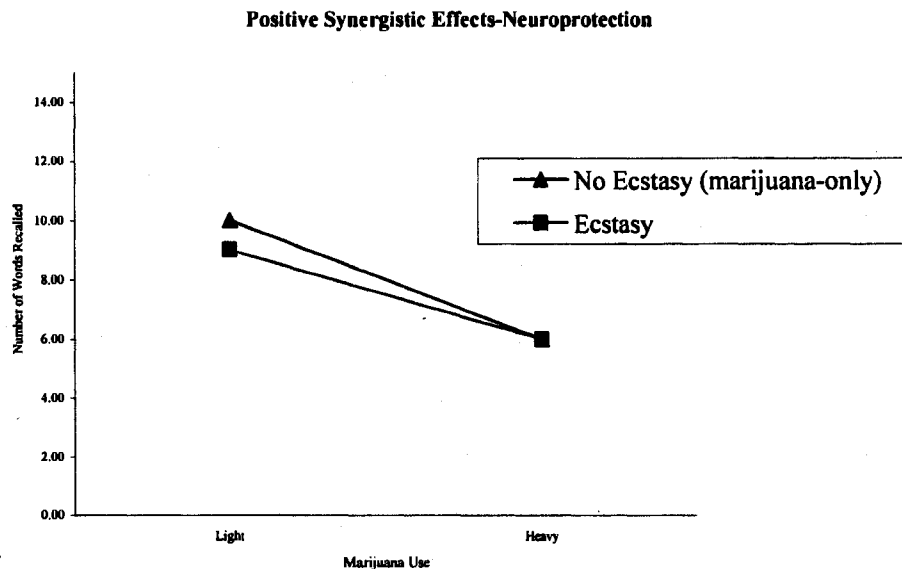
Figure 3.   Predictions for positive synergistic effects between ecstasy and marijuana use on the number of words recalled on the AVLT. Ecstasy and marijuana use are not independent, rather marijuana acts synergistically with ecstasy to minimize recall deficits caused by the addition of ecstasy use. The reduced effect of ecstasy is even greater in the marijuana heavy condition.

Negative Interactive Effects (Negative Synergistic Effects). The other potential

outcome that could occur is that marijuana interacts synergistically with ecstasy to

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produce memory impairment that is greater than that observed by the sum of the deficits

produced by either ecstasy or marijuana alone (see Figure 4 for an example). This

prediction is based on Young et al.'s (2005) findings in rats, which demonstrated

synergistic disruption in working memory performance in rats that were co-administered

MDMA and THC. The amount of synergistic disruption produced was dependent upon

the dose of marijuana, such that greater synergistic disruption was observed under high

marijuana dose conditions compared to lower marijuana dose conditions.

Negative Synergistic Effects
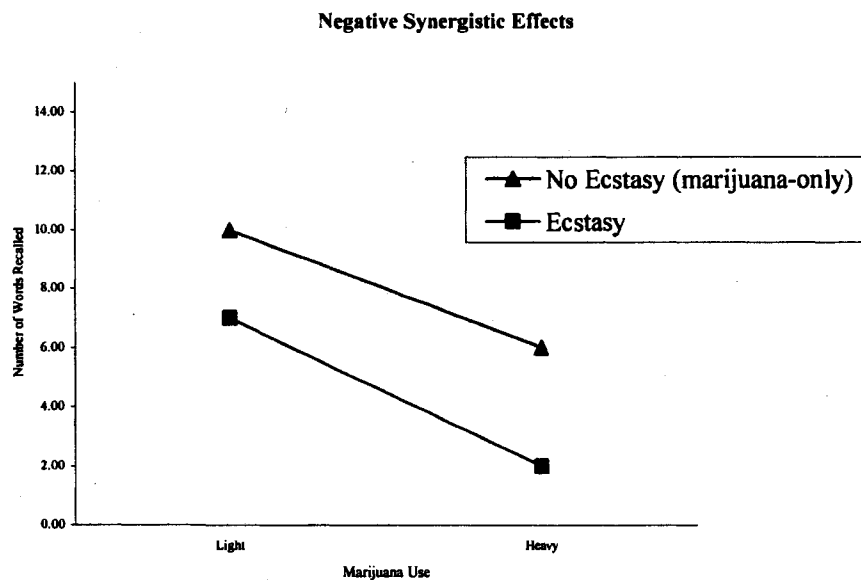
Figure 4.   Predictions for negative synergistic effects between ecstasy and marijuana use on the number of words recalled on the AVLT.

Marijuana and ecstasy use do not act independently to impair performance, rather

ecstasy interacts synergistically with marijuana to produce greater impairment than that

observed by the sum of the deficits produced by each drug alone. The magnitude of the

impairment depends on the extent of marijuana use. A greater synergistic disruption of

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recall performance is seen in ecstasy-marijuana heavy users versus ecstasy-marijuana light users.

If these data are applicable to human verbal memory performance, then among the drug users in this study, the combined ecstasy-marijuana users should exhibit more impaired word recall than the marijuana-only users. Moreover, the magnitude of impairment observed in the ecstasy-marijuana heavy users would be greater than that observed in the ecstasy-marijuana light users $[(M_L - E+M_L) = (10 - 7) = 3 < (M_H - E+M_H) = (6 - 2) = 4]$.

Statistical Analyses

Statistical analyses were performed using SPSS 15.0 software for Windows (SPSS Inc., Chicago, IL). An alpha level of 0.05 was used for all analyses. A Multivariate Analysis of Variance (MANOVA) was conducted on the descriptive statistics of the participants' age, gender, education level, and verbal intelligence scores as measured by the WAIS-III vocabulary subtest, with group assignment as the single between-subject factor (i.e., C, M_L, M_H, $E+M_L$, and $E+M_H$). Similarly, a MANOVA was performed on the participants' drug use characteristics and included age of onset of use, frequency of use episodes, per week and per month, total lifetime use, and the number of years that have elapsed since the onset of use. Two additional drug use characteristics were computed for ecstasy: a) the average number of pills taken in an episode, and b) the largest number of pills taken in an episode.

Two separate sets of Multivariate Analyses of Covariance (MANCOVAs) were performed on the AVLT and the BFLT-E data, with group assignment as the single

between-subject factor. The first set of MANCOVA analyses treated age, education, and verbal intelligence scores as covariates. It is well established that these factors affect verbal learning and memory performance (Lezak, 2004). Furthermore, since visual memory tests correlate with performance on tests of verbal learning and memory these same factors were also treated as covariates in the BFLT-E analyses (Lezak, 2004).

In addition to age, education, and verbal intelligence, the second set of MANOCVA analyses of the word and figure data treated monthly use of alcohol and nicotine and cumulative lifetime use of drugs other than ecstasy and marijuana as covariates. Selection of these drugs specifically was based on MANOVA findings that indicated the use of these drugs was significantly different among the groups. In particular, cumulative lifetime uses of the following drugs were accounted for: cocaine, mushrooms, LSD, solvents, heroin, oxycontin (hyrdrocodone), muscle relaxers, xanax, percocet, valium, ritalin/adderall, ambien/lunesta, morphine, methadone, and demerol.

Separate Analyses of Covariances (ANCOVAs) were calculated for each of the dependent measures that reached significance in both the first and second sets of MANCOVA analyses. Scheffé post-hoc tests and simple effects analyses via ANCOVAs were performed on the AVLT and BFLT-E dependent measures that reached significance in each of the MANCOVA analyses.

The AVLT dependent measures examined were the total number of words recalled on trial 1 (supraspan), trials 2-4, trial 5 (final acquisition level), interference (trial B), trial 6 (immediate recall), and trial 7 (delayed recall). Additionally, total acquisition (sum of the number of words recalled on trial 1 through trial 5), the amount learned in five trials (trial 5 - trial 1), proactive interference (trial 1 - trial B), retroactive interference (trial 5 - trial

6), number of repetitions (words that were repeated), sum of error associations across trials 1 through 7 and trial B (words semantically or phonemically related to those in the stimulus list), and sum of error confabulations (words unrelated to those in the stimulus list) were measured.

Also, AVLT recognition hits and recognition errors were measured. Specifically, the types of recognition errors that were observed included: semantic association with either a List A (SA) or B (SB) word, phonemic association with either a List A (PA) or B (PB) word, and semantic-phonemic association with either a List A (SPA) or B (SPB) word.

The dependent measures examined on the BFLT-E included the number of figures recalled on trial 1 (supraspan), trials 2 - 4, trial 5 (final acquisition level), interference distracter trial (List B figures), trial 6 (immediate recall), trial 7 (delayed recall). In addition, recognition performance, the sum of figures recalled on trials 1 through trial 5 (total acquisition), the amount learned in five trials (trial 5 - trial 1), scores on the reproduction trials, and extraneous responses were included in the MANCOVA analyses.

Extraneous responses were summed for all of the BFLT-E trials, except the recognition trial. Both perseverations and extraneous responses constituted extra responses. Perseverations were defined as the repetition of a design, whereas, an extra response meant drawing a design that was unrelated to those in the stimulus list.

In the first MANCOVA analyses, where age, education, and WAIS-III vocabulary scores were covaried, the AVLT dependent measures that were significantly different among the groups were total acquisition, interference, immediate recall, delayed recall, and recognition. Also, gender X drug group interactions were observed for interference (trial B), proactive interference (trial 1 - trial B), and error associations. The BFLT-E

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dependent measures that reached statistical significance on the first MANCOVA analyses were immediate recall and extra responses. No interactions were observed on the BFLT-E data.

The second MANCOVA analyses, which additionally controlled for cumulative lifetime use of other illicit drugs (i.e., drugs other than ecstasy and marijuana), yielded the same set of significant outcomes on the AVLT measures as the first analyses, except for one the gender X drug group interaction for interference. Thus, significant findings were observed for total acquisition, interference, immediate recall, delayed recall, and recognition. Subsequently, gender X drug group interactions were observed for proactive interference and error associations on the AVLT. In contrast, none of the BFLT-E dependent measures that reached significance in the first MANCOVA analyses yielded significance in the second MANCOVA analyses.

Regression analyses were used to predict the contribution of drug use as reported by polydrug users in this study to memory performance on both the AVLT and BFLT-E. Total lifetime drug consumption as indicated by the total number of times a drug was used was selected as the parameter of interest since lifetime consumption of cocaine and methamphetamine, for example, has previously been observed to correlate negatively with both immediate and delayed recall scores on the AVLT (Croft et al., 2001; Reneman et al., 2001; Thomasius et al., 2003).

In addition, regression analyses were used to examine the relationship of weekly and monthly marijuana use, and the average and largest dose of ecstasy consumed in an episode, to memory performance. The current frequency of regular use of ecstasy and

marijuana were thought to indicate most effectively the extent of pattern of use, with

higher frequencies of use more likely to impart an influence on memory function.

CHAPTER 4

RESULTS

Descriptive Statistics

Descriptive statistics including means, standard deviations, range, and gender ratios

for the groups are shown in Table 5. MANOVA analyses conducted on these data

indicated that the groups did not differ with respect to age, education, or verbal IQ ($p >$

1). Additionally, the ratio of males to females was not statistically different among the

groups. However, there were approximately half as many females to males in the M_H and

$E+M_H$ user groups compared to the M_L and $E+M_L$ user groups who were more evenly

matched (see Table 5).

Table 5   Demographic characteristics in the control group and the drug user groups.

Descriptive Variable	Group				
	$\underline{C}$	$\underline{M_L}$	$\underline{M_H}$	$\underline{E+M_L}$	$\underline{E+M_H}$
N	25	28	22	15	19
Age in years (SD)	20 (2.6)	20 (1.8)	20 (1.7)	21 (2.1)	21 (2.9)
r= range	r = 18-27	r=18-25	r=18-23	r=18-25	r=18-29
Gender	15 F/10 M	12F/16M	8F/14M	8F/7M	6F/13M
Education in years (SD)	14 (1.3)	14 (1.4)	14 (1.5)	15 (2.0)	15 (2.1)
r=range	r=12-16	r=12-18	r=13-17	r=12-20	r=12-19
Estimated IQ (SD)	12 (2.4)	11 (2.6)	12 (2.1)	13 (2.4)	12 (2.8)

Means and standard deviations were computed for age, education, and estimated IQ. The range (r) is also
reported for age and education. The number of females (F) and males (M) in each group is reported in the
row labeled gender.

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Information pertaining to drug use is reported in Table 6 (see Appendix I). The means and standard deviations represented in Table 6 are based on the total number of participants in each group who reported use of a particular drug. In some instances, only one participant in a group reported using the drug and so just that participant's individual data are reported. For example, only one participant in the M_H group reported methamphetamine-amphetamine use, so the subsequent data for that group in Table 6 represent the drug use by that one participant only.

Because of the exclusionary criteria used to establish group membership the only drug use reported by participants assigned to the control group (C) was alcohol and nicotine. MANOVA analyses of the drug use data across groups yielded a main effect of group for the following alcohol use characteristics: number of years used, $F(1,4) = 3.163$, $p < 0.017$, weekly use, $F(1,4) = 4.671$, $p < 0.002$, and monthly use, $F(1,4) = 5.016$, $p < 0.001$. For nicotine, the drug use characteristics that were significantly different among the groups were age of onset, $F(1,4) = 7.627$, $p < 0.001$, number of years used, $F(1,4) = 5.957$, $p < 0.001$, weekly use, $F(1,4) = 5.711$, $p < 0.001$, and monthly use, $F(1,4) = 3.831$, $p < 0.006$.

Scheffé post-hoc tests conducted on the drug use characteristics related to alcohol showed the C group had used alcohol for a lesser number of years ($p < 0.022$) and consumed fewer alcoholic beverages on both a weekly ($p < 0.003$) and monthly ($p < 0.002$) basis than the $E+M_H$ group. None of the other group comparisons were significant.

For nicotine, Scheffé post-hoc tests indicated that the C group started using cigarettes at a significantly older age than the M_L users ($p < 0.010$), $E+M_L$ users ($p < 0.042$), and the $E+M_H$ users ($p < 0.010$). The $E+M_H$ users had smoked for a longer period of time ($p <$

0.010) and smoked more cigarettes a month ($p < 0.007$) than the C group. Weekly use of cigarettes was greatest among the combined user groups (i.e., E + M_L and E+M_H) ($p < 0.010$ for both).

With regard to ecstasy use, participants retrospectively assigned to either the E+M_L or E+M_H groups all exceeded the apriori criterion for assignment to the ecstasy use groups, which was consumption of at least ten ecstasy tablets within the past year. As expected, the MANOVA analyses yielded a significant main effect of group for all ecstasy drug use characteristics.

Scheffé post-hoc tests confirmed the ecstasy user groups (E+M_L and E+M_H) were similar on every aspect of ecstasy use, except the largest number of pills taken in an episode. The E+M_H users reported taking a significantly larger number of pills in an episode (mean = 3.5 pills) compared to the E+M_L users (mean = 2.2 pills) ($p < 0.028$).

Participants assigned to either the combined ecstasy-marijuana user groups or the marijuana-only user groups reported consistent marijuana use over the past year. Recall that participants were classified as light marijuana users if they reported use of marijuana fewer than five times per week, whereas participants who reported using marijuana five or more times per week were classified as heavy marijuana users. None of the participants assigned to the marijuana-only user groups reported ever using ecstasy.

For marijuana use, the MANOVA analyses indicated significant main effects of group, as expected from the group assignments, for age of onset, $F(1,4) = 289.506, p < 0.001$, number of years used, $F(1,4) = 19.093, p < 0.001$, time since last use, $F(1,4) = 10.631, p < 0.001$, cumulative lifetime use, $F(1,4) = 6.780, p < 0.001$, weekly use, $F(1,4) = 15.154, p < 0.001$, and monthly use, $F(1,4) = 16.398, p < 0.001$. Scheffé post-hoc

comparisons showed that both the M_L and $E+M_L$ user groups smoked less marijuana a week and less a month compared to the M_H and $E+M_H$ user groups ($p < 0.001$; $p < 0.001$). Moreover, the comparisons of marijuana use between the M_L and $E+M_L$ users and the M_H and $E+M_H$ users were not significant ($p > 1$), which indicated that these groups frequency of marijuana use was similar to each other.

Marijuana abstinence periods (i.e., time since last use in weeks) were significantly longer in the M_L users compared to both the M_H and the $E+M_H$ user groups ($p < 0.001$; $p < 0.001$) indicating that the heavier marijuana user groups used marijuana more recently than the lighter user groups. There was not a significant difference in the time since last marijuana use in the M_L and $E+M_L$ users ($p > 1$).

The M_L and $E+M_H$ users also differed significantly with regard to the number of years they had used marijuana ($p < 0.001$) and in the total number of times that they had used in their lifetime ($p < 0.004$). The $E+M_H$ group smoked marijuana for a longer period of time ($p < 0.007$) and smoked far more times in their lifetime than the M_L users ($p < 0.005$). None of the marijuana user groups differed significantly from each other with respect to the age at which they began smoking marijuana.

With respect to other drug use (i.e., drugs other than marijuana and/or ecstasy), participants in the drug user groups reported use of the following drugs in the drug use questionnaire: cocaine, mushrooms, methamphetamine/amphetamine, LSD, solvents, heroin, oxycontin (hyrdrocodone), muscle relaxers, xanax, percocet, valium, ritalin/adderall, ambien/lunesta, morphine, methadone, and demerol. While data were collected for each of these drugs and drug use characteristics, cumulative lifetime use was used to assess the quantity of drug use among the groups because this measure reflected

the total number of times a drug was used in a participant's lifetime. Furthermore, cumulative drug use is one of the most widely used drug use characteristic evaluated in drug investigations. For example, there is evidence that shows cumulative use of cocaine for example is closely associated with deficits on AVLT trial 7 (Fox et al., 2001; Thomasius et al., 2004).

The MANOVA and subsequent ANOVA analyses conducted on cumulative lifetime uses of other drugs showed that there were significant differences in the total number of times the drug user groups had taken cocaine ($F_{(1,3)} = 10.051, p < 0.001$), LSD ($F_{(1,3)} = 5.060, p < 0.003$), oxycontin (hydrocodone) ($F_{(1,3)} = 2.962, p < 0.037$), percocet ($F_{(1,3)} = 2.780, p < 0.046$), and xanax ($F_{(1,3)} = 2.886, p < 0.041$). The M_L user group consumed the least amount of cocaine compared to the other drug user groups ($M_H, p < 0.039$; $E+M_L, p < 0.007$, $E+M_H, p < 0.001$). The M_H users and the $E+M_L$ users' lifetime cocaine use did not differ but cocaine use was greater in the $E+M_H$ users compared to the M_H users.

Participants in the $E+M_H$ users also had taken a significantly greater amount of LSD across their lifetime than each of the other groups ($M_L, p < 0.001$; $E+M_L, p < 0.003$; $E+M_H, p < 0.004$). Hyrdocodone use was greater in the M_H ($p < 0.007$) and $E+ M_H$ user groups ($p < 0.036$) compared to the M_L user group. No differences were observed in the $E+M_L$ user group. The cumulative use of percocet was significantly higher in the $E+M_H$ user group relative to the M_L users ($p < 0.026$) and $E+M_L$ users ($p < 0.040$). Furthermore, with respect to cumulative use of xanax, the M_H users reported a significantly greater lifetime use of xanax compared to the M_L ($p < 0.013$) and $E+M_L$ ($p < 0.049$) user groups. There were no significant difference in cumulative use of xanax among the M_H users and

E+M$_H$ users ($p > 1$). When these findings are taken together, they indicate that the E+M$_H$ user group consumed both a wider variety of other drugs, as well as a greater amount of those drugs, relative to the other drug user groups.

With the exception of hydrocodone and xanax use in the M$_H$ users, the mean total number of times drugs other than marijuana and/or ecstasy were used did not exceed the apriori exclusionary criterion of not more than ten uses of any drug other than alcohol and nicotine in a lifetime. This criterion was relaxed post-hoc to not more than 15 lifetime uses for each of the drugs inventoried in this study. This was done in order to include a few participants who reported greater than ten lifetime uses of one or two of the drugs surveyed. Moreover, this had the advantage of increasing the power of the statistical analyses by increasing the number of participants in the drug user groups.

AVLT Task Data

Total Acquisition. Group means and standard deviations for total acquisition are reported in Table 7. The first column in Table 7 reflects the observed group means and standard deviations, that is, the means for each group prior to the treatment of factors as covariates in the MANCOVA and subsequent ANCOVA analyses. The second column represents the group means and standard deviations after age, education, and verbal IQ scores were treated as covariates. The third column reflects the group means and standard deviations after monthly use of alcohol and nicotine and cumulative lifetime use of other drugs were added as covariates (in addition to age, education, and verbal IQ).

As mentioned earlier, the initial MANCOVA analyses conducted on the AVLT data treated age, education, and verbal IQ as covariates. The results indicated that there was a significant main effect of group for total acquisition scores, $F(1,4) = 4.133, p < 0.004$.

Table 7   Mean total acquisition scores on the AVLT for each group (standard deviations are in parentheses)

Group	Observed Means*	Adjusted Means**	Adjusted Means***
C	58.120 (4.2)	57.558 (2.3)	58.073 (2.7)
M_L	56.071 (6.5)	56.965 (2.2)	57.081 (2.4)
M_H	53.773 (6.4)	53.660 (2.4)	52.629 (2.8)
$E+M_L$	52.773 (6.7)	52.135 (3.0)	51.236 (3.2)
$E+M_H$	52.316 (5.7)	52.342 (2.6)	53.396 (3.5)

Notes: * = means before the covariate analyses; ** = means after age, education, and verbal IQ were treated as covariates; *** = means after age, education, verbal IQ, monthly alcohol and nicotine, and cumulative lifetime use of other drugs were treated as covariates.

Figure 5 illustrates group mean total acquisition scores and standard errors before the adjustment for covariates. Subsequent Scheffé post-hoc tests showed that the sum of words recalled across trials 1 through 5 was significantly higher for group C and the M_L users compared to the M_H ($p < 0.020; p < 0.044$), $E+M_L$ ($p < 0.005; p < 0.011$), and $E+M_H$ users ($p < 0.004; p < 0.008$). Total acquisition scores were similar among the M_H, $E+M_L$, and $E+M_H$ users ($p > 1$).

Drug Group Means-Total Acquisition (AVLT)
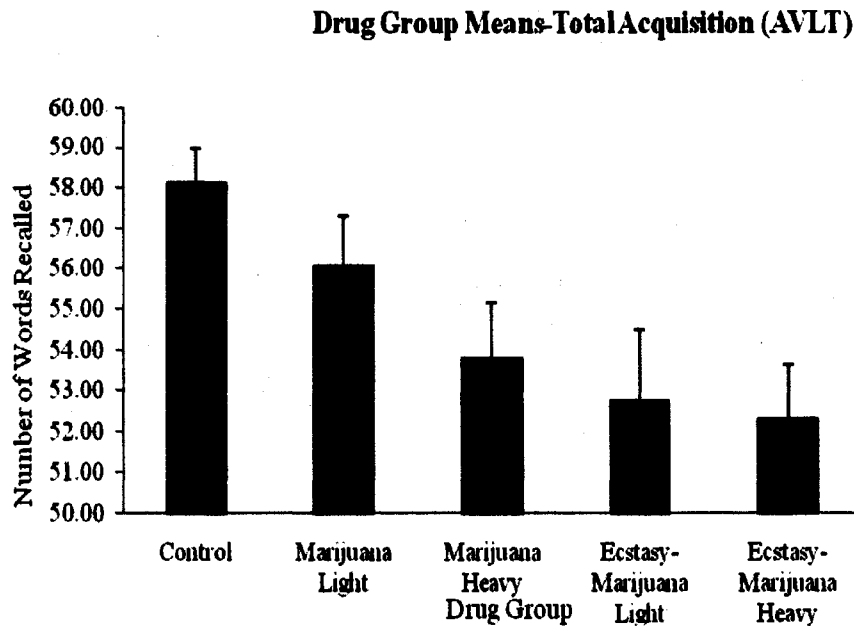
Figure 5   Mean AVLT total acquisition scores and standard errors for each group.

When monthly use of alcohol and nicotine and cumulative lifetime use of other drugs

were added as covariates in the MANCOVA analyses, the pattern of findings was

identical to that given above. A main effect of group was observed, $F(1,4)$, = 3.403, $p <$

0.013, where the sum of the words recalled on trials 1 through 5 was highest for group C

(M_H, $p < 0.008$; E+M_L, $p < 0.003$; E+M_H, $p < 0.006$) and M_L users (M_H, $p < 0.023$;

E+M_L, $p < 0.006$; E+M_H, $p < 0.001$). AVLT total acquisition scores were similar among

the M_H, E+M_L, and E+M_H users ($p > 1$).

Taken together, these findings showed a dose response effect of marijuana use and a

possible neuroprotective effect of ecstasy on marijuana. Heavier or more frequent use of

marijuana affected word learning more profoundly than lighter marijuana use. This was

evidenced by the difference in total acquisition scores between the M_L and M_H users.

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In contrast, when ecstasy use was present, the dose response effect for marijuana was attenuated. The lack of difference between total acquisition scores in the combined user groups ($E+M_L$ and $E+M_H$) might reflect a "basement effect." However, since the $E+M_L$ and $E+M_H$ user groups were matched on every aspect of ecstasy use and differed with respect to their marijuana use, it is possible that ecstasy use attenuated the degree to which heavy marijuana use produced the observed impairment in the acquisition of words across five learning trials. Finally, the lack of significant differences in total acquisition scores among group C and the M_L users ($p > 1$) suggests that the M_L users particular pattern of marijuana use was not sufficient to impact adversely the ability to learn a list of words.

Interference Trial. Scores on interference trial B represented the number of words recalled following a single presentation of a new word list (List B). List B assessed participants' supraspan ability immediately following learning, that is, the attentional processes related to the acquisition of information prior to storage. Group means and standard deviations for the interference trial are presented in Table 8.

Table 8   Mean number of words recalled on the interference trial for the groups (standard deviations are included in parentheses)

Group	Observed Mean*	Adjusted Means**	Adjusted Means***
C	6.800 (1.9)	6.611 (0.7)	6.540 (0.8)
M_L	7.321 (2.1)	7.514 (0.7)	7.545 (0.7)
M_H	6.046 (1.7)	6.042 (1.3)	5.764 (0.9)
$E+M_L$	6.667 (1.5)	6.501 (0.9)	6.108 (1.0)
$E+M_H$	5.895 (1.6)	5.994 (0.8)	6.676 (1.1)

Notes: * = means before the covariate analyses; ** = means after age, education, and verbal IQ were treated as covariates; *** = means after age, education, verbal IQ, monthly alcohol and nicotine, and cumulative lifetime use of other drugs were treated as covariates.

The initial MANCOVA and subsequent ANCOVA analyses showed that there were significant group differences in the number of words recalled on List B, $F(1,4) = 3.034$, $p < 0.021$. The number of words recalled from the interference list (List B) was similar for group C and each of the drug user groups. However, the M_L users recalled significantly more words on the interference trial than the M_H users ($p < 0.004$) and the E+M_H users (p < 0.004). Figure 6 displays the observed mean number of words recalled on the interference trial for the groups.

Drug Group Means-Interference (AVLT)
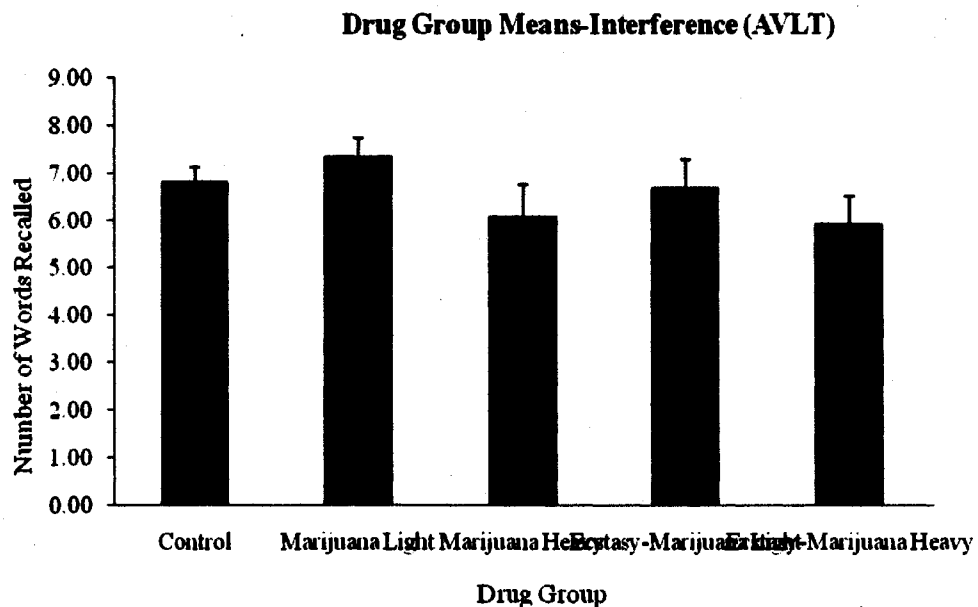
Figure 6   Mean number of words recalled on the interference trial (List B) of the AVLT for each group.

These findings along with a lack of significant differences between the M_H users and the E+M_L and E+M_H users indicates that heavier marijuana use and not ecstasy use, is

more closely associated with producing a decrease in the number of words recalled or

disruptions in attentional processes needed to learn a new list of words.

The first analyses also indicated there were differences in the number of words

recalled by males and females on the interference trial. This was supported by

MANCOVA-ANCOVA findings of a significant gender X group interaction, $F(1,4) =$

$2.512, p < 0.047$. Interference trial means and standard deviations for males and females

in the groups are reported in Table 9.

Table 9   Interference scores for males and females in each group (means and standard deviations)

Group	Observed Means*		Adjusted Means**		Adjusted Means***	
	Females	Males	Females	Males	Females	Males
C	6.200 (1.9)	7.700 (1.6)	6.009 (0.9)	7.987 (1.1)	6.034 (1.0)	7.949 (1.2)
M_L	7.846 (1.9)	6.867 (2.1)	7.696 (1.0)	6.997 (1.0)	7.228 (1.2)	7.402 (1.1)
M_H	6.250 (1.4)	5.928 (1.9)	6.123 (1.2)	6.001 (0.9)	6.168 (2.1)	5.975 (1.4)
$E+M_L$	7.250 (1.8)	6.000 (0.8)	6.771 (0.9)	6.547 (0.9)	7.034 (1.1)	6.247 (1.2)
$E+M_H$	5.714 (1.4)	6.000 (1.8)	5.369 (1.5)	6.201 (1.1)	6.175 (0.8)	5.733 (0.9)

Notes: * = means before the covariate analyses; ** = means after age, education, and verbal IQ were treated as covariates; *** = means after age, education, verbal IQ, monthly alcohol and nicotine, and cumulative lifetime use of other drugs were treated as covariates.

Tests of simple effects conducted via ANCOVA analyses revealed that females in

group C recalled significantly fewer words than males ($p < 0.010$). Figure 7 illustrates the

gender differences in interference performance. The finding of poorer recall performance

in the females assigned to the C group was unexpected, since females tend to perform

better on tests of verbal learning and memory than males (Lezak, 2004).

Gender x Drug Group Interaction Means-Interference (AVLT)
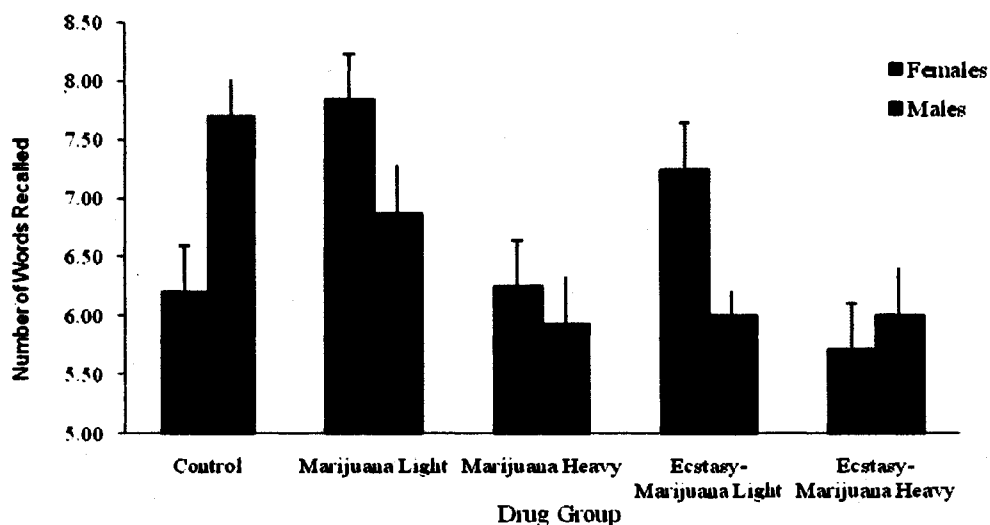
Figure 7   Observed means and standard errors for females and males in each group on the interference trial of the AVLT.

When monthly and cumulative use of other drugs were added as covariates, in the second MANCOVA-ANCOVA analyses, the main effect of group remained significant for interference scores, $F(1,4) = 2.577$, $p < 0.043$. Likewise, post-hoc tests confirmed the dose response effect of marijuana use. This was demonstrated by the finding that the M_L users recalled more words from interference List B than the M_H users ($p < 0.004$).

Unlike the post-hoc findings in the first analyses, however, the $E+M_H$ user group's word recall performance was no longer significantly worse than the M_L users' ($p > 1$). This result demonstrates that other drug use is associated with the word recall deficit observed for interference in the $E+M_H$ users and highlights the importance of accounting for polydrug use in ecstasy research.

An effect of ecstasy use on AVLT interference performance was also observed in the second analyses. This was demonstrated by the fact the E+M_L users recalled significantly fewer words from interference List B compared to the M_L users ($p < 0.028$). Given that these groups were matched for marijuana use and that other drug use was treated as a covariate, the increased impairment observed in the E+M_L users is likely attributable to ecstasy use. It is possible that ecstasy use affected word recall in the E+M_H users, too, but may have been masked by the effects generated from taking other drugs. Finally, the gender x drug group interaction for interference observed in the initial analyses was not observed in the second set of analyses.

Proactive Interference. Proactive interference scores were calculated for each participant by subtracting the sum of words recalled on interference trial B from the sum of words recalled on trial 1 (trial 1 – trial B). This measure reflects the extent to which List A learning interfered with the ability to learn words from List B. Greater word recall scores in trial 1, compared to trial B (e.g., +1.1) indicate a more pronounced effect of proactive interference, while scores of zero or lower (e.g., -1.1) indicate that List A learning did not interfere with word learning in List B or that no proactive interference effect was obtained.

Table 10 contains the observed means and standard deviations calculated for AVLT proactive interference for each group. There were significant differences in the amount of proactive interference exhibited among males and females within a group. This was confirmed in the first set of MANCOVA-ANCOVA analyses by a significant gender X group interaction, $F(1,4) = 2.512, p < 0.047.$

Table 10   Proactive interference scores for males and females in each group (means and standard deviations)

Group	Observed Means* Females	Males	Adjusted Means** Females	Males	Adjusted Means*** Females	Males
C	1.133 (2.0)	0.100 (1.4)	1.256 (0.9)	-0.084 (1.1)	1.617 (1.1)	0.146 (1.3)
M_L	-0.692 (2.1)	0.267 (2.2)	-0.591 (1.1)	0.179 (1.0)	-0.152 (1.1)	0.113 (1.0)
M_H	0.625 (2.2)	1.214 (1.7)	0.750 (1.4)	1.143 (1.0)	0.675 (1.5)	0.785 (1.2)
$E+M_L$	-0.750 (2.4)	0.714 (1.5)	-0.424 (1.4)	0.342 (1.6)	-0.218 (1.5)	0.698 (1.6)
$E+M_H$	1.714 (2.1)	0.417 (2.3)	2.695 (1.8)	-0.155 (1.3)	2.733 (1.9)	-1.091 (1.5)

Notes: * = means before the covariate analyses; ** = means after age, education, and verbal IQ were treated as covariates; *** = means after age, education, verbal IQ, monthly alcohol and nicotine, and cumulative lifetime use of other drugs were treated as covariates.

Figure 8 illustrates proactive interference scores on the AVLT for females and males in each group. Scheffé post-hoc comparisons after the first set of analyses showed that females in the $E+M_H$ user group had greater difficulty learning List B words because of interference created by List A learning than males ($p < 0.004$).
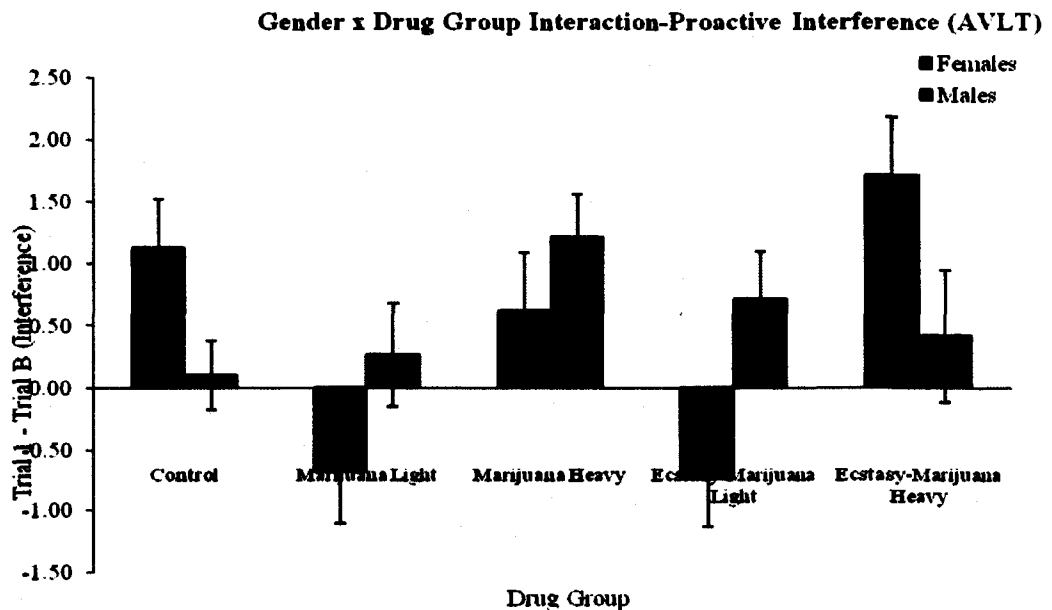
Figure 8   Observed means and standard errors calculated for proactive interference for each group.

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The gender X group interaction for proactive interference scores remained significant after accounting for other drug use, $F(1,4) = 3.487$, $p < 0.011$. Likewise, post-hoc tests also showed that the female E+M_H users experienced more proactive interference from List A learning than the males ($p < 0.001$) which indicates that females showed a decreased ability to suppress previous List A learning during the acquisition of List B words.

Trial 6 (Immediate Recall). Scores on trial 6 of the AVLT reflect the number of words recalled from List A, immediately following a single presentation and recall of interference List B. Group means and standard deviations for the number of words recalled on AVLT trial 6 are displayed in Table 11. The initial MANCOVA-ANCOVA analyses showed there were significant group differences in the number of words recalled on trial 6, $F(1,4) = 3.112$, $p < 0.018$.

Table 11   AVLT trial 6 (immediate recall) scores for each group (means and standard deviations are reported)

Group	Observed Means*	Adjusted Means**	Adjusted Means***
C	13.040 (1.6)	12.959 (2.3)	12.972 (1.1)
M_L	12.214 (2.2)	12.436 (1.0)	12.643 (1.0)
M_H	11.000 (3.4)	11.011 (1.0)	10.096 (1.2)
E+M_L	11.333 (2.4)	11.071 (1.3)	11.148 (1.4)
E+M_H	11.000 (2.7)	10.974 (1.1)	11.650 (1.5)

Notes: * = means before the covariate analyses; ** = means after age, education, and verbal IQ were treated as covariates; *** = means after age, education, verbal IQ, monthly alcohol and nicotine, and cumulative lifetime use of other drugs were treated as covariates.

Figure 9 displays the group means and standard errors for the AVLT immediate recall trial. Post-hoc tests showed that immediate recall performance for groups C and M_L were

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similar ($p > 1$). However, group C recalled significantly more words after the presentation of the interference list than the M_H ($p < 0.023$), $E+M_L$ ($p < 0.044$) and $E+M_H$ user groups ($p < 0.011$).

Additionally, a dose response effect of marijuana use was demonstrated by the fact that the M_L users recalled significantly more words after the presentation of the interference list than the M_H users ($p < 0.047$). Immediate recall performance in the M_L users was also significantly higher than the $E+M_L$ ($p < 0.024$) and $E+M_H$ user groups ($p < 0.012$). There were no observed differences in scores on trial 6 among the M_H users and either of the combined user groups ($E+M_L$ and $E+M_H$) (for both $p > 1$).

Drug Group Means-Immediate Recall (AVLT)
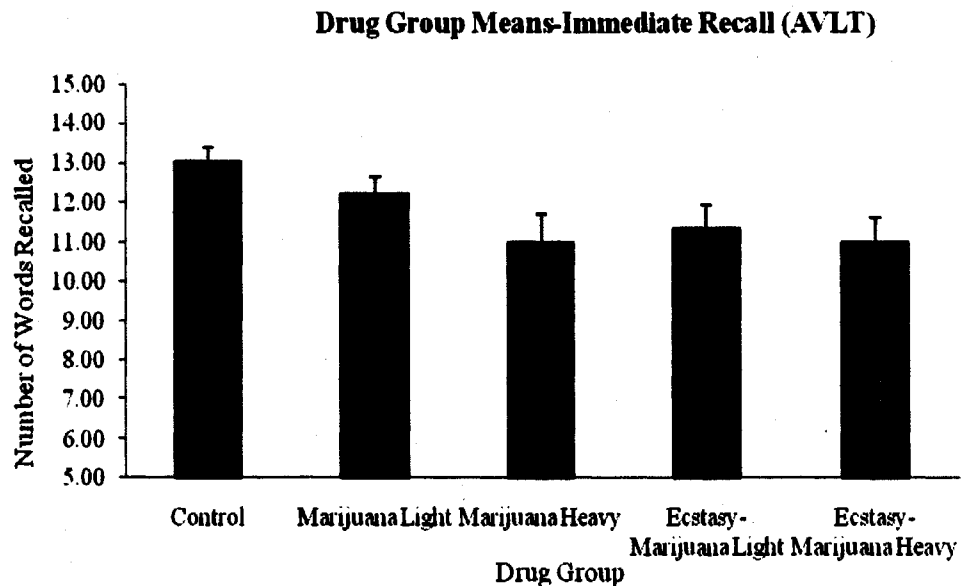
Figure 9   Mean number of words recalled on AVLT trial 6 for each group.

When cumulative use of other drugs were controlled for in the second MANCOVA-ANCOVA analyses, group main effects remained significant for trial 6, $F(1,4) = 3.448$, p

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< 0.012. However, the post-hoc comparisons that reached significance were different in the second set of analyses. For instance, neither of the combined user groups (E+M_L and E+M_H) no longer recalled significantly fewer words than group C or M_L users (for both p > 1), which indicates that the word recall deficits observed in the E+M_L and E+M_H user groups in the first set of analyses are probably more appropriately attributed to the use of other drugs. The M_H users recalled fewer words from List A following the interference trial than M_L users ($p < 0.002$) suggesting that there may be a dose response effect for marijuana use on immediate recall.

Trial 7 (Delayed Recall). Group means and standard deviations for trial 7 of the AVLT are displayed in Table 12. The groups differed with respect to the number of words recalled after a 20-minute delay. This was evidenced by a main effect for group in the first MANCOVA-ANCOVA analyses, $F(1,4) = 5.119$, $p < 0.001$.

Table 12   Trial 7 (delayed recall) scores for each group (means and standard deviations)

Group	Observed Means*	Adjusted Means**	Adjusted Means***
C	13.440 (1.4)	13.361 (0.9)	13.200 (1.0)
M_L	12.464 (2.0)	12.706 (0.8)	12.818 (0.9)
M_H	11.636 (2.6)	11.639 (0.9)	11.243 (1.0)
E+M_L	11.200 (2.3)	10.936 (1.1)	11.109 (1.2)
E+M_H	11.000 (2.8)	10.954 (1.0)	11.322 (1.3)

Notes: * = means before the covariate analyses; ** = means after age, education, and verbal IQ were treated as covariates; *** = means after age, education, verbal IQ, monthly alcohol and nicotine, and cumulative lifetime use of other drugs were treated as covariates.

Figure 10 illustrates the differences between the groups performance on AVLT trial 7. Group C recalled more words after the 20-minute delay than the M_H ($p < 0.007$), the E+M_L ($p < 0.001$), and E+M_H user groups ($p < 0.001$). The M_L users recalled significantly

more words after the long delay than the E+M$_L$ users ($p < 0.013$) and the E+M$_H$ users ($p < 0.008$).

Drug Group Means-Delayed Recall (AVLT)
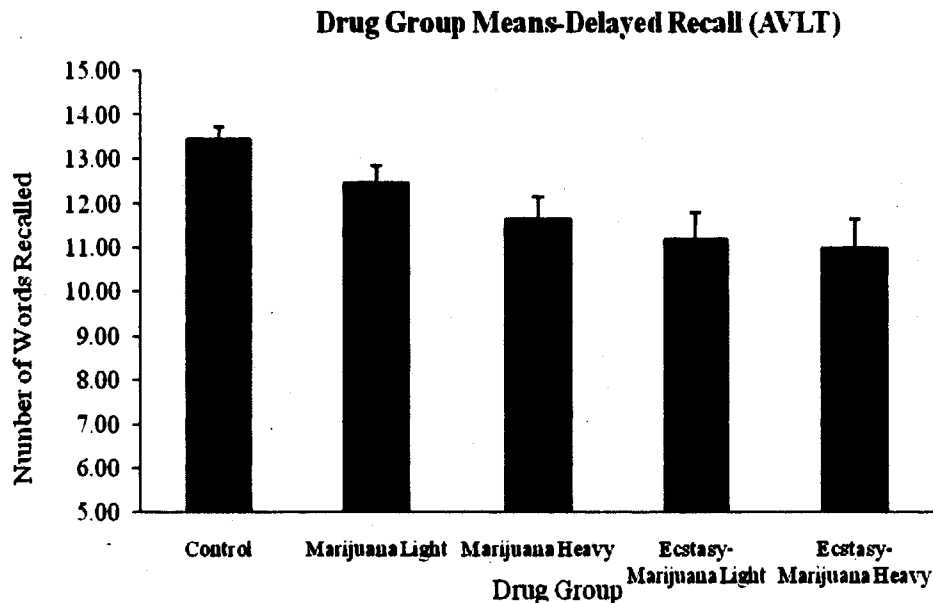
Figure 10 Mean number of words recalled on trial 7 of the AVLT for each group.

The main effect of group remained significant in the second MANCOVA-ANCOVA analyses, $F(1,4) = 2.925$, $p < 0.026$. Post-hoc tests indicated that group C recalled more words after the 20-minute delay than the M$_H$ ($p < 0.008$), the E+M$_L$ ($p < 0.011$), and E+M$_H$ users ($p < 0.037$). Moreover, the M$_L$ users recalled significantly more words than the M$_H$ users ($p < 0.026$) and the E+M$_L$ users ($p < 0.024$) on trial 7. The comparison between the E+M$_H$ users and the M$_L$ users delayed recall performance was not far from approaching significance ($p < 0.067$).

Taken together, these findings suggest that the frequency of marijuana use primarily affects delayed recall performance. Heavier marijuana use was associated with greater

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reductions in the number of words recalled on trial 7 than lighter use. While ecstasy use

also had a negative impact on delayed recall scores, its effects tended to be less robust.

Recognition. Group means and standard deviations for hits or the number of words

accurately discriminated as List A words on the AVLT recognition trial are reported in

Table 13. There were significant differences among the groups with respect to hits on the

recognition trial. This was confirmed in the initial MANCOVA and subsequent

ANCOVA analyses yielded a main effect of group, $F(1,4) = 3.181$, $p < 0.017$ on

recognition scores.

Table 13   Recognition scores for each group (means and standard deviations)

Group	Observed Means*	Adjusted Means**	Adjusted Means***
C	14.880 (0.4)	14.809 (0.4)	14.805 (0.4)
M_L	14.429 (0.8)	14.539 (0.3)	14.544 (0.1)
M_H	14.318 (0.7)	14.293 (0.4)	14.015 (0.4)
E+M_L	13.867 (1.5)	13.821 (0.5)	13.858 (0.5)
E+M_H	14.368 (1.0)	14.364 (0.4)	14.656 (0.5)

Notes: * = means before the covariate analyses; ** = means after age, education, and verbal IQ were treated as covariates; *** = means after age, education, verbal IQ, monthly alcohol and nicotine, and cumulative lifetime use of other drugs were treated as covariates.

Figure 11 graphically displays group performance on the AVLT recognition trial. The

C group accurately recognized more words from List A than the M_H users ($p < 0.043$)

and E+M_L users ($p < 0.001$). Recognition performance was also significantly better in the

M_L users than in the E+M_L users ($p < 0.013$). There were no detectable differences among

the M_H users, E+M_L users, and E+M_H users ($p > 1$).

Drug Group Means-Recognition (AVLT)
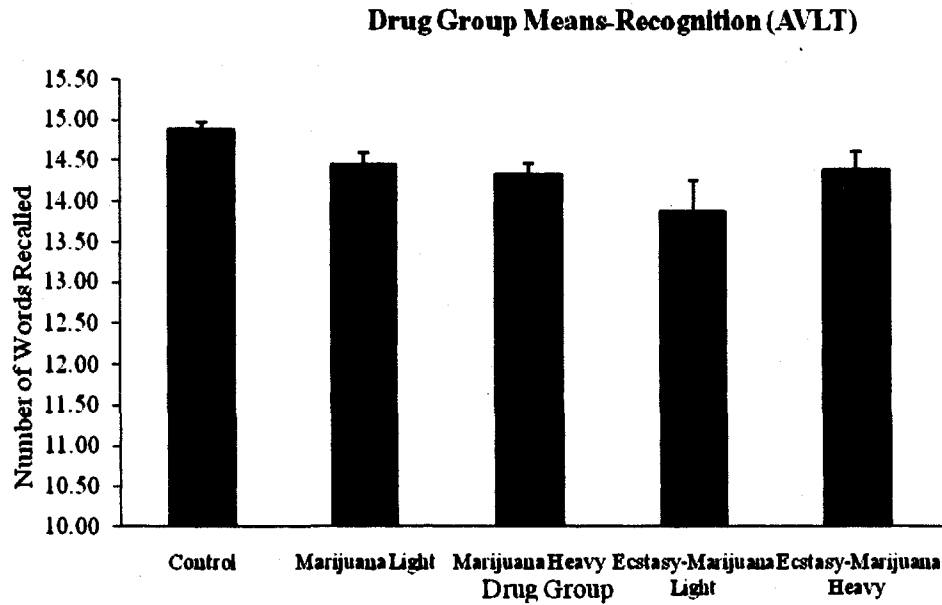
Figure 11   Observed group means and standard errors for hits on the AVLT recognition trial.

Group differences remained significant when other drug use was controlled in the

second MANCOVA-ANCOVA analyses, $F(1,4) = 3.680$, $p < 0.008$. Scheffé post-hoc

tests showed that group C recognized more words than the M_H users ($p < 0.006$) and the

$E+M_L$ users ($p < 0.003$). The M_L users recognized more words than the $E+M_L$ users ($p <$

0.019), which illustrates a negative impact of ecstasy use given these groups were

matched for marijuana use and other drug use was treated as a covariate. Interestingly,

the $E+M_H$ users recognized more words than the $E+M_L$ users ($p < 0.018$) and did not

differ statistically from the other groups ($p > 1$). No obvious reason for this result is

apparent in the data.

Error Associations. An error association was defined as the recall of a word that

was either semantically or phonemically related to a word in the stimulus list. An

increase in association errors is indicative of retrieval problems such as "tip-of-the-tongue" syndrome, where participants' reveal they know the correct word but are unable actually to recall it (Brown & McNeil, 1966). Error associations were summed for AVLT trials 1 through 7 and the interference trial.

In the initial set of MANCOVA-ANCOVA analyses, a significant gender X group interaction was observed for AVLT error associations, $F(1,4) = 3.478$, $p < 0.011$, demonstrating that there were differences in the number of associations committed by males and females in a group. Error association means and standard deviations for males and females in each group are reported in Table 14.

Table 14   Error association scores for males and females in each group (means and standard deviations)

Group	Observed Means* Females Males	Adjusted Means** Females Males	Adjusted Means*** Females Males
C	0.1 (0.3) 0.9 (1.6)	0.0 (0.6) 0.9 (0.7)	0.1 (0.9) 0.8 (1.1)
M_L	0.5 (0.7) 0.4 (0.8)	0.5 (0.4) 0.3 (0.4)	0.6 (0.9) 0.4 (1.0)
M_H	0.1 (0.4) 1.0 (1.3)	0.2 (0.7) 1.0 (0.5)	0.1 (1.2) 0.7 (1.0)
$E+M_L$	0.8 (1.5) 2.0 (3.0)	0.7 (2.0) 2.0 (2.1)	0.6 (1.2) 2.3 (1.3)
$E+M_H$	2.1 (3.6) 0.3 (0.6)	2.8 (2.1) 0.2 (1.5)	2.7 (1.5) 0.2 (1.2)

Notes: * = means before the covariate analyses; ** = means after age, education, and verbal IQ were treated as covariates; *** = means after age, education, verbal IQ, monthly alcohol and nicotine, and cumulative lifetime use of other drugs were treated as covariates.

Figure 12 illustrates the mean number of associations made by males and females in the groups. Tests of simple effects revealed that the females in the $E+M_H$ user group made significantly more error associations on the AVLT than the male $E+M_H$ users ($p < 0.050$) suggesting that ecstasy use combined with heavier marijuana use produced greater difficulty with word retrieval in females.
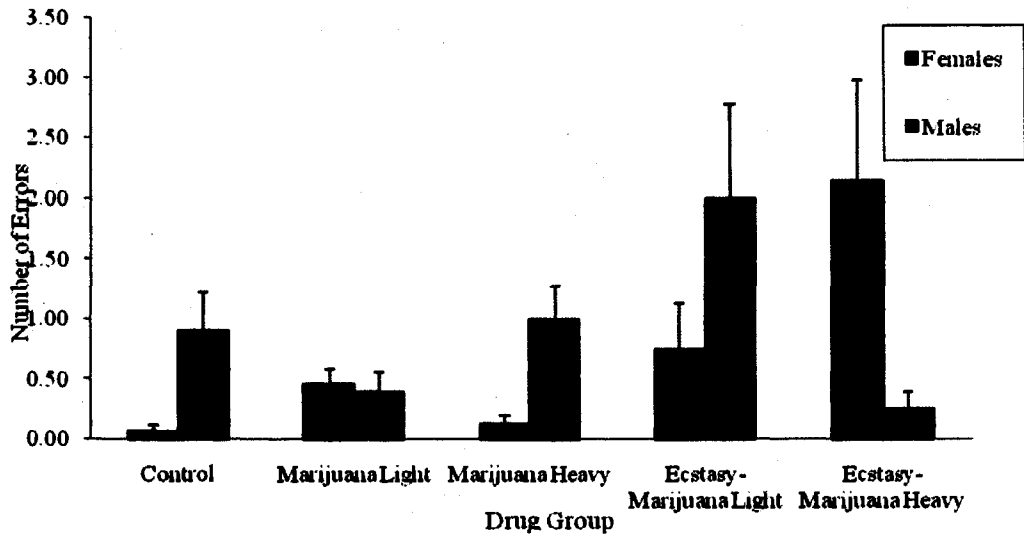
Figure 12   Mean number of error associations made by males and females in each group on the AVLT.

Similarly, the gender X group interaction for AVLT error associations was observed in the second analyses, $F(1,4) = 4.513$, $p < 0.050$. Tests of simple effects revealed the males in the E+M$_L$ user group made significantly more AVLT error associations than females in the E+M$_L$ group ($p < 0.049$). Alternatively, females in the E+M$_H$ user group made significantly more association errors than the male E+M$_H$ users ($p < 0.048$).

BFLT-E Tasks

Trial 6 (Immediate Recall). Like the AVLT, trial 6 of the BFLT-E represents immediate recall, that is, the number of figures recalled from List A following the presentation of a new list of figures (List B). The initial MANCOVA-ANCVOA analyses that treated age, education, and verbal IQ scores as covariates yielded a main effect of

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group for BFLT-E immediate recall scores, $F(1,4) = 2.676, p < 0.014$. The observed and

adjusted group means and standard deviations for the immediate recall trial on the BFLT-

E are reported in Table 15.

Table 15   BFLT-E immediate recall scores for each group (means and standard deviations)

Group	Observed Means*	Adjusted Means**	Adjusted Means***
C	39.320 (5.3)	39.571 (2.3)	39.905 (1.3)
M_L	37.750 (5.9)	38.362 (2.2)	37.873 (1.2)
M_H	37.727 (4.5)	37.847 (2.4)	37.738 (1.4)
E+M_L	36.933 (6.8)	35.871 (3.0)	37.571 (1.6)
E+M_H	35.105 (6.7)	34.573 (2.6)	33.638 (1.7)

Notes: * = means before the covariate analyses; ** = means after age, education, and verbal IQ were treated as covariates; *** = means after age, education, verbal IQ, monthly alcohol and nicotine, and cumulative lifetime use of other drugs were treated as covariates.

Figure 13 illustrates BFLT-E immediate recall performance for each of the groups.

Scheffé post-hoc tests showed that the E+M_H user group recalled significantly fewer

figures from List A following the presentation and recall of a new list of figures

compared to group C ($p < 0.005$) and the M_L user group ($p < 0.028$). None of the other

comparisons were significant.

Drug Group Means-Immediate Recall (AVLT)
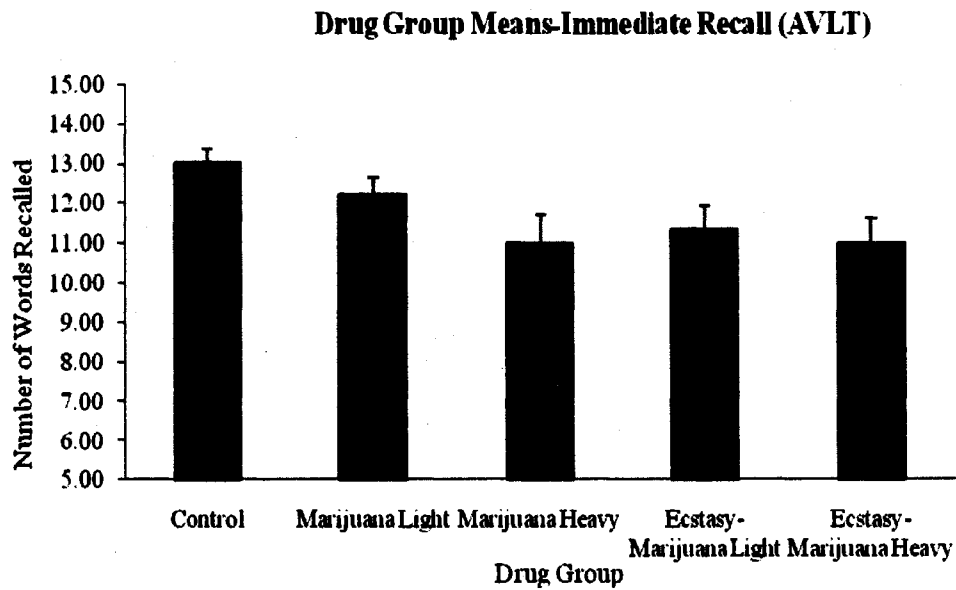
Figure 13   Observed group means and standard errors for the BFLT-E immediate recall trial.

When monthly use of alcohol and nicotine and the cumulative use of other drugs were added as covariates in the second set of MANCOVA-ANCOVA analyses, immediate recall scores were no longer significantly different between the groups ($p > 1$). This indicates that the use of other drugs accounted for a significant proportion of the immediate recall impairment observed in the E+M_H drug user group in the first set of analyses.

Extra Responses. Extra responses were summed for all of the BFLT-E trials, except the recognition trial. Both perseverations and extraneous responses constituted extra responses. Perseverations were defined as the repetition of a design, whereas, an extra response meant drawing a design that was unrelated to those in the stimulus list. Means and standard deviations for BFLT-E extra response data for each group are presented in Table 16.

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Table 16   BFLT-E extra responses for each group (means and standard deviations)

Group	Observed Means*	Adjusted Means**	Adjusted Means***
C	0.200 (0.4)	0.231 (1.6)	0.483 (0.9)
M_L	1.464 (2.8)	1.144 (1.5)	1.598 (0.8)
M_H	2.546 (5.2)	2.454 (1.7)	2.321 (1.0)
E+M_L	2.667 (6.8)	3.256 (2.0)	2.968 (1.1)
E+M_H	4.211 (6.7)	4.282 (1.8)	3.663 (1.2)

Notes: * = means before the covariate analyses; ** = means after age, education, and verbal IQ were treated as covariates; *** = means after age, education, verbal IQ, monthly alcohol and nicotine, and cumulative lifetime use of other drugs were treated as covariates.

Initial MANCOVA-ANCOVA analyses conducted on the BFLT-E extra response scores yielded a main effect of group, $F(1,4) = 3.454$, $p < 0.011$, demonstrating that there were significant differences in the number of extra responses made across the groups. Post-hoc tests confirmed that the ecstasy-marijuana user groups (E+M_L and E+M_H) made more extra responses than group C ($p < 0.022$; $p < 0.001$). Also, the E+M_H users committed more errors on this BFLT-E measure than the M_L users ($p < 0.009$). Figure 14 displays the differences in the number of BFLT-E extra response committed for each group.

Drug Group Means-Extra Responses (BFLT-E)
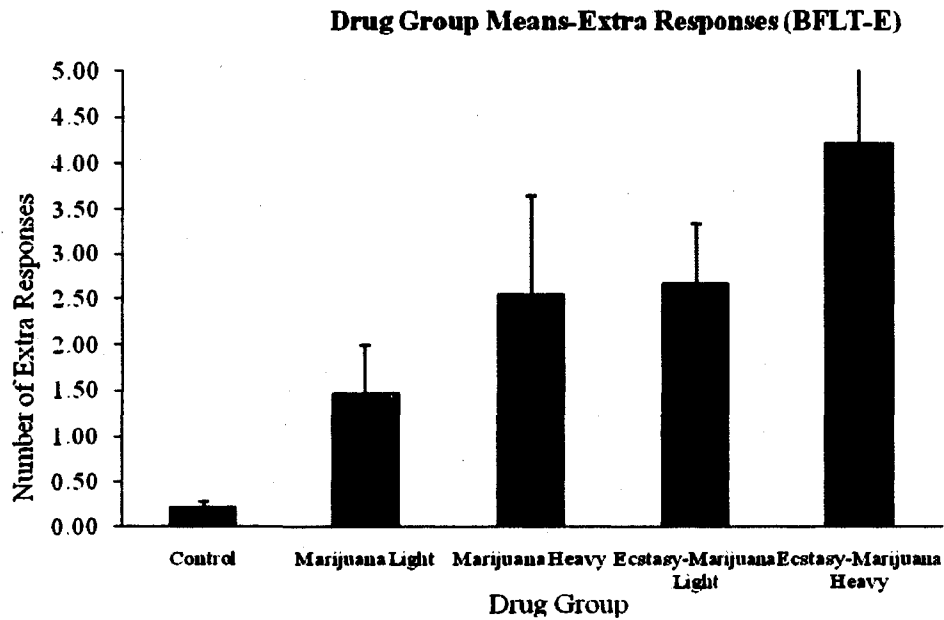
Figure 14   The observed mean total number of extra responses made on BFLT-E trials 1 through 7 and on interference trial B for each group.

In contrast, the main effect of group for the BFLT-E extra response data did not reach significance in the second set of MANCOVA-ANCOVA analyses ($p > 1$). This suggests that the group differences initially observed in the first set of analyses were closely associated with the consumption of drugs other than ecstasy and marijuana.

Taken together, the second set of analyses conducted on the immediate recall and extra response data emphasize the importance of accounting for polydrug use in recreational ecstasy users. Moreover, these findings call into question the conclusions drawn in previous studies that did not take into account the use of drugs other than ecstasy.

Regression Analyses

Two standard multiple regression analyses were conducted to examine the degree to which ecstasy, marijuana, and other drug use predicted performance on the AVLT dependent measures that were significant in the MANCOVA-ANCOVA analyses which treated age, education, verbal IQ, and other drug use as covariates. In both regression analyses, the following AVLT dependent measures were treated as criterion variables: total acquisition, interference, immediate recall, delayed recall, and recognition.

In the first regression analysis, one drug use characteristic for ecstasy and six drug use characteristics for marijuana were used as predictor variables. The drug characteristic used as a predictor for ecstasy was cumulative lifetime use. This decision was based on regression analyses conducted earlier on all eight ecstasy use characteristics (refer to Table 6 for the drug use characteristics associated with ecstasy) which revealed cumulative lifetime ecstasy use was the only significant predictor, $R^2 = .030$, $F(1, 101) = 2.10$, $p < .05$. The following marijuana use characteristics were treated as predictors: age of onset, number of years used, time since last use, amount of weekly use, amount of monthly use, and cumulative lifetime use.

The seven predictors accounted for 16.3 percent of the variance in total acquisition scores on the AVLT, $R^2 = .163$, $F(1, 101) = 2.80$, $p < .05$. The simultaneous solution suggested that the number of years marijuana had been used was the primary predictor that explained AVLT total acquisition scores, $\beta = -.374$, $t(101) = -3.07$, $p = .003$. This indicates that more deficits were observed in word learning performance with longer use of marijuana. Furthermore, none of the other marijuana use or ecstasy use predictors were

found significantly to explain the variance for the other AVLT dependent variables: interference, immediate recall, delayed recall, and recognition.

The second multiple regression analysis treated monthly use of alcohol and nicotine and cumulative use of cocaine, LSD, oxycontin (hydrocodone), xanax, and percocet as predictors to examine the contribution that these drugs had on verbal learning and memory performance on the same significant AVLT dependent measures evaluated in the first regression analysis. These drugs were selected as predictor variables because prior MANOVA analyses conducted on the drug use data revealed the groups differed significantly with respect to the total number of times these drugs had been used.

Collectively, the seven predictor variables accounted for 4.5 percent of the variance of AVLT total acquisition scores, $R^2 = .045$, $F(1, 95) = 5.08$, $p < .05$. This indicates that more deficits were observed in word learning performance when total lifetime uses of cocaine, LSD, oxycontin (hydrocodone), xanax, and percocet were greater. No one predictor contributed significantly to the variance of the total number of words recalled on the first five AVLT learning trials, although, cumulative LSD use was found to approach significance, $\beta = -.170$, $t(95) = -1.81$, $p = .072$.

Likewise, the seven predictors together accounted for 11 percent of the variance in delayed recall scores on the AVLT, $R^2 = .110$, $F(1, 95) = 5.08$, $p = .05$. The most important predictor observed was cumulative LSD use, $\beta = -.304$, $t(95) = -2.92$, $p < .05$, which is consistent with previous findings (Croft et al., 2001; Fox et al., 2001). These findings demonstrate that greater lifetime uses of cocaine, oxycontin (hydrocodone), xanax, percocet, and especially LSD are associated with reductions in the number of words recalled after a long delay. None of the other predictors were found to be

significant for interference, immediate recall, or delayed recall performance on the AVLT.

In summary, the regression analyses corroborated findings obtained in the secondary AVLT MANCOVA-ANCOVA analyses, which showed effects of ecstasy, marijuana, and other drug use on total acquisition and delayed recall performance. With respect to total acquisition, more deficits were observed in word learning performance with longer use of marijuana and to a lesser extent, with greater lifetime use of ecstasy. Still further, larger deficits were observed for total acquisition when total lifetime uses of cocaine, LSD, oxycontin (hydrocodone), xanax, and percocet were greater. The fact that cumulative LSD use approached significance in the regression analyses suggests that total LSD use may affect word learning to a greater extent than the other drugs examined. Finally, greater reductions in word recall after a long delay were observed with greater lifetime use of other drugs, especially LSD use.

CHAPTER 5

DISCUSSION

The primary goal of the present study was to investigate the extent to which word learning and memory deficits, previously observed in studies of recreational ecstasy users, are associated with concomitant marijuana use and/or the use of other drugs rather than ecstasy per se. The results that emerged from this study both complement and contradict the findings of earlier studies that have investigated the effects of ecstasy use on verbal learning and memory performance.

The results in the present study demonstrate that verbal learning and memory deficits occurred on the AVLT in the combined ecstasy-marijuana users relative to non-drug using controls, which is consistent with a number of previous memory studies of recreational ecstasy users (e.g., Croft et al., 2001; Dafters et al., 1999; Fox et al., 2001; Gouzoulis-Mayfrank et al., 2000; Klugman et al., 1999; Lamers et al., 2006; McCann et al., 1998; McCardle et al., 2004; Morgan, 1999; Parrott & Lasky, 1998;Parrott et al., 1998; Quednow et al., 2006; Reneman et al., 2001; Thomasius et al., 2003; Verkes et al., 2001; Wareing et al., 2000; Yip & Lee, 2005). Similarly, greater word recall deficits were observed in heavier marijuana users than in non-drug using controls (e.g., Block & Ghoneim, 1993; Bolla et al., 1998; Bolla et al., 2002; Croft et al., 2001; Dafters et al., 2004; Fletcher et al., 1996; Gouzoulis-Mayfrank et al., 2000; Kanayama et al., 2004;

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Lamers et al., 2006; Pope et al., 2001; Pope & Yurgelun-Todd, 1996; Solowij et al., 2002).

Of more direct relevance to the primary research question was the finding that, generally speaking, verbal learning and memory impairments in the concurrent ecstasy-marijuana user groups resembled those in the heavy marijuana-only user group, indicating that the deficits observed in the combined ecstasy-marijuana users may be more attributable to marijuana use than ecstasy use. Moreover, marijuana's negative effects on word learning and memory were dose dependent, which is consistent with other published findings (e.g., Accordino et al., 2006; Bolla et al., 2002; Bolla et al., 1998; Fletcher et al., 1996; Fried et al., 2002; Hall et al., 2004; Kouri et al., 1995; Solowij et al., 1998). In this context, it should also be noted that the illicit use of psychoactive substances other than ecstasy or marijuana also negatively impacted word recall in the drug user groups.

More specifically with regard to the use of marijuana, dose response effects were demonstrated for total acquisition, interference, immediate recall, and delayed recall trials on the AVLT. On each of these dependent measures, heavier marijuana-only users experienced greater difficulty learning two lists of words and subsequently retrieving words from those lists than lighter marijuana-only users. Subsequently, heavier marijuana use disrupted the ability to freely recall words from List A both immediately after list presentation (immediate recall) and 20-minutes following List A presentation (delayed recall). In contrast, to its effects on free recall, marijuana has no effect on recognition of previously presented words within a list of old and new words. As previously mentioned, these dose-response effects of marijuana are in agreement with other published findings.

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For example, Block and Ghoneim (1993) have reported that relative to a matched group of non-drug using controls, heavy marijuana users had significant impairments in memory retrieval along with deficits in verbal expression and mathematical reasoning. Similarly, a large prospective study using younger and older populations of Costa Rican marijuana users and matched controls found that prolonged use of marijuana is associated with deficits in free recall and list learning tasks (Fletcher et al., 1996).

The results also imply that lighter marijuana users are not impaired to an extent that would interfere with memory functioning in their daily lives. The M_L drug user group performed similarly to the non-drug control group on total acquisition, immediate recall, delayed recall, and recognition trials of the AVLT. The M_L users reported smoking marijuana 243 times in their lifetime, an average of once a week over a period of three years, with two weeks elapsing since the time of their last use. In contrast, the M_H user group reported using marijuana a total of 2,241 times in a four year period, smoking an average of 12.5 times a week, with less than half a week elapsing since they had last used marijuana.

Two lines of evidence suggest that the deficits in the combined ecstasy-marijuana drug user groups were not related primarily to ecstasy consumption. The first is that if ecstasy or the combination of ecstasy and marijuana were responsible for the cognitive deficits seen on the AVLT, then it would be expected that the participants who used both ecstasy and marijuana would perform more poorly than those who had used only marijuana, whereas if marijuana were primarily responsible for the deficits then there should be no difference between the groups. Thus, the present finding that neither of the ecstasy-marijuana user groups performed worse than the heavier users of just marijuana

on total acquisition, interference, immediate recall, and delayed recall trials suggests that the deficits obtained in the combined user groups were not primarily associated with ecstasy use. Second, that the number of years of marijuana use was the best predictor of AVLT total acquisition performance in the regression analyses further substantiates marijuana's contribution to the word learning and memory deficits observed in the current work.

Further support for the argument that ecstasy use is not predominantly responsible for poorer word recall performance can be derived from the second set of MANCOVA-ANCOVA analyses, which treated other drug use as a covariate (i.e., monthly use of alcohol and nicotine and the cumulative lifetime use of cocaine, amphetamine-methamphetamine mushrooms, LSD, solvents, heroin, oxycontin (hyrdrocodone), muscle relaxers, xanax, percocet, valium, ritalin/adderall, ambien/lunesta, morphine, methadone, and demerol). This other drug use was responsible for a significant proportion of the differences among the drug user groups on interference, immediate recall, and delayed recall scores on the AVLT. Moreover, the regression analyses showed that other drug use explained 4.5 percent of the differences in total acquisition scores on the AVLT, with LSD falling just short of approaching significance as the best predictor of total acquisition performance. Indeed, LSD accounted for the largest proportion of the variance observed in delayed recall scores among the drug user groups. Similarly, other illicit drug use was strongly associated with figure recall deficits and errors committed on the BFLT-E dependent measures.

Although heavier marijuana and other illicit drug use were closely associated with the observed word learning and retrieval failures in the present study, subtle negative effects

of ecstasy use were, in fact, found. For example, $E+M_L$ users exhibited greater difficulty

learning new sets of words, as shown by lower total acquisition and interference scores,

than the M_L users. Moreover, female $E+M_H$ users experienced a greater inability to

suppress previous List A learning while trying to acquire List B words than male $E+M_H$

users. Additionally, males in the $E+M_L$ user group and females in the $E+M_H$ user group

made significantly more errors of association than the corresponding marijuana-only user

groups. Finally, the $E+M_L$ users also had more difficulty with word retrieval after the 20-

minute delay and with word recognition than the M_L users.

Taken together, the above articulated subtle effects of ecstasy do not invalidate the

robust verbal learning and memory deficits reported in other ecstasy research, they just

were not observed in the present study. Differences in word recall performance were

primarily associated with heavier marijuana use and the illicit use of other psychoactive

substances. To some extent, ecstasy use negatively affected word learning rates, free

recall abilities, and the number of errors committed on the AVLT. However, the extent of

ecstasy's contribution to verbal impairment seems far less reaching than that of marijuana

and other drugs.

The disparity between the results observed in this study and other published research

on ecstasy may be, in part, explained by differences in participants' ecstasy use

characteristics. The total number of ecstasy tablets taken among the ecstasy-marijuana

user groups in this study was substantially less than in previous studies (see Table 3 in

Appendix I). For example, in this study, the ecstasy-marijuana user groups reported a

mean cumulative lifetime use of 30.3 ($E+M_L$) and 33.4 ($E+M_H$) ecstasy tablets compared

to ecstasy users in the Thomasius et al. (2003) study, who reported a mean cumulative

use of 1,033 ecstasy tablets and relative to the ecstasy users in the Quednow et al. (2006) study who had used 457 ecstasy pills in their lifetime.

It should be noted that heavy marijuana smokers (M_H and $E+M_H$) reported a higher rate of use of other drugs, which is consistent with findings from other investigations (Bolla et al., 1998; Hall et al., 1995; Kouri et al., 1995; Pope et al., 2001; Solowij et al., 2002). Both of the heavier marijuana groups used a wider variety of drugs and more of them. Other studies show that as polydrug use widens, it also intensifies, with polydrug users being also the heaviest users of alcohol, tobacco, and other stimulants (e.g., Kouri et al., 1995; Milani et al., 2000; Parrott et al., 2001).

The present study extends the existing ecstasy literature related to cognitive and memory function. This study dealt with the methodological shortcomings and confounding variables that have plagued a number of earlier ecstasy-related investigations by adequately matching participants with regard to intellectual function, education level, gender and age. Moreover, specific consideration for the concomitant use of other illicit drugs by ecstasy users, specifically marijuana, was controlled.

Given that the cause of the learning and memory deficits obtained in this research seems to lie primarily at the feet of marijuana, it seems appropriate to devote the balance of this discussion to a number of potential neurochemical explanations for the observed verbal learning and memory impairments in heavy marijuana users, whether or not they are concurrently using ecstasy. In so doing, this researcher does not intend to imply that ecstasy and other psychoactive drugs do not have adverse effects on learning and memory but instead that the effects of marijuana in this context seem to be pervasive and deserving of further consideration.

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The serotonin (5-HT) system is a diverse and intricate system composed of at least 14 identified receptor subtypes (Barnes & Sharp, 1999). Serotonergic nerve fibers originate in the raphe nuclei of the hindbrain and project widely throughout the brain innervating almost every major brain structure (Abrams et al., 2004). One interesting aspect of the serotonin system is the reciprocal interactions many of its receptors have with one another. For example, $5-HT_{1A}$ and $5-HT_{2A}$ receptors appear to exhibit opposing roles (Araneda & Andrade, 1991; Darmani et al., 1990). Specifically, activation of $5-HT_{1A}$ receptors typically results in cellular hyperpolarization and inhibition of cell firing, whereas activation of $5-HT_{2A}$ receptors induces cellular depolarization and increased cell firing (Araneda & Andrade, 1991). Additionally, these two receptors appear to elicit opposing behavioral responses, with $5-HT_{1A}$ receptor activation inducing hyperphagia, increased male sexual behavior, anxiolysis, and hypothermia, whereas activation of the $5-HT_{2A}$ receptor induces hyperthermia, reduced male sexual behavior, anxiogenesis, and hypophagia (Abdel-Fattah et al., 1995). Concomitant activation of one serotonin receptor results in functional inhibition of another. This suggests that the net effect of serotonergic activity is delicately regulated by the balance of serotonin receptors (Hill et al., 2003).

The endocannabinoid system is a neuromodulatory system in the brain that shares a high level of overlap with the serotonergic system in terms of the physiological processes it regulates. For example, both the serotonergic and endocannabinoid systems regulate body temperature, feeding behavior, sleep and arousal, and emotional processes (Chaperon & Thiebot, 1999; Hill et al., 2005).

In vitro and in vivo work has suggested that cannabinoids might influence 5-HT release. Cannabinoid receptor (CB_1) agonists suppress electrically- and calcium -

stimulated 5-HT release from cortical slices (Nakazi et al., 2000) and THC inhibits the release of 5-HT in the hippocampus (Egashira et al., 2002). This suppression of serotonergic neurotransmission by cannabinoids is believed to be involved in the memory deficits produced by THC. Pretreatment with a 5-HT precursor, 5-hydroxytryptophan (5-HTP), or a 5-HT reuptake inhibitor, clomipramine, reverses these THC-induced deficits (Egashira et al., 2002).

Biochemical work has further suggested that endocannabinoids may enhance $5\text{-}HT_{1A}$ receptor-mediated responses but attenuate $5\text{-}HT_{2A}$ receptor-mediated responses (Boger et al., 1998). This finding is supported by behavioral studies that have found that both short and prolonged administration of potent CB_1 receptor agonists potentiated $5\text{-}HT_{2A}$ behaviors while reducing $5\text{-}HT_{1A}$ receptor behaviors (e.g., Cheer et al., 1999; Darmani, 2001; Gorzalka et al., 2005; Hill et al., 2003).

Shifting our consideration to another neurotransmitter, cannabinoids increase dopamine neurotransmission in the nucleus accumbens (Di Chiara & Imperato, 1988; Nestler, 2002; Wise, 2002). Cannabinoids participate in the regulation of dopamine synthesis, release and turnover (Gardner & Vorel, 1998). It is possible that the negative memory effects observed in the present study were associated with the sustained use of marijuana which is known to produce decreased dopamine neural transmission via systemic down regulation of dopamine receptors in the hippocampus, especially D_2 receptors (Fujishiro et al., 2005).

Hippocampal dopamine neurons project from the ventral tegmental area, with some of dopamine fibers in the posterior hippocampus originating from the substania nigra

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(Verney et al., 1985). In fact several studies have shown that disturbances in dopaminergic systems induce learning and memory in rats (Fujishiro et al., 2005).

Herkenham and colleagues (1990) demonstrated that cannabinoid receptors (CB_1) are located throughout the brain by using a synthesized ligand (CP 55940) that is structurally similar to THC. They found that this ligand exhibited high density binding to CB_1 receptors in the cerebellum, basal ganglia, cerebral cortex and hippocampus. The finding that CB_1 receptors are located in the hippocampus and that the THC-like ligand readily binds to these receptors correlates with marijuana's negative effects on learning and memory function.

The hippocampus is located in the inferior medial temporal lobe. It has been shown to be involved in memory functioning through studies with brain-damaged patients who, in extreme cases, suffer anterograde amnesia, which is the inability to form new long-term memories due to damage to the bilateral hippocampus (Gazzaniga et al. 1998). Rather than the hippocampus actually storing or retrieving memories, it is critical in the transfer of short-term memories into long-term memories by encoding and consolidating new information.

Chan and colleagues (1998) have investigated the neurotoxicity of THC on cultured rat hippocampal neurons and slices. THC not only caused the shrinkage of cell bodies and nuclei of neurons, but also caused genomic DNA strands to break. Neuronal toxicity was found even with low doses, which were comparable to normal human consumption, by Chiang & Barnett (1984). As expected, the rate of cell death increased with THC concentration. There is speculation, which is consistent with findings of Herkenham et al. (1990), that THC targets hippocampal neurons because there is an abundance of CB_1

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receptors in the hippocampus. When THC binds to these CB_1 receptors, it sets off transcriptional-dependent cell death. It would seem to follow that there would also be neurotoxicity of cells in the basal ganglia, cerebellum, and the cerebral cortex, since CB_1 receptors have also been found in abundance there. However, Chan et al. (1998) found that hippocampal neurons are more sensitive to THC than other cultured cortical neurons.

Chan et al. (1998) proposed that because THC is hydrophobic, neuronal death may be due to interactions with membrane lipids rather than with the CB_1 receptors. However, they found that the CB_1 receptor antagonist SR141716A completely inhibited neuronal death, which led Chan and colleagues to conclude that the actual binding of THC to cannabinoid CB_1 receptors in hippocampal neurons was responsible for the observed neuronal death.

Although Chan et al.'s (1998) research was well-controlled and informative; this experiment was done on rat hippocampal neurons in vitro, which begs the question of whether it can be extrapolated to human hippocampal neurons in vivo. Even if this extrapolation were accepted, it needs still to be determined in humans whether permanent memory loss would occur due to the neuronal death of these cells by THC because previous human data suggests that the effects of marijuana use on learning and memory are reversible (e.g., Pope et al., 2001; Solowij et al., 2002; Sullivan, 2006).

Brain imaging studies have also tried to pinpoint the neural physiological alterations induced by marijuana use. For example, Amen and Waugh (1998) attempted to find a correlation between chronic marijuana usage and changes in localized brain activity using single photon emission computer tomography (SPECT). SPECT measures changes in cerebral blood flow by radioactive decay, which can then be visualized and interpreted as

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metabolically active regions in the brain. In Amen and Waugh's (1998) study, patients diagnosed with attention deficit/hyperactivity disorder (ADHD) were compared with other ADHD patients who used marijuana. The ADHD controls showed only a decreased perfusion in the prefrontal cortex but no abnormalities in the temporal lobes. In contrast, the ADHD-marijuana smokers exhibited a greater, dose related, decrease in activity of the prefrontal cortex and decreased perfusion in the temporal lobes. Based on these results, Amen and Waugh concluded that chronic marijuana usage changed the cerebral perfusion pattern of the brain, specifically in the temporal lobe region. In this context, it should be noted that Kandel and Schwartz (1985) had previously demonstrated that memory deficits were associated with abnormal activity in the temporal lobes.

While Amen and Waugh's study was thorough, their reasoning behind using only ADHD subjects can be questioned. Their justification for not studying a normal group of marijuana users with a normal control group was that even a normal group adds an element of uncertainty because so many marijuana users have additional diagnoses. This is a weak argument since it seems ADHD patients who smoke marijuana will have the complication of not only having ADHD, but additional diagnoses, since they too are marijuana users. Nonetheless, their work sets the stage for future imaging studies to examine the degree to which heavy marijuana use changes the brain physiologically with respect to memory.

In a study of hippocampal lesioned patients, Drew et al. (1980) used a test battery consisting of a series of psychometric tests including Babock Story Recall, Digit Span, Paired-Associate Learning, and Murdock Retention Test. These tests were used to assess recent memory function where the standard procedure was to provide a list of items that

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marijuana intoxicated subjects first memorized and then were asked to recall immediately and after a delay. During the delay, the subject was engaged in another mental activity (i.e., counting backwards in three's) to prevent rehearsal.

Drew and colleagues (1980) results showed that acute marijuana intoxication did not affect memory retrieval from short term/working memory when the list was recalled immediately after learning. However, after the delay period the number of items recalled by the intoxicated subjects significantly decreased compared to the control group. The interesting portion of this study here is that the performance of marijuana- intoxicated subjects was also compared with hippocampal brain damaged patients. The results indicated that these two groups performed similarly on the test battery. These findings suggest that being under the influence of marijuana may be similar to creating a temporary lesion in the hippocampus with respect to impaired memory function.

Given the range of possible reductive mechanisms that might underlie the behavioral data obtained in the present study, more research is clearly needed to evaluate the long-term, and possibly permanent, effects of marijuana use on memory. Future experiments should examine acute users, chronic users, and ex-users of marijuana, and the effect of the length and frequency of marijuana use on memory functions. Furthermore, behavioral studies and brain imaging investigations should prove beneficial in more adequately pinpointing the physiological aspects that lead to functional memory impairments in marijuana users. A direct benefit of understanding fully the memorial effects of marijuana is that it would permit a better understanding of the combined effects of marijuana and other psychotropic drugs, starting with the combined effects of marijuana and ecstasy.

APPENDIX I

TABLES

Table 1   Studies investigating explicit long-term verbal learning and memory in ecstasy users with relatively strong control over the influence of drugs apart from ecstasy

Investigation	Immediate Recall	Delayed Recall	Memory Test	Variables Controlled
Croft et al. (2001)	.ns#	.ns	Coughlan List and Design Learning Test	compared MDMA-cannabis users, cannabis-only controls and non-drug users; matched on cannabis and IQ; performed covariate analyses for total cannabis, total MDMA, frequency of cannabis and MDMA use
Curran & Verheyden (2003)	.ns	sig.+DD	RBMT Prose Recall & Buschke Selective Reminding Task	compared male ex- and current-MDMA; users with male polydrug controls matched for cannabis use and IQ and non-drug users; manipulated MDMA
Dafters, Hoshi, & Talbot (2004)	.ns#	.ns#	RBMT Immediate & Delayed Passage Recall	use in MDMA-cannabis group-heavy/light; matched on cannabis and IQ; performed; covariate analyses for other drug use
Fox, Toplis et al. (2001)	sig.+DD	sig.+DD	AVLT	compared short-term and long-term MDMA; users and polydrug controls; statistically; controlled for other drug use; matched for IQ
Gouzoulis-Mayfrank et al. (2000)	sig.+DD	sig.	VLMT-German version AVLT	compared MDMA-cannabis, cannabis-only and non-drug users; matched for cannabis use; cannabis use was associated with some VLMT measures
Halpern et al. (2004)	.ns	.ns	WMS-Verbal Paired Associates/CVLT	compared MDMA and polydrug users
Lamers et al. (2006)	.ns#	.ns	AVLT	compared MDMA-cannabis and cannabis only users with non-drug users
McCardle et al. (2004)	sig.	sig.	AVLT	compared MDMA and polydrug users; statistically controlled for cannabis use; matched for IQ
Montgomery, Fisk, & Newcombe (2005)	sig.	.ns	Verbal Paired Associates	compared MDMA and polydrug users matched on other drug use and IQ; covariate analyses revealed cannabis use affected performance

Table 1 continued

Investigation	Immediate Recall	Delayed Recall	Memory Test	Variables Controlled
Quednow et al. (2006)	.ns	sig.+DD; recall consistency; recognition, retroactive interference	German version-AVLT	compared abstinent MDMA users cannabis-only users, and non-drug users; statistically controlled for cannabis use
Reneman, Majoie et al. (2001)	sig.+DD	.ns	AVLT	SERT densities were lower in recent ecstasy users but not in abstinent ecstasy users
Semple et al. (1999)	.ns	.ns+DD	CVLT	compared MDMA users and non-users; after controlling for IQ results were .ns; lifetime doses of MDMA was associated; with memory impairment
Simon & Mattick (2002)	.ns	.ns	WMS-III Auditory Memory	regression analyses approached sig. for the effect of current frequency of cannabis use
Thomasius et al. (2003)	sig.+DD	sig.+DD	AVLT	compared ex- and current-MDMA users; ex-users memory was worse than current users; SERT availability was reduced only in current users
Yip & Lee (2005)	sig.	sig.+DD	Chinese version-AVLT; recognition	compared "pure" MDMA users and non- drug users; matched IQ

Note. **sig.** = significant deficit in ecstasy uses compared to controls. Unless otherwise stated, the findings shown are in comparison to a control group of drug users who don't use ecstasy. .ns = no significant difference between ecstasy users and controls, $p > .05$. .ns# = no difference between ecstasy users and other drug users, but significantly different from non-drug using controls. **DD** = Dose Dependence to some measure of ecstasy use.

Table 2   Verbal learning and memory studies that exercised less control over the influence of drugs apart from ecstasy and other possible covariates

Investigation	Immediate Recall	Delayed Recall	Memory Test	Notes
Back-Madruga et al. (2003)	.ns	.ns	AVLT	no drug use exclusion criteria were applied to controls
Bhattachery & Powell (2001)	sig.+DD	sig. +DD	RBMT-Prose recall	compared novice-, regular-, abstaining MDMA users and non-drug users; matched on IQ; differed on frequency of cannabis use over past month
Bolla et al. (1998)	sig.+DD	.ns	AVLT	no statistical control over the influence of cannabis or other drugs; controlled for IQ
Curran & Travill (1997)	sig.	sig.	Prose recall	compared MDMA users and alcohol drinkers; no statistical control over the influence of cannabis use or other potential covariates
Fox, Parrott et al. (2001)	.ns	.ns	24 single words drawn from 6 semantic categories	no statistical control of cannabis or other drugs
Krystal et al. (1992)	sig.	sig.	WMS Initial & delayed paragraph	compared MDMA users to age-matched normative data
Morgan (1999)	sig.	sig.	RBMT-Story recall	statistical differences between groups on IQ and other drug use
Parrott & Lasky (1998)	sig.	sig.	Auditory word recall	compared novice- and regular - MDMA users with non-drug users; no statistical control over cannabis use or IQ
Reneman, Lavalaye et al., (2001)	.ns	sig.	AVLT	no statistical control over the influence of cannabis use or other possible covariates
Rodgers (2000)	sig. .ns	sig. .ns	WMS-Verbal Paired Associative/ Logical Memory	compared MDMA-cannabis and cannabis only and non-drug users groups; considerable cannabis use among both user grps; MDMA use was light (20 tabs)
Verkes et al. (2001)	.ns	sig.	Word recognition	compared moderate- and heavy-MDMA users with non-drug users; no statistical control over the influence of cannabis use or other potential covariates
Zakzanis & Young (2001)	sig.	sig.	RBMT-Story recall	longitudinal study (over 1 yr) of 15 MDMA users; memory declined from baseline to follow-up; MDMA use increased as did other drug use

Note. sig. = significant deficit in ecstasy uses compared to controls. Unless otherwise stated, the findings shown are in comparison to a control group of drug users who don't use ecstasy. .ns = no significant difference between ecstasy users and controls, $p > .05$. .ns# = no difference between ecstasy users and other drug users, but significantly different from non-drug using controls. DD = Dose Dependence to some measure of ecstasy use.

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Table 3   Cumulative lifetime dose (unless otherwise specified) of MDMA and cannabis use in studies investigating explicit long-term verbal memory performance in ecstasy users

Investigation	Ecstasy/MDMA Use	Marijuana/Cannabis Use
Back-Madruga et al. (2003)	M = 74.6 (SD = 100.6) MDMA users M = not reported for non-drug users	M = not reported MDMA users M = not reported for non-drug users
Bolla et al. (1998)	M = 60 MDMA users M = 0 non-drug users	M = not reported MDMA users M = not reported non-drug users
Croft et al. (2001)	M = 41.9 (SD = 49.3) MDMA users M = 0.6 (SD = 1.3) Cannabis-only users M = 0 non-drug users	M = 10,964.9 (SD = 13,235.5) MDMA users M = 7762.4 (SD = 14,480.9) Cannabis-only users M = 0.5 (SD = 0.8) non-drug users
Curran & Travill (1997)	M = not reported MDMA users M = not reported non-drug users	M = not reported MDMA users M = not reported non-drug users
Curran & Verheyden (2003)	M = 4.33 (2.89) yrs of use current MDMA users M = 3.49 (2.63) yrs of use ex-MDMA users M = 0 non-drug users	M = 6.7 (4.2) yrs of use current MDMA users M = 7.2 (5.1) yrs of use ex-MDMA users M = 7.4 (6.7) yrs of use non-drug users
Dafters et al. (2004)	less than 50 tabs MDMA light-cannabis users 50 or more tabs MDMA heavy-cannabis users M= 0 Cannabis-only users M = 0 non-drug users	M = 1252.9 (SD = 1078.1) MDMA light-cannabis users M = 1680.7 (SD = 838.2) MDMA heavy-cannabis users M = 1023.1 (SD = 670.7) Cannabis-only users M = 0 non-drug users
Fox, Parrot et al. (2001)	M = 364.6 MDMA users M = 0 Polydrug users	M = not reported MDMA users M = not reported Polydrug users
Fox, Toplis et al. (2001)	M = 811.5 (SD = 981.8) Long-term MDMA users M = 223.9 (SD = 387.3) Short-term MDMA users M = 0.6 ± 0.9 Polydrug users	M = 10,306.8 (SD = 22,119.5) Long-term MDMA users M = 1617.3 (SD = 2898.4) Short-term MDMA users M = 447.3 (SD= 629.2) Polydrug users
Gouzoulis-Mayfrank et al. (2000)	M = 93.4 (SD = 119.9) MDMA users M = 0 Cannabis-only users M = 0 non-drug users	M = 650 (SD = 635) avg daily dose mg MDMA users M = 724 (SD = 608) avg daily dose mg Cannabis-only users M = 0 non-drug users
Halpern et al. (2004)	M = not reported MDMA users M = not reported non-drug users	M = not reported MDMA users M = not reported non-drug users
Krystal et al. (1992)	M = 133.8 (SD = 101.3) MDMA users	M = not reported MDMA users
Lamers et al. (2006)	M = not reported MDMA users M = 0 Cannabis-only users M = 0 non-drug users	M = 932.4 (SD = 873) MDMA users M = 1581.6 (SD = 1432.5) Cannabis-only users M = 1.2 (SD = 2.1) non-drug

Table 3 continued

Investigation	MDMA Use	Cannabis Use
McCann et al. (1999)	M = 215 (SD = 33) MDMA users M = 0 non-drug users	M = not reported MDMA users M = not reported non-drug users
McCardle et al. (2004)	M = 30 MDMA users M = 0 non-drug users	M = smoke occasionally; not specifically reported MDMA users M = 0 non-drug users
Morgan (1999)	M = not reported MDMA users M = 0 Polydrug users M = 0 non-drug users	M = 13.74 (SD = 11.6) joints consumed per week MDMA users M = 9.28 (SD = 11.5) joints consumed per week Polydrug users M = 0 non-drug users
Montgomery, Fisk, & Newcombe (2005)	M = 315.30 (SD = 330.10) MDMA users M = 0 non-drug users	M = 2,128.71 (SD = 2,401.96) MDMA users M = 1,082.54 (SD = 1,439.33) non-drug users
Parrott & Lasky (1998)	M = not reported MDMA users M = not reported Non-drug users	M = not reported MDMA users M = not reported Non-drug users
Quednow et al. (2006)	M = 457.9 (SD = 433.9) MDMA users M = 6.7 (SD = 24) Cannabis-only users	M = 547.1 (SD = 502.7) MDMA users M = 1033.4 (SD = 1348.6) Cannabis-only users
Reneman et al. (2001)	M = 485 (SD = 598) Current MDMA users M = 268 (SD = 614) Ex-MDMA users M = 0 non-drug users	M = 326.9 (SD = 514.9) joints in past year Current MDMA users M = 456.7 (SD = 881.9) joints in past year Ex-MDMA users M = 15.3 (SD = 16) joints in past year non-drug users
Rodgers (2000)	M = 20 times (over a 5-yr period) MDMA users M = 0 Cannabis-only users M = 0 non-drug users	M = 4 days per week (over a 10-yr period) MDMA users M = 4 days per week (over a 11-yr period) Cannabis-only users M = 0 non-drug users
Semple et al. (1999)	M = 672 (SD = 647) M = 0 Polydrug users	M = not reported MDMA users M = not reported Polydrug users
Simon & Mattick (2002)	M = 258 (SD = 574) MDMA users M = 5 Cannabis-only users	M = 67.9 joints per month MDMA users M = 62.6 joints per month Cannabis-only users
Thomasius et al. (2003)	M = 1,033.77 (SD = 1702.44) Current Male users M = 600.42 (SD = 565.28) Current Female users M= 987.31 (SD = 824.50) Ex-Male users M = 533.80 (SD = 317.22) Ex-Female users	M = 566.78 (SD = 1187.98) Current MDMA users M = 2132.91 (SD = 2199.77) Ex-MDMA Users M = 1247.66 (SD = 1290.57) Polydrug Users

Table 3 continued

Investigation	MDMA Use	Cannabis Use
Verkes et al. (2000)	M = 741 Heavy MDMA users M = 169 Moderate MDMA users M = 0 non-drug users	M = 1,850 Heavy MDMA users M = 1,890 Moderate MDMA users M = 0 non-drug users
Yip & Lee (2005)	M = 35.84 (SD =13.21) Ex-MDMA users M = 0 non-drug users	M = 0 Ex-MDMA users M = 0 non-drug users
Zakzanis & Young (2001)	M = 19 MDMA users (at baseline) M = 55 MDMA users (at follow-up)	M = 14% of MDMA users reported cannabis use (at baseline) M = 15% of MDMA users reported cannabis use (at follow-up)

Table 6   Patterns of drug use by drug in the drug user groups and the control group (means and standard deviations)

Ecstasy

Group	Age of Onset	# of Yrs Used	Time Since Last Use	Total # of Times Used	# of Times Used a Week	# of Times Used a Month	Avg # of Pills Taken in an Episode	Lrgest # of Pills Taken in an Episode
C	0	0	0	0	0	0	0	0
M_L	0	0	0	0	0	0	0	0
M_H	0	0	0	0	0	0	0	0
E+ M_L	18.1 (1.4)	2.6 (2.1)	34.5 (61.8)	30.3 (71.4)	0.1 (0.5)	0.7 (2.1)	1.6 (0.7)	2.2 (1.5)
E+ M_H	18.8 (1.7)	2.1 (2.0)	14.3 (11.0)	33.4 (43.2)	0.3 (1.2)	1.6 (4.6)	1.9 (1.0)	3.5 (2.4)

Marijuana

Group	% of Users in Each Group	Age of Onset	# of Yrs Used	Time Since Last Use	Total # of Times Used	# of Times Used a Week	# of Times Used a Month
C	0	0	0	0	0	0	0
M_L	100%	16.1 (2.6)	3.3 (2.5)	1.9 (1.8)	242.9 (564.6)	1.3 (0.9)	5.2 (3.6)
M_H	100%	15.6 (2.1)	4.3 (2.9)	0.3 (0.5)	2241.2 (4261.6)	12.5 (13.6)	49.9 (54.3)
E+ M_L	100%	16.0 (2.0)	4.4 (2.8)	1.4 (2.3)	509.5 (437.3)	2.0 (1.3)	8.3 (5.0)
E+ M_H	100%	15.3 (2.4)	6.1 (3.0)	0.3 (0.4)	3178.9 (3700.1)	16.8 (15.9)	65.2 (55.9)

Cocaine

Group	% of Users in Each Group	Age of Onset	# of Yrs Used	Time Since Last Use	Total # of Times Used	# of Times Used a Week	# of Times Used a Month
C	0	0	0	0	0	0	0
M_L	14%	18.3 (2.1)	1.5 (1.3)	96.3 (44.4)	1.0 (0.0)	0.0 (0.0)	0.0 (0.0)
M_H	50%	17.8 (1.3)	0.8 (0.9)	43.6 (43.9)	3.8 (2.9)	0.0 (0.0)	0.5 (1.2)
E+ M_L	40%	18.3 (2.5)	2.0 (1.6)	15.8 (27.7)	6.8 (3.1)	0.0 (0.1)	0.0 (0.0)
E+ M_H	68%	19.0 (2.0)	1.7 (1.6)	43.4 (72.9)	7.2 (2.9)	0.0 (0.0)	0.2 (0.4)

Table 6 continued

Methamphetamine/Amphetamine

Group	% of Users in Each Group	Age of Onset	# of Yrs Used	Time Since Last Use	Total # of Times Used	# of Times Used a Week	# of Times Used a Month
C	0	0	0	0	0	0	0
M_L	11%	17.3 (2.5)	1.3 (1.5)	93.7 (54.0)	1.0 (0.0)	0.0 (0.0)	0.0 (0.0)
M_H	5%	15	3	108	10	0	0
E+ M_L	20%	19.0 (3.0)	2.0 (1.0)	89.3 (57.9)	1.3 (0.6)	0.0 (0.0)	0.0 (0.0)
E+ M_H	21%	19.5 (4.0)	1.2 (0.9)	139.0 (83.4)	6.8 (2.2)	0.0 (0.0)	0.0 (0.0)

Mushrooms

Group	% of Users in Each Group	Age of Onset	# of Yrs Used	Time Since Last Use	Total # of Times Used	# of Times Used a Week	# of Times Used a Month
C	0	0	0	0	0	0	0
M_L	25%	17.1 (2.3)	2.5 (2.0)	81.9 (135.7)	6.9 (5.5)	0.0 (0.1)	0.1 (0.4)
M_H	41%	18.6 (1.9)	1.1 (1.2)	33.8 (42.5)	3.3 (3.5)	0.0 (0.0)	0.0 (0.0)
E+ M_L	53%	18.0 (0.9)	2.6 (1.8)	70.0 (60.9)	5.1 (3.0)	0.0 (0.0)	0.0 (0.0)
E+ M_H	79%	18.5 (2.9)	1.9 (2.0)	87.5 (105.6)	4.7 (3.1)	0.0 (0.0)	0.0 (0.0)

LSD

Group	% of Users in Each Group	Age of Onset	# of Yrs Used	Time Since Last Use	Total # of Times Used	# of Times Used a Week	# of Times Used a Month
C	0	0	0	0	0	0	0
M_L	0	0	0	0	0	0	0
M_H	5%	17	1	16	4	0	0
E+ M_L	7%	18	4	208	1	0	0
E+ M_H	37%	19.9 (4.1)	0.7 (0.4)	133.9 (153.3)	4.6 (4.0)	0.0 (0.0)	0.3 (0.5)

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Table 6 continued

Solvents

Group	% of Users in Each Group	Age of Onset	# of Yrs Used	Time Since Last Use	Total # of Times Used	# of Times Used a Week	# of Times Used a Month
C	0	0	0	0	0	0	0
M_L	14%	17.8 (3.3)	1.6 (2.9)	98.5 (69.5)	1.5 (1.0)	0.0 (0.0)	0.0 (0.0)
M_H	18%	17.0 (2.6)	2.3 (2.1)	72.5 (40.1)	5.5 (4.2)	0.0 (0.0)	0.0 (0.0)
$E+ M_L$	13%	18.0 (0.0)	2.0 (2.8)	55.0 (69.3)	2.0 (1.4)	0.0 (0.0)	0.0 (0.0)
$E+ M_H$	32%	18.0 (2.1)	1.5 (1.6)	104.8 (156.1)	3.0 (1.5)	0.0 (0.0)	0.0 (0.0)

Heroin

Group	% of Users in Each Group	Age of Onset	# of Yrs Used	Time Since Last Use	Total # of Times Used	# of Times Used a Week	# of Times Used a Month
C	0	0	0	0	0	0	0
M_L	0	0	0	0	0	0	0
M_H	0	0	0	0	0	0	0
$E+ M_L$	7%	19	3	104	10	0	0
$E+ M_H$	5%	19	0	1	1	0	0

Hydrocodone

Group	% of Users in Each Group	Age of Onset	# of Yrs Used	Time Since Last Use	Total # of Times Used	# of Times Used a Week	# of Times Used a Month
C	0	0	0	0	0	0	0
M_L	25%	17.0 (2.1)	2.3 (2.0)	91.9 (74.2)	5.4 (5.2)	0.0 (0.0)	0.1 (0.4)
M_H	50%	17.8 (1.1)	2.0 (1.7)	33.2 (50.7)	12.8 (8.0)	0.0 (0.0)	0.3 (0.5)
$E+ M_L$	60%	17.2 (1.9)	3.2 (1.4)	94.3 (101.4)	7.8 (8.4)	0.0 (0.0)	0.3 (0.5)
$E+ M_H$	68%	18.0 (1.6)	4.2 (6.1)	69.4 (99.3)	7.9 (5.7)	0.0 (0.0)	0.2 (0.6)

Table 6 continued

Muscle Relaxers

Group	% of Users in Each Group	Age of Onset	# of Yrs Used	Time Since Last Use	Total # of Times Used	# of Times Used a Week	# of Times Used a Month
C	0	0	0	0	0	0	0
M_L	7%	16.5 (0.7)	3.5 (0.7)	130.0 (36.8)	6.5 (4.9)	0.0 (0.0)	0.0 (0.0)
M_H	5%	18	1	4	10	0	1
E+ M_L	13%	18.0 (0.0)	1.0 (0.0)	10.5 (13.4)	3.0 (1.4)	0.0 (0.0)	0.0 (0.0)
E+ M_H	21%	18.0 (1.4)	1.8 (1.8)	51.0 (37.7)	8.3 (3.5)	0.0 (0.0)	0.0 (0.0)

Xanax

Group	% of Users in Each Group	Age of Onset	# of Yrs Used	Time Since Last Use	Total # of Times Used	# of Times Used a Week	# of Times Used a Month
C	0	0	0	0	0	0	0
M_L	11%	16.7 (0.6)	2.7 (1.5)	95.3 (65.4)	2.7 (2.1)	0.0 (0.0)	0.0 (0.0)
M_H	27%	17.7 (1.6)	1.5 (0.8)	39.0 (50.6)	13.7 (8.9)	0.0 (0.0)	0.2 (0.4)
E+ M_L	20%	17.7 (2.1)	1.7 (2.1)	156.0 (52.0)	2.7 (2.1)	0.0 (0.0)	0.0 (0.0)
E+ M_H	32%	18.8 (1.0)	2.0 (1.3)	92.8 (121.4)	9.5 (6.2)	0.0 (0.0)	0.2 (0.4)

Percocet

Group	% of Users in Each Group	Age of Onset	# of Yrs Used	Time Since Last Use	Total # of Times Used	# of Times Used a Week	# of Times Used a Month
C	0	0	0	0	0	0	0
M_L	11%	17.0 (1.0)	3.3 (0.6)	69.7 (59.5)	1.3 (0.6)	0.0 (0.0)	0.0 (0.0)
M_H	23%	18.0 (1.9)	1.8 (2.5)	30.2 (32.9)	8.2 (8.7)	0.0 (0.0)	0.0 (0.0)
E+ M_L	0	0	0	0	0	0	0
E+ M_H	37%	17.9 (1.8)	5.2 (8.3)	93.0 (141.1)	6.1 (3.0)	0.0 (0.0)	0.0 (0.0)

Table 6 continued

Valium

Group	% of Users in Each Group	Age of Onset	# of Yrs Used	Time Since Last Use	Total # of Times Used	# of Times Used a Week	# of Times Used a Month
C	0	0	0	0	0	0	0
M_L	4%	16	4	104	5	0	0
M_H	9%	16.0 (0.0)	1.0 (1.4)	79.5 (108.2)	6.0 (5.7)	0.0 (0.0)	0.0 (0.0)
E+ M_L	7%	17	4	208	5	0	0
E+ M_H	11%	18.0 (1.4)	2.5 (0.7)	87.0 (89.1)	7.5 (3.5)	0.0 (0.0)	0.0 (0.0)

Ritalin/Adderall

Group	% of Users in Each Group	Age of Onset	# of Yrs Used	Time Since Last Use	Total # of Times Used	# of Times Used a Week	# of Times Used a Month
C	0	0	0	0	0	0	0
M_L	0	0	0	0	0	0	0
M_H	5%	16	2	108	4	0	0
E+ M_L	13%	19.0 (1.4)	0.5 (0.7)	114.0 (132.9)	1.0 (0.0)	0.0 (0.0)	0.0 (0.0)
E+ M_H	26%	19.0 (1.7)	0.2 (0.4)	78.2 (97.0)	5.0 (8.5)	0.0 (0.0)	0.4 (0.9)

Ambien/Lunesta

Group	% of Users in Each Group	Age of Onset	# of Yrs Used	Time Since Last Use	Total # of Times Used	# of Times Used a Week	# of Times Used a Month
C	0	0	0	0	0	0	0
M_L	0	0	0	0	0	0	0
M_H	5%	18	0	52	2	0	0
E+ M_L	0	0	0	0	0	0	0
E+ M_H	0	0	0	0	0	0	0

Morphine

Group	% of Users in Each Group	Age of Onset	# of Yrs Used	Time Since Last Use	Total # of Times Used	# of Times Used a Week	# of Times Used a Month
C	0	0	0	0	0	0	0
M_L	0	0	0	0	0	0	0
M_H	0	0	0	0	0	0	0
E+ M_L	0	0	0	0	0	0	0
E+ M_H	11%	20.0 (1.4)	0.5 (0.7)	14.0 (15.6)	4.5 (4.9)	0.0 (0.0)	0.0 (0.0)

Table 6 continued

Methadone

Group	% of Users in Each Group	Age of Onset	# of Yrs Used	Time Since Last Use	Total # of Times Used	# of Times Used a Week	# of Times Used a Month
C	0	0	0	0	0	0	0
M_L	0	0	0	0	0	0	0
M_H	0	0	0	0	0	0	0
E+ M_L	0	0	0	0	0	0	0
E+ M_H	5%	21	1	52	6	0	0

Demerol

Group	% of Users in Each Group	Age of Onset	# of Yrs Used	Time Since Last Use	Total # of Times Used	# of Times Used a Week	# of Times Used a Month
C	0	0	0	0	0	0	0
M_L	0	0	0	0	0	0	0
M_H	0	0	0	0	0	0	0
E+ M_L	0	0	0	0	0	0	0
E+ M_H	5%	22	1	3	5	0	1

Alcohol

Group	% of Users in Each Group	Age of Onset	# of Yrs Used	Time Since Last Use	# of Times Used a Week	# of Times Used a Month
C	84%	16.9 (2.3)	3.2 (3.7)	21.9 (39.9)	1.2 (2.3)	4.7 (8.9)
M_L	84%	15.3 (2.1)	4.5 (2.9)	1.8 (2.7)	4.3 (4.3)	18.0 (19.5)
M_H	91%	15.7 (2.2)	4.5 (2.5)	2.8 (6.9)	4.3 (3.7)	17.3 (14.4)
E+ M_L	100%	15.9 (1.3)	4.6 (2.7)	29.8 (107.0)	4.3 (3.3)	17.6 (13.0)
E+ M_H	100%	15.1 (2.2)	6.1 (3.4)	1.6 (2.4)	6.2 (6.2)	24.6 (21.0)

Nicotine

Group	% of Users in Each Group	Age of Onset	# of Yrs Used	Time Since Last Use	# of Times Used a Week	# of Times Used a Month
C	12%	15.7 (1.5)	3.7 (4.0)	89.3 (105.1)	0.7 (1.2)	3.3 (5.8)
M_L	61%	15.4 (2.8)	3.6 (3.2)	45.4 (120.0)	22.9 (44.8)	94.8 (185.9)
M_H	50%	16.0 (1.9)	3.4 (1.7)	9.6 (20.9)	15.7 (20.7)	132.5 (252.0)
E+ M_L	60%	15.8 (1.9)	5.2 (3.2)	0.4 (1.3)	26.2 (22.2)	104.7 (89.0)
E+ M_H	84%	16.1 (2.1)	5.3 (3.6)	34.4 (129.6)	52.5 (57.6)	212.5 (234.6)

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APPENDIX II

DRUG USE HISTORY QUESTIONNAIRE

Instructions

Part I: Demographic and Health Information

Now we will complete the drug use history questionnaire. The questionnaire is divided into two parts. For the first part, I will ask you to provide me with basic demographic and health information. There are 11 questions for this portion. For some of the questions, if you answer yes, you will be asked to provide additional information. For the last item on this portion of the questionnaire, I will ask you if you're currently taking any prescribed medications. Please report only those medications that a doctor has specifically prescribed to you and you are taking in the recommended manner. I will ask you to report illicit prescription drug use in the second portion of the drug use questionnaire.

Part II: Drug Use Inventory

In the second portion of the questionnaire, I will ask you to report your drug use history for a variety of drugs. For each drug that you have taken, I will ask you: at what age did you begin using the drug, how many times have you used in your lifetime, weekly and monthly usage, and time since last use. Specific to ecstasy, I will also ask you how many pills you take on average per drug episode and what was the largest number of

pills you ever used in an episode. On the last item on this portion of the questionnaire, I will ask you if you have ever illicitly used prescription drugs. Illicit prescription drug use refers to taking a medication that was not specifically prescribed to you and/or taking a medication that was prescribed to you, but not in the manner it was prescribed (e.g., taking more than was prescribed).

Demographic and Health Information

1. Age　　　　　　　　　　　　　　_____

2. Gender　　　　　　　　　　　　_____

3. Years of Education　　　　　　　_____

4. Do you have a history of head
   injury with loss of consciousness
   requiring hospitalization?　　　　_____

5. Do you have a past or present
   history of medical illness?

   If yes, please explain.　　　　　_____

6. Have you ever been diagnosed
   with a major psychiatric disorder?
   If yes, please explain.　　　　　_____

7. Have you ever been diagnosed
   with a learning disorder? If yes,
   please explain.　　　　　　　　_____

8. Is your health good?　　　　　　_____

9. Are you currently taking any prescribed medications?　　_____

Drug Use Inventory

Drug	Age of Onset	# of Yrs Used	Time Since Last Use	Total # of Times Used	# of Times Used a Week	# of Times Used a Month	Average # of Pills Taken in an Episode	Largest # of Pills Taken in an Episode
Ecstasy								
Marijuana								
Cocaine								
Methamphetamine/ Amphetamine								
LSD								
Mushrooms								
Heroin								
Solvents								
Alcohol								
Nicotine								
Prescription Drugs								
Prescription Drugs								
Prescription Drugs								
Prescription Drugs								

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Dissertation Title: The Effect of Concomitant Ecstasy-Marijuana Use on Auditory Verbal
Learning and Memory Performance

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