The Nature of Memory Impairment in Recreational MDMA-Users: Enduring encoding dysfunction in current and two-year abstinent MDMA-users

Kate Hall

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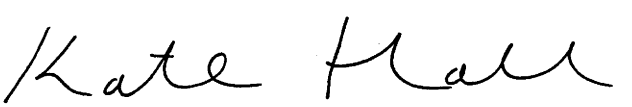
I hereby certify that the work embodied in this thesis is the result of original research and contains acknowledgement of all non-original work.



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ABSTRACT

The popular recreational drug MDMA or 'Ecstasy' is a selective serotonin neurotoxin in non-human primates, and has been demonstrated to specifically affect the hippocampus and neocortex, brain regions involved in memory and general cognitive functioning. The enduring nature of this neurotoxicity has been demonstrated in studies of non-human primates 7 years after administration of MDMA. Neuroimaging, neuroendocrine and CSF serotonin metabolite studies have demonstrated that similar patterns of neurotoxicity may occur in recreational users of MDMA. Memory dysfunction has been identified as a functional consequence of MDMA-induced neurotoxicity in recreational users of the drug. The study of memory dysfunction in recreational MDMA-users to date has failed to present a revealing clinical picture of the nature of memory impairment. Furthermore, these studies have failed to adequately control for the potentially confounding influence of other factors known to affect memory and cognitive functioning, such as anxiety and depression. Therefore, the first of the two studies conducted sought to determine whether memory impairment occurred as a result of encoding, storage or retrieval dysfunction, while controlling for the effects of potential confounding variables. Thirty-one current recreational MDMA-users were compared to 30 controls in terms of their memory performance on the Wechsler Memory Scale-Third Edition (WMS-III). MDMA-users demonstrated significant impairment in immediate and delayed memory when compared to controls and the nature of memory impairment was consistent with dysfunction in encoding processes. The second study sought to determine if this pattern of memory impairment was enduring. Thirty two-year abstinent MDMA-users were compared with 30 controls for memory performance on the WMS-III. Abstinent users demonstrated significant

impairment in immediate, delayed and working memory and manifested impairment that was also consistent with encoding dysfunction. A more pervasive pattern of memory impairment was evident in abstinent MDMA-users when compared to controls, than was evident in the cohort of current MDMA-users. In comparison to the current MDMA-users, the abstinent cohort reported a very high frequency of use and the more pervasive impairment evident in this group may be due to this factor. The results suggest that recreational MDMA-users are at risk for incurring enduring memory impairment and encoding dysfunction. The cognitive implications of frequent regimens of MDMA use and the replication of encoding dysfunction in other cohorts of recreational users are highlighted as important areas for future research.

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CHAPTER 1

MDMA-Induced Memory Impairment: The functional implications of the selective serotonergic neurotoxicity of MDMA

1.1 THE PHARMACOLOGY AND RECREATIONAL USE OF MDMA

1.1.1 The Chemical Composition of MDMA

MDMA is the accepted abbreviation for the ring-substituted amphetamine 3,4-methylendioxymethamphetamine, a commonly used recreational drug of abuse. Chemically, MDMA can be designated as N-methyl-1(3,4-methylenedioxyphenyl)-2-aminopropane and structurally, it is related to the psychomotor stimulant amphetamine and the hallucinogen mescaline (Steele, McCann & Ricaurte, 1994). It is a member of a group of drugs (amphetamines and derivatives) which include amphetamine ('speed'), methamphetamine, ('speed' or 'ICE'), para-methoxyamphetamine (PMA), and methylenedioxyamphetamine (MDA). The reactions of humans to this class of drugs range from stimulant effects with little or no hallucinogenic properties to LSD-like hallucinogenic effects (White, Irvine & Bochner, 1996). It has been proposed that the psychoactive effects of MDMA are unique and distinct from other hallucinogenic amphetamine analogues, leading some researchers to suggest that it represents a new class of drugs, for which the name 'entactogens' has been conceived (Nichols & Oberlender, 1990).

1.1.2 Acute Changes in Monoamine Concentrations Following MDMA Use

In vitro studies indicate that MDMA evokes the release of brain monoamines and inhibits their re-uptake inactivation. MDMA influences dopamine and noradrenaline, however, its serotonergic effects appear to be the more prominent (Steele et al., 1994). MDMA induces an acute release of serotonin and dopamine. This acute release then leads to depletion of intraneural serotonin stores (Sprague, Everman & Nichols, 1998). The change in serotonin concentrations following administration of MDMA is thought to be due to alterations in the synthesis, uptake and release of serotonin (Schmidt & Taylor, 1990). Although it is difficult to identify the specific behavioural consequences of these alterations in monoamine concentrations, it has been proposed that a sudden increase in dopamine may be related to feelings of euphoria and increased sociability, energy and activity. Serotonin is thought to be involved in the inhibition of both behaviour and emotions (Zuckerman, 1984).

1.1.3 Duration of Acute and Residual Effects of MDMA

A pharmacokinetic study of MDMA in humans found that the half-life of the drug was 7.6 hours with peak plasma concentration (mean = 105.6ng/ml) occurring after 2 hours (White et al., 1996). In Solowij, Hall & Lee's (1992) survey of 'Ecstasy' users in Sydney, Australia, the effects of one dose or tablet of MDMA were reported to last anywhere between 1 and 12 hours. The acute effects of the drug were more commonly reported to endure for 3 to 6 hours, depending on the individual and the dose taken, with the effects first noted within half an hour following administration. In an additional half hour to an hour, a plateau of effects was reported to occur and symptoms of intoxication largely dissipated in an additional two hours except for mild residual stimulation (White et al., 1996; Shulgin, 1990).

1.1.4 Modes of Administration in the Recreational Use of MDMA

The Solowij et al. (1992) study of recreational users in Sydney found that MDMA was most frequently taken in tablet form, however, it is also reportedly available in capsule and powdered forms. In Australia it is generally accepted that a tablet of 'Ecstasy' contains between 60-150mg of MDMA (White et al., 1996; Solowij et al., 1992; Boot, McGregor & Hall, 2000). Solowij et al. (1992) found that, among their sample, 'Ecstasy' was ingested orally 98 percent of the time, however, snorting, injecting and suppositories were also reported as modes of administration by a small proportion of users. In a more recent study of 'Ecstasy' users sampled from three major Australian capital cities, 99 percent of the sample had swallowed 'Ecstasy', 30 percent had snorted the drug, 16 percent of the sample had injected the drug and 12 percent had smoked the drug mixed with cannabis (Topp, Hando, Dillon, Roche & Solowij, 1999).

Different modes of administration have been reported to result in different experiences with the drug (Topp et al., 1999). Injecting is described as having the quickest onset and producing a more intense but shorter lasting experience. Snorting is identified as acting more quickly than an oral dose, but lasting for a shorter period of time, while a suppository produces a slow onset but a more intense and prolonged experience (Solowij et al., 1992).

1.1.5 Patterns of Recreational Use of MDMA

Although MDMA was initially patented as an appetite suppressant, it was used therapeutically in the United States as an adjunct to psychotherapy in the late 1970's (Steele et al., 1994). The emotional effects of MDMA, including an increased sense of intimacy and heightened communication skills, contribute to its role as a facilitator for

interpersonal relationships, making it an attractive adjunct to psychotherapy. Despite interest in its therapeutic potential, MDMA was placed on schedule 1 of controlled substances in the United States in 1985 as a result of increasing recreational usage and animal studies demonstrating toxic effects of the drug and its potential for abuse (Steele et al., 1994).

Studies of recreational use of 'Ecstasy' throughout Europe, America and Australia have established that MDMA is commonly used within dance party or 'rave' settings in addition to amphetamine and LSD (Lenton, Boys & Norcross, 1997; Forsyth, 1996; Gerra, Zaimovic, Giucastro, Maestri et al., 1998; Steele et al., 1994). The rave scene reportedly began in the United Kingdom in the late eighties and has evolved from underground dance parties held in secret venues to more mainstream dance events held in licensed clubs (Lenton et al., 1997). Accordingly, it has been noted that 'Ecstasy' use in some groups in Australia has become increasingly mainstream (Lenton et al., 1997). In a survey of 'Ecstasy' users living in the metropolitan regions of three Australian capital cities, Topp et al. (1999) found that users were typically young adults who were relatively well educated and who were generally employed or students. In a survey exploring the patterns of MDMA use in Sydney in the early 1990's, 'Ecstasy' users reported that dance parties were the most popular venues for taking MDMA, followed by private parties and nightclubs (Solowij et al., 1992). Similar patterns of use have been noted in Perth (Boys, Lenton & Norcross, 1997) and Glasgow in the mid 1990's (Forsyth, 1996). In accordance with this pattern of use, the most popular time for taking 'Ecstasy' was found to be on weekends, usually in the late evenings, and preferably when the user was not working the following day (Solowij et al., 1992).

The frequency of 'Ecstasy' use is highly variable. However, a survey of Australian users in the late 1990's found that 'Ecstasy' was used on average every 10 days in the preceding 6 months (Topp et al., 1999). Over a third of the sample had taken 'Ecstasy' between 1 and 6 days in the preceding 6 months, a further third had used between 7 and 12 days, 19 percent had used between 13 and 24 days, and 12 percent had used 'Ecstasy' on more than 24 days in the preceding 6 months. An earlier survey of Sydney users found that one third of the sample used MDMA somewhere between once a month to once every 3 months (Solowij et al., 1992). Approximately one quarter of the sample used 'Ecstasy' more frequently and roughly 18% used only on special occasions. The authors reported that patterns of use appear to be affected by the drug's availability, personal preferences and the social climate. Similar patterns of use have been documented by researchers from Europe and America, where it has been reported that individuals generally use MDMA once or twice a month, although more frequent use of the drug is sometimes reported (Steele et al., 1994).

A distinctive feature of drug use amongst both the dance and rave scene is polydrug use. A survey of rave goers in Western Australia reported that a significant proportion of respondents used more than one 'dance drug' concurrently (Boys et al., 1997). Similar patterns of use among MDMA-users have been documented in other Australian capital cities (Topp et al., 1999; Solowij et al., 1992) and in Europe (Forsyth, 1996; Boys et al., 1997; Williamson, Gossop, Powis, Griffiths et al., 1997). In these studies, the term 'dance drug' is used to describe 'Ecstasy', LSD and amphetamines, however, concurrent use of nitrous oxide, amyl nitrate, cocaine and methylenedioxyamphetamine (MDA) has also been documented. Topp et al. (1999) identified that polydrug use was the norm among their sample of Australian MDMA-users with 93 percent using other drugs in combination with 'Ecstasy' at least two-thirds of the time. The drugs typically

used in conjunction with 'Ecstasy' include tobacco, cannabis, amphetamine, alcohol, amyl nitrate and nitrous oxide. Mixing MDMA with other 'dance drugs' such as amphetamine was reported to increase stamina for dancing. Drinking alcohol, smoking cannabis and taking benzodiazepines after MDMA is also commonly reported in the 'coming down' phase to help induce relaxation and sleep (Topp et al., 1999; Boys et al., 1997). On the basis of these patterns of polydrug use, Topp et al. (1999) concluded that 'Ecstasy' users are adept at obtaining drugs to self medicate the adverse physical and psychological effects of MDMA and other drug use.

The use of multiple doses of 'Ecstasy' or 'binges' are also commonly reported among MDMA-users. Over half of the 'Ecstasy' users sampled in Sydney ingested more than one dose of MDMA on the one occasion (Solowij et al., 1992) and the use of 'booster' doses to prolong the effects of the drug are commonly reported in other studies (White et al., 1996; Beck & Rosenbaum, 1994). Topp et al. (1999) reported that more than one-third of their sample had 'binged' on 'Ecstasy' in the preceding 6 months, which was defined as using the drug on a continuous basis without sleep for 48 hours or more. Subjective reports indicate that larger doses of MDMA change the nature and intensity of its effects, in that the stimulant properties and negative side effects appear to be highlighted (Green, Cross & Goodwin, 1995).

Of particular interest to Australian patterns of MDMA use is an observation made by Topp et al. (1999) who noted differences in the features of MDMA use in their sample collected from three Australian capital cities in the late 1990's when compared to the Solowij et al. (1992) study, conducted in Sydney in 1990. While acknowledging that comparing two cross-sectional surveys is problematic, Topp et al. (1999) ascertained that their more recent sample reported increased quantity and frequency of MDMA use,

greater levels of concurrent polydrug use and a wider range of contexts of use. If this is the case, it is evident that the use of MDMA is spreading beyond the rave scene and that Australian MDMA-users are progressively placing themselves at a greater risk for harm associated with high dose regimens and the unknown effects of concomitant polydrug use.

1.2 SHORT-TERM SEQUELAE OF RECREATIONAL MDMA USE

The short-term physical, emotional, and cognitive sequelae of recreational MDMA-use have been studied from varying professional perspectives and are reviewed in the following section. The survey of recreational MDMA-users in Australia and overseas has examined the subjective experience of MDMA use. The acute and residual, psychological and physical effects of MDMA, commonly reported by recreational users, are discussed in the following review of the literature. Objective examinations of the cognitive and emotional effects of MDMA have also been conducted, and these are examined subsequently. Finally, the clinical investigation of cases of adverse physical reactions to MDMA and psychopathological sequelae associated with its use are reviewed. The long-term consequences of MDMA-use are discussed in later sections.

1.2.1 Self-Reported Short-Term Effects of Recreational MDMA Use

The unique psychoactive effects of MDMA have been described as an elevated mood state encompassing feelings of euphoria, intimacy and closeness to other people, which are experienced in conjunction with additional stimulant and hallucinogenic effects (White et al., 1996). The acute stimulant effects of MDMA include increased alertness and energy, talkativeness, increased heart rate, increased blood pressure, dry mouth, decreased appetite, and jaw clenching (Steele et al., 1994; Peroutka, 1990). Although some hallucinogenic properties of MDMA are reported, unlike LSD, they are described as mild changes in perception without significant distortions of consciousness or

disorientation. Sensory disruption and loss of contact with reality have not been commonly reported with MDMA (Peroutka, 1990). The acute effects of MDMA reported in surveys are listed in Table 1.1.

Table 1.1: Reported Acute Effects of MDMA

Positive Acute Effects Reported	**Negative Acute Effects Reported**
Elevated mood	Loss of appetite
Euphoria	Jaw clenching / tension and grinding of teeth
Increased physical and emotional energy	Nausea
Heightened sensual awareness	Ataxia or transient gait disturbance
Increased self-esteem and confidence	Tremors and motor restlessness
Increased sense of intimacy	Dry mouth
Heightened sensuality	Tachycardia
Enhanced communication skills	Insomnia
Facilitator for interpersonal relations	Hot and cold flushes
Increased sensual properties of sex	Increased sweating and sweaty palms
Lowered inhibitions	Poor concentration
	Nystagmus
	Blurred vision
	Panic and Paranoia
	Dehydration
	Increased skin sensitivity / touch sensitivity
	Reduced urine flow

The residual effects of MDMA persist for up to 24 hours after acute intoxication wears off and include drowsiness, a continuing sense of 'closeness' to others, tight jaw muscles, depression, difficulty concentrating, muscle aches, and fatigue (Steele et al., 1994; Gerra et al., 1998; Curran & Travill, 1997; Topp et al., 1998). The residual effects reported in surveys of recreational MDMA-users are listed in Table 1.2. Some residual psychological effects have been reported to last up to 5 days including mood

disturbance and deficits in concentration and attention (Curran & Travill, 1997) and these will be discussed in greater detail in the following section.

Table 1.2: Reported Residual Effects of MDMA

Psychological Residual Effects	Physical Residual Effects
Irritability	Energy loss / lethargy
Insomnia	Muscular aches
Confusion	Hot / cold flushes
Anxiety	Blurred vision
Paranoia	Numbness / tingling
Depression	Profuse sweating
Hallucinations	Dizziness
Panic attacks	Tremors
Poor Concentration	Headaches
Increased aggressive behaviour	Stomach pain
	Dental problems from jaw grinding

1.2.2 Psychometric Assessment of the Acute and Residual Sequelae of Recreational MDMA Use

The short-term psychological consequences of recreational MDMA use have been investigated by studies examining cognitive and emotional sequelae in the week following self-administration of MDMA. In their study of the acute and residual effects of MDMA on both mood and cognition, Curran and Travill (1997) compared MDMA-users with alcohol using controls over three days on measures of working memory, depression, and immediate and short-term memory. The first day of testing was carried out in a dance club setting whilst each of the participants was under the influence of either alcohol or MDMA. Subjects were then assessed the following day (Day 2) and mid-week (Day 5). The authors assessed subjects' mood with both the Beck Depression Inventory (BDI) and a mood rating scale. Working memory was assessed via a serial sevens task and both immediate and short-term memory were assessed using an

immediate and delayed prose recall task. The researchers reported that participants had refrained from using any illicit substances between Days 1 and 5. Comparison of the MDMA and alcohol groups revealed deficits in working memory in MDMA-users compared to controls over the three days. MDMA-users made fewer subtractions in the serial sevens task on all three test days, however this difference was more marked on Day 2. The authors noted that there was no significant difference between the two groups in the number of errors made. Although the authors did not interpret their data in this fashion, a plausible clinical interpretation of these results suggests that MDMA-users had slower processing speed than alcohol users, however the accuracy of their responses was not affected. There were no significant differences between the two groups' immediate and short-term memory performance on the prose recall tasks.

In their assessment of depression (BDI), Curran and Travill (1997) found that MDMA-users rated lower depression on Day 1, whilst under the influence of MDMA, when compared to controls who were under the influence of alcohol, but showed similar ratings of depression on the 'hangover' Day 2. While Alcohol users returned to Day 1 baseline levels on Day 5, MDMA-users rated even higher depression, which in some cases reached clinical levels. The higher rating of depression on Day 5 was interpreted as indicative of an MDMA-induced 'mid-week low', which is consistent with self-reported lowered mood in surveys of 'Ecstasy' users (Topp et al., 1999). For the remaining mood measures, the authors described a similar pattern of results, which emerged over the three assessment days, for the two groups. While alcohol users showed a 'U' shape curve over the three days, with participants rating a slightly lower mood on Day 2 compared to 1 and 5, MDMA-users rated progressively lower mood from Days 1 to 5. These findings suggest that the residual effects of MDMA use include elevated depression mid-week, which in some cases reaches clinical levels. The

authors postulate that the lowered mood experienced mid-week after using MDMA on the weekend may be a functional consequence of depleted serotonin levels, following acute elevation of serotonin after administration of MDMA, a pattern observed in the study of the pharmacological effects of MDMA in animals.

Evidence for MDMA's neurotoxic potential, which will be discussed at length in a later section, has been obtained from both animal studies and examinations of serotonin metabolites in cerebrospinal fluid (CSF) and brain imagery studies in humans. Although consequences of long-term neurotoxicity were not examined in the Curran and Travill study, it has been demonstrated that MDMA use results in persistent cognitive and mood disturbance (Steele et al., 1994; Morgan, 1999). The fact that over half of the alcohol using controls in the Curran and Travill study were also recreational MDMA-users is a significant confound, because the presence of enduring cognitive and mood disturbance was a possible feature of both groups. Consequently, the comparison between alcohol users and MDMA-users may not accurately reflect the residual effects of MDMA use. This may have contributed to the researchers' failure to find significant group differences on the prose recall tasks and may have underestimated the residual effects of MDMA on mood and cognition.

Comparative studies with controls without a history of MDMA use are needed to accurately determine the extent of mood and cognitive disturbance in the week following MDMA use. A further criticism of the Curran and Travill (1997) study was the researchers' failure to establish a drug free baseline to control for pre-existing group differences. Parrott and Lasky (1998) addressed these problems in their subsequent study of the residual effects of MDMA on mood and cognition. The performance of regular MDMA-users (over 10 occasions of use) was compared to novice MDMA-users

(less than 10 occasions of use) and controls who had never taken MDMA, on measures of verbal memory, visual scanning and mood. The assessment of mood and cognition was carried out on four separate occasions and a drug free baseline was established to which the acute and residual effects of the drug were compared. The cognitive assessment included a measure of verbal memory involving an auditory word recall task and a visual search task involving the scanning and discrimination of stimuli. Sixteen mood states were also assessed using visual analogue scales rating from 1 to 100, including depression, clear headedness, calmness, energy levels and sadness. At Time 1 the baseline measurement was obtained when participants were drug free and had not used MDMA for a week or other illicit drugs for more than 24 hours. The assessment at Time 2 was carried out at a London nightclub, between 2 and 16 hours after self-administration of MDMA, while participants were under the influence of MDMA and other recreational drugs. The controls, who were also assessed whilst intoxicated, reported being under the influence of alcohol, cannabis and cocaine. Mood and cognitive assessments were then carried out two and seven days after attendance at the nightclub.

Statistical analyses revealed that both novice and regular recreational MDMA-users displayed significantly worse memory scores than controls whilst under the influence of MDMA and at two and seven days after administration of MDMA. At the baseline measurement, regular MDMA-users' performance on the word recall task was worse than both novice users and controls, indicating comparative deficits in verbal memory for regular users whilst drug free, and when free of the residual effects of MDMA. This group difference may reflect the enduring cognitive consequences of long-term MDMA-induced neurotoxicity mentioned earlier. Novice MDMA-users had comparable memory performances to controls at baseline. Whilst intoxicated, both

novice and regular MDMA-users displayed deficits in verbal memory when compared to controls, and two days after self-administration of MDMA, regular users exhibited deficits in verbal memory when compared to both novice users and controls. These deficits continued to be apparent 7 days after self-administration of MDMA for both novice and regular users. The verbal memory deficits evident in MDMA-users, when compared to controls, contradict Curran and Travill's (1997) earlier findings, however, this anomaly may be attributed to the use of MDMA-naïve controls. Indeed the difference between the two groups at baseline measurement of verbal memory in the Parrott and Lasky study indicates memory deficits were apparent independent of the acute or residual effects of MDMA. An examination of comparative deficits in memory performance within each group over the four assessment times would have determined whether the group differences evident in the seven days following self-administration of MDMA reflected residual effects of the drug or simply emulated the baseline variance, however the researchers failed to examine this factor. It is apparent, however, that the memory deficits evident during the acute effects of MDMA, for both novice and regular users, were greater than those manifested at baseline and two and seven days after MDMA use, indicating the presence of significant cognitive difficulties whilst under the acute influence of MDMA. The researchers claim that memory deficits were more pronounced in regular users, suggesting that there might be a dose-response relationship between MDMA use and memory disturbance. However, the researchers failed to take an extensive history of MDMA use from participants and instead arbitrarily classified them as novice or regular users on the basis of whether the self-reported number of 'Ecstasy' tablets taken exceeded ten. It is therefore impossible to conclude that a true dose-response relationship exists from the available data.

Parrott and Lasky (1998) found that participants' performance on the visual search task was similar for all three groups at baseline, however, visual scanning skills of regular MDMA-users were impaired when compared to novice users and controls when under the acute influence of MDMA. Unlike verbal memory, the visual performance of MDMA-users was unimpaired in the seven days following self-administration of MDMA. The assessment of mood over the seven days revealed similar mood for all three groups at baseline and on the Saturday night whilst participants were intoxicated. Group differences became apparent two days after self-administration of MDMA when users of the drug reported significant elevations in a range of negative mood states, including depression, sadness, unsociability, unpleasantness and abnormality. It was noted that while mood fluctuated markedly over the week in MDMA-users, it remained fairly stable over time for the controls.

In summary, through their examination of the acute and residual effects of MDMA upon mood and cognition, Parrott and Lasky (1998) demonstrated that MDMA-users manifested verbal memory impairment when compared to controls, both before and after MDMA administration. Furthermore, visual scanning and verbal memory dysfunction was apparent whilst under the acute influence of MDMA. However, despite the researchers' claim to have examined the acute effects of MDMA on mood and cognition, the wide variation among subjects in the amount of time lapsed between self-administration of MDMA and the assessment, prevents reliable conclusions from being drawn from these data. Indeed, it can be argued that in some cases the delay of up to 16 hours after MDMA administration prevented the researchers from examining acute effects in these participants. Finally, fluctuating mood in the week following self-administration of MDMA was also apparent in MDMA-users when compared to controls.

1.2.3 Systemic Toxic Effects of MDMA Use Associated with Fatality

As the popularity of MDMA has grown, the reported number of adverse medical sequelae associated with MDMA use, such as acute toxicity and even death, have increased. Adverse medical sequelae following administration of MDMA have included: cardiac abnormalities including arhythmias and cardiovascular collapse; rhabdomyolysis; disseminated intravascular coagulation; hypertension; convulsions; liver necrosis; metabolic disturbance; hyperthermia; acute renal failure; and hepatotoxicity (White et al., 1996). A review of the case reports of fatalities in the literature indicates that the pattern of events associated with severe morbidity and fatality after ingestion of MDMA is consistent with malfunction of normal temperature control and water balance (White et al., 1996). However, the illicit source of 'Ecstasy' in these cases has made it difficult to determine whether contaminants play a role in severe morbidity or death (Steele et al., 1994).

1.2.4 Short-Term Psychopathological Sequelae of Recreational MDMA Use

While we are presently unable to fully understand the contribution of MDMA use to the onset of psychiatric disturbances, MDMA has been associated with lasting psychopathological sequelae (Schifano, DiFuria, Forza, Minicuci et al., 1998; McCann & Ricaurte, 1991). In a survey of MDMA using patients presenting at an addiction treatment unit in Italy, over half of the sample was affected by one or more psychopathological problem (Schifano et al., 1998). The most frequently reported problem were depression, psychotic disorders, cognitive disturbances, bulimic episodes, impulse control disorders, panic disorders and social phobia. Although no implication of causality between MDMA use and psychopathology can be made from the survey, the researchers found that psychopathological disturbance was associated with longer-

term and larger dose MDMA users. Similarly, reports of psychological disturbance have been found in non-clinical populations. In a study of 15 MDMA users who had ceased taking the drug 3 weeks prior to the psychological assessment, the researchers found evidence for dysphoria and mood changes in over half the sample (Gerra et al., 1998). It is apparent that psychiatric morbidity developed in the context of MDMA use is identical to psychopathology unrelated to the use of MDMA. One study compared cases of psychosis which had developed in the context of MDMA abuse with cases unrelated to substance abuse and found no difference between the two presentations (McGuire, Cope & Fahy, 1994).

Although several studies have described various forms of psychiatric morbidity in MDMA users, the majority of these have been examinations of a small number of cases from clinical populations. In a recent study of light MDMA users (1 - 20 occasions) and heavy MDMA users (30 – 1000 occasions) from a non-clinical sample, the researchers found that heavy users reported significantly higher scores than controls on measures of paranoid ideation, psychoticism, somatisation, obsessionality, anxiety, hostility, phobic anxiety, impulsiveness, alteration in appetite and restlessness during sleep (Parrott, Sisk & Turner, 2000). Light users reported significantly higher scores than controls on a measure of psychoticism and significantly lower scores than heavy users on measures of anxiety, paranoid-ideation, and alterations in appetite. It is apparent from these studies that MDMA has been associated with a variety of psychiatric morbidity, however, the nature of MDMA's role in the development of this psychopathogy is unclear. It has, however, been proposed that the lasting effects of MDMA on the serotonergic system may contribute to the development of psychopathology. Serotonin has been implicated in the pathophysiology of several psychiatric syndromes, including depression, anxiety, panic, eating disorders and

psychosis. McGuire et al. (1994) claim that an association between MDMA use and the development of psychopathology might therefore be expected on theoretical grounds. However, the observation that only some individuals develop psychiatric morbidity after MDMA use suggests that certain predisposing factors make some individuals more susceptible than others (Steele et al., 1994). Alternatively, it has been suggested that individuals with serotonin depletion related psychopathology are attracted to MDMA as a result of its serotonin releasing properties and that MDMA has no causal relationship with the development of psychopathology.

1.3 MDMA-INDUCED SEROTONERGIC NEUROTOXICTY

The neurotoxic effects of MDMA have been widely demonstrated and explored in various animal species and there is a considerable body of literature documenting the pharmacological effects of MDMA among experimental animals. Of particular significance to the recreational use of MDMA in humans is the examination of this process in non-human primates. Evidence of MDMA's neurotoxic potential derived from animal studies has lead researchers to investigate whether similar patterns of toxicity are found in human recreational users of MDMA. The following review of the literature will firstly examine the characteristics of MDMA-induced neurotoxicity in experimental animals and non-human primates, and discuss a proposal for the mechanism of neurotoxicity. The evidence supporting the presence of MDMA-induced neurotoxicity in human recreational users will then be discussed.

1.3.1 Evidence for MDMA-Induced Neurotoxicity from Animal Studies

MDMA has been demonstrated both histologically and biochemically to be a selective neurotoxin for serotonin pathways in many species of experimental animals, including the mouse, rat, guinea pig and dog, (reviewed in Green et al., 1995). Animals given

MDMA show long-term reductions in concentrations of biochemical markers for serotonergic functioning, including direct measures of brain serotonin levels, the number of serotonin uptake sites (reflecting destruction of brain serotonin terminals), and the level of serotonergic metabolites in cerebrospinal fluid (CSF). Anatomical studies indicate that MDMA produces these neurochemical deficits by damaging serotonergic nerve fibres (Ricaurte, DeLanney, Wiener, Irwin et al., 1988a).

Animal studies have revealed that MDMA-induced neurodegeneration is related to both the dose and frequency of administration (O'Shea, Granados, Esteban, Colado et al., 1998; Commins, Vosmer, Virus, Woolverton et al., 1987). Long-term neurotoxic effects have been found to occur after either a single large dose or when several lower doses were administered subcutaneously over a short period of time (Green et al., 1995). Early animal studies of the toxic effects of MDMA in the rat brain demonstrated that one large dose or repetitive low doses of MDMA administered twice daily over four days, produced lasting decreases in biochemical markers for serotonergic functioning (Sprague et al., 1998). Studies in this area found that the administration of MDMA to rats resulted in a decrease in serotonin levels for up to 8 weeks after a single dose (Commins et al., 1987) and for 6 to 12 months after multiple doses administered twice daily for four days (Sprague et al., 1998). The most severe reductions in serotonin levels were found in the neocortex, striatum, and hippocampus, while much smaller decreases were found in the brainstem and the hypothalamus (Sprague et al., 1998). Animal studies have also revealed that MDMA causes a reduction in the density of serotonin uptake sites (Commins et al., 1987). Notably, the density of uptake sites for dopamine and noradrenaline are not affected to the same extent by MDMA and require much higher doses before evidence of neurotoxicity is apparent (Steele et al., 1994;

Sprague et al., 1998). These findings suggest that MDMA is a selective serotonin neurotoxin.

The neurochemical changes and the depletion of biochemical markers of serotonergic functioning evidenced after MDMA administration have been attributed to serotonergic axonal damage. It has been demonstrated that MDMA produces a profound loss of fine serotonergic axons in the rat brain. Studies using the Fink-Heimer staining method to detect degenerating axon terminals and cell bodies have identified axonal damage in several brain regions after administration of MDMA (Commins et al., 1987). Those regions of the brain rich in serotonin terminals, such as the cerebral cortex and hippocampus, show more damage than those areas containing cell bodies or fibres of passage such as the brainstem or hypothalamus (Steele et al., 1994). It is apparent that MDMA selectively destroys the fine serotonergic axons, which generally innervate the cortex, while the cell bodies and thick beaded axonal fibres remain intact (Sprague et al., 1998). Serotonergic toxicity has been further demonstrated by immunocytochemical studies in the rat brain. These studies have shown that neurodegenerative changes occur after administration of MDMA, including increased serotonin axon calibre, huge swollen varicosities, fragmentation and dilated axon stumps, and the loss of forebrain serotonin terminals (Green et al., 1995). The findings in rat brains that the cell bodies appear resistant to MDMA induced damage suggests that there may be potential for regeneration of the damaged serotonergic axons in the rat brain (Sprague et al., 1998).

While the pattern of MDMA-induced serotonergic neurodegeneration in experimental animals is replicated in non-human primates, there is evidence to indicate that the neurotoxicity of MDMA is prolonged and possibly permanent in non-human primates

and that they may be more sensitive than rodents to the neurotoxic effects of MDMA. Insel, Battaglia, Johannessen, Marra et al., (1989) administered high doses of MDMA (10 mg/kg) to rhesus monkeys twice daily for 4 days. This produced selective and significant neurochemical decreases in both CSF concentrations of serotonergic metabolites and brain concentrations of serotonin. A selective decrease in serotonin uptake sites was also observed. In a second study, the monkeys were monitored for 14 weeks after administration of MDMA (10 mg/kg twice daily for 4 days). Throughout this period the MDMA-treated animals had decreased levels of serotonergic metabolites in CSF when compared to controls. Post-mortem analyses revealed significant decreases in the concentration of serotonin, serotonergic metabolites and uptake sites in the cerebral cortex and striatum, indicating prolonged damage. An indication of long term neurotoxic effects was also revealed by a study which found that seven years after administration of MDMA to squirrel monkeys, abnormal brain serotonergic innervation patterns were still evident in the neocortex, hippocampus, and striatum (Hatzidimitriou, McCann & Ricaurte, 1999). However, deficits in some areas, including the hypothalamus and thalamus, were less severe than those observed two weeks after administration and there was evidence for complete recovery in some regions of the hypothalamus and thalamus.

Numerous other studies have documented the effect of MDMA on different sites of the non-human primate brain. Studies of squirrel and Macaque monkeys treated with repeated doses of MDMA have demonstrated degeneration of fine serotonergic terminals and decreased serotonin levels in many brain regions and similar patterns have been demonstrated using PET studies of the baboon brain (see Sprague et al., 1998 for review).

One issue regarding the mode of administration of MDMA in animal studies warrants clarification. In the majority of animal studies MDMA is injected subcutaneously, which is 2-3 times more neurotoxic than oral administration of the drug as a result of higher peak blood concentrations (Boot et al., 2000). Although a small minority of recreational users inject MDMA, the preferred route of administration is oral. Therefore, the applicability of animal studies, employing subcutaneous methods of administration, to humans has been questioned. The neurotoxic effects of orally administered MDMA were demonstrated when low oral doses of MDMA (2.5mg/kg), given twice daily, were found to lower the levels of serotonin and its metabolites in the hippocampus of rhesus monkeys (Sprague et al., 1998). This study indicates that orally administered MDMA results in serotonergic degeneration in non-human primates.

The studies demonstrating serotonergic degeneration in non-human primates have important ramifications for humans. Significantly, these primate studies have used weight-adjusted doses and dose regimens that are similar to those typically used by humans at raves and dance parties (Sprague et al., 1998). The lowest effective dose of MDMA capable of producing long-term depletion of serotonin in primates is roughly equivalent to a dosage of about one or two tablets in humans (Schifano et al., 1998). Also of concern is the finding that when administered orally MDMA results in damage to central serotonergic neurons in non-human primates. A study by Ricaurte, DeLanney, Irwin and Langston (1988b) indicates that when MDMA is given to monkeys in a manner similar to that employed by humans it continues to affect central serotonergic neurons. Animal studies have also confirmed that levels of metabolites of serotonin in CSF can be employed to detect MDMA-induced central nervous system (CNS) serotonergic damage. Monkeys found to have decreased concentrations of serotonergic CSF metabolites after administration of MDMA also displayed reductions

in CNS serotonin in post-mortem analyses (Ricaurte et al., 1988a). The findings from studies in non-human primates have important implications for both the incidence and detection of serotonergic neurodegeneration in humans. Firstly, both the dose and mode of administration of MDMA typically employed by humans has been found to result in serotonergic neurotoxicity in non-human primates. Secondly, levels of serotonergic metabolites in CSF may be used as a marker for brain serotonin levels to determine the existence of CNS serotonergic damage in human recreational users of MDMA.

1.3.2 A Proposed Mechanism of Neurotoxicity

Evidence for long-term neurotoxicity of serotonin neurons and receptors after administration of MDMA has been demonstrated by the depletion of markers such as brain serotonin, its metabolite 5-hydroxyindoleacetic acid (5-HIAA), and the number of serotonin uptake sites (Sprague et al., 1998; Green et al., 1995). The mechanism involved in MDMA-induced neurotoxicity of serotonergic neurons is thought to be highly complex and many of the explanations proposed are speculative. Studies on the rat brain have shown that the loss of serotonin after administration of MDMA occurs in two phases. After an initial release of serotonin, a massive and rapid depletion in serotonin content of the brain occurs within 4 hours of MDMA injection, with reports of an 80% loss in the content of brain serotonin and its metabolites (Green et al., 1995). Serotonin levels start to return to normal within 24 hours, however, after approximately 24 hours, brain serotonin content (particularly in the cortex, hippocampus and striatum) starts to fall again. This decrease becomes unequivocal by 2-3 days and concentrations continue to decrease for up to a year indicating long-term neurotoxicity. Immunocytochemistry studies have demonstrated that while the fine serotonergic axons throughout the rat forebrain are degenerated after MDMA administration, the cell bodies remain intact, indicating the potential for regeneration of serotonergic

projections. Indeed, regeneration has been shown to occur both in rats and non-human primates, however, the pattern of reinnervation is abnormal with some regions showing hyperinnervation and others deinnervation, (Sprague et al., 1998).

Although currently there is no one theory that can account for all of the data available, Sprague et al. (1998) have proposed an integrated hypothesis for the mechanisms involved in serotonergic neurodegeneration after MDMA administration. The authors state that MDMA induces an acute release of serotonin and dopamine. This acute release then leads to depletion of intraneural serotonin stores. The initially released serotonin also activates post-synaptic serotonin receptors located on gamma-aminobutyric acid (GABA) interneurons. The role of the GABAergic system in the neurotoxic process appears to be predominately as a modulator of dopamine activity. Activation of post-synaptic serotonin receptors on GABA interneurons results in a decrease in inhibitory GABAergic transmission, and this leads to an increase in the production and release of dopamine. Dopamine has been shown to play a clear role in MDMA-induced neurotoxicity. A linear correlation has been demonstrated between the release of dopamine and the extent of long-term damage to serotonin terminals (Sprague et al., 1998). Moreover, when the synthesis of dopamine is inhibited prior to the administration of MDMA, serotonin terminals are protected against degeneration and complete elimination of MDMA-induced neurotoxicity occurs when dopamine terminals are destroyed. Conversely, when dopamine levels are elevated MDMA-induced neurotoxicity increases (Steele et al., 1994; Sprague et al., 1998; Stone, Johnson, Hanson & Gibb, 1988). The serotonin released by MDMA is therefore thought to be largely responsible for the activation of post-synaptic serotonin receptors, which in turn enhance the release and synthesis of dopamine, resulting in markedly amplified concentrations of dopamine in the CNS.

In light of the observation of excessive dopamine production and release following MDMA treatment and the known relationship between dopamine and MDMA-induced neurotoxicity the role of dopamine in the destruction of serotonin terminals has been the subject of speculation. It has been proposed that the excessive dopamine released is transported into the depleted serotonin terminal. Consistent with this hypothesis is the observation that the serotonin uptake carrier will also transport dopamine. The dopamine is then deaminated by monoamine oxidase B (MAO-B) located within the serotonin terminal. One of the products of this deamination process is hydrogen peroxide, which may lead to selective destruction of the serotonin terminal (Sprague et al., 1998).

The potential role for dopamine in the destruction of serotonin terminals raises an important issue, which has not been addressed by animal studies of MDMA-induced serotonergic neurotoxicity to date. The effect of polydrug regimens on the mechanism of neurotoxicity has not been examined despite its relevance to human MDMA use. Human patterns of MDMA use typically involve the intake of other drugs either voluntarily or inadvertently such as when other drugs are compounded within the 'Ecstasy' tablet (Topp et al., 1999). It can be hypothesised that other drugs, commonly used in conjunction with MDMA, that potentiate monoamine transmission, such as amphetamine and cocaine, may increase susceptibility to neurotoxicity.

1.3.3 Evidence for MDMA-Induced Neurotoxicity in Humans from the Biological Assessment of Central Nervous System (CNS) Functioning

Findings from animal studies have lead researchers to hypothesize that similar patterns of MDMA-induced neurotoxicity may be found in recreational users of 'Ecstasy'. As

noted in the previous section, the neurotoxic dose of MDMA in non-human primates is similar to the dose range of MDMA typically taken by recreational users and oral administration of MDMA, the mode preferred by recreational users, is neurotoxic in non-human primates (Ricaurte et al., 1988b). Moreover, there is evidence to suggest that non-human primates are more susceptible than other species to MDMA-induced serotonergic degeneration and that MDMA-induced neurotoxicity is prolonged and possibly permanent (Insel et al., 1989; Hatzidimitriou et al., 1999). These findings have led to a growing concern that human MDMA-users might also incur serotonergic degeneration.

Studies in this area have attempted to establish whether patterns of neurotoxicity found in non-human primates generalize to humans, however, there are currently no available methods for directly evaluating the integrity of serotonin neurones in the living human brain. Therefore studies of MDMA's neurotoxic potential in humans have employed indirect methods to assess the integrity of serotonergic functioning in the central nervous system (CNS), including the measurement of metabolites of serotonin, such as 5-hydroxyindoleacetic acid (5-HIAA), in cerebrospinal fluid (CSF) and the assessment of neuroendocrine functioning. As noted in the discussion of the literature above, studies in non-human primates indicate that concentrations of serotonergic metabolites in CSF, such as 5-HIAA, can be used to reliably detect damage to the CNS serotonergic system. Through post-mortem analyses Ricaurte et al. (1988a) established that the measurement of concentrations of 5-HIAA in CSF effectively detected brain serotonergic damage in squirrel monkeys. Moreover the concentrations of CSF 5-HIAA underestimated the extent of serotonergic damage in the brain. The authors generalised from these findings to suggest that concentrations of serotonergic metabolites in CSF

may be useful for detecting MDMA-induced neuronal damage in humans (Ricaurte et al., 1988a).

Human CSF studies examining concentrations of serotonergic metabolites after exposure to MDMA have found evidence in support of serotonergic degeneration. McCann, Ridenour, Shaham and Ricaurte (1994) compared abstinent MDMA-users to matched controls, in a controlled inpatient setting, on several biological measures of central serotonergic functioning, including concentrations of CSF 5-HIAA. As expected, MDMA-users were found to have lower concentrations of 5-HIAA in CSF than controls. The authors concluded that this pattern of results was consistent with the hypothesis that recreational MDMA use is associated with an alteration in central serotonergic metabolism (McCann et al., 1994). The authors caution that the nature of these alterations is difficult to establish on the basis of CSF data alone. However, the fact that similar decrements have been observed in MDMA-treated monkeys, with known serotonergic CNS deficits, supports the conclusion that CSF 5-HIAA reductions in recreational MDMA-users reflect MDMA-induced neurotoxicity (McCann et al., 1994). This hypothesis has received further support through replications of these findings in similar studies (Bolla, McCann & Ricaurte, 1998; McCann, Mertl, Eligulashvili & Ricaurte, 1999).

An alternative biological index of central serotonergic functioning can be obtained through analyses of neuroendocrine functioning. Gerra et al. (1998) found evidence for neuroendocrine functional deficits in MDMA-users, suggesting impairment in the serotonergic system. The researchers found that when compared to controls, MDMA-users had blunted prolactin and cortisol responses to D-fenfluramine, a serotonin agonist, which suggests serotonin receptor downregulation or dysfunction. However,

McCann et al. (1994) failed to find a difference between MDMA-users and controls on a similar measure of neuroendocrine functioning. The researchers found the prolactin response to L-tryptophan, which is thought to provide a measure of CNS serotonergic functioning, to be similar in MDMA-users and controls. The authors postulated that their failure to find differences in neuroendocrine functioning may be attributable to the long period of abstinence in their sample of MDMA-users and the possibility of axonal recovery. However, prolonged effects of MDMA on serotonergic functioning have been observed after long periods of abstinence (Gerra, Zaimovic, Ferri, & Zambelli, 2000). Gerra et al. (2000) found that reductions in prolactin response to D-fenfluramine observed in three week abstinent MDMA-users were unchanged after twelve months of abstinence. In contrast, reductions in cortisol response to D-fenfluramine in the same three-week abstinent cohort were restored after twelve months of abstinence. The authors concluded that the restored cortisol response indicated that MDMA-induced neuroendocrine impairment may be partially reversible. Finally, the observation of cortisol recovery after twelve months of abstinence from MDMA, in conjunction with the correlation between time of exposure to MDMA and neuroendocrine changes, lend further support to the hypothesis regarding the neurotoxic potential of MDMA on the human brain.

1.3.4 Evidence for MDMA-Induced Neurotoxicity in Humans from Neuroimaging Techniques

Alternative methods used to assess serotonergic functioning in the living human brain include neuroimaging techniques such as positron emission tomography (PET) and electroencephalography (EEG). Dafters, Duffy, O'Donnell and Bouquet (1999) used quantitative EEG measures in an attempt to identify abnormal brain states in MDMA-users. Although some abnormalities consistent with brain damage were found there was

no control group and the observed abnormalities were not correlated with the extent of MDMA exposure.

Neuroimaging techniques such as PET have also been used to assess the status of serotonin neurons in living humans. McCann, Szabo, Scheffel, Dannals et al. (1998) found that heavy MDMA-users (over 200 occasions of MDMA use) had a lower density of brain serotonin transporter sites, which is indicative of serotonergic neural injury, when compared to controls. Moreover decreases in serotonin transporter sites were positively correlated with the extent of MDMA use. Participants had abstained from all psychoactive drug use for three weeks prior to the study to ensure that the decreases observed were not due to the acute or residual pharmacological effects of MDMA (McCann et al., 1998). In another PET study measuring general metabolic activity through the examination of glucose metabolic uptake, the researchers found significant differences between MDMA-users and controls in several brain regions, including the amygdala, the hippocampus and Brodman's area 11 (Obrocki, Buchert, Vaterlein, Thomasius et al., 1999). Importantly the affected brain regions identified in this human study are consistent with post-mortem animal studies examining the effects of MDMA-induced neurotoxicity, which lends further support to the occurrence of MDMA-induced neurotoxicity in humans (Obrocki et al., 1999).

Recent developments in neuroimaging techniques have enabled researchers to assess the density of post-synaptic serotonin receptors in the living human brain. Reneman, Booij, Schmand, van den Brink et al. (2000) used single photon emission computed tomography (SPECT) in conjunction with a radioligand with a high affinity and selectivity for postsynaptic serotonin receptors, to assess the density of serotonin receptors in five abstinent MDMA-users. The researchers found evidence for

significant serotonergic depletion in the occipital cortex of MDMA-users. High densities of postsynaptic receptors are an indirect measure of serotonergic depletion and the researchers found significantly higher densities in the occipital cortex of MDMA-users when compared to controls. Alternatively, SPECT and Magnetic Resonance Imaging (MRI) have been combined to study the effects of MDMA on regional cerebral blood flow (rCBF), a function believed to be regulated by serotonergic mechanisms (Chang, Grob, Ernst, Itti, et al., 2000). Two week abstinent MDMA-users showed mild but non-significant reductions in blood flow when compared to control subjects, indicating that either recreational MDMA use does not substantially alter serotonergic regulation of rCBF or a process of adaptation to serotonergic abnormalities occurs after long-term exposure to MDMA. Decreases in rCBF were, however, observed in individuals after the administration of MDMA in a controlled clinical setting. Decreases in rCBF were evident in most brain regions, including the caudate, superior parietal cortices and the frontal cortex, and these alterations were dose related (Chang et al., 2000). Thus, through the use of neuroimaging techniques, several studies have identified suggestions of MDMA-induced neurotoxicity and it is apparent that MDMA use has lasting implications for the integrity of serotonergic receptors in humans.

It is evident from the discussion of the literature in the previous sections that the neurotoxic effects of MDMA have been demonstrated in a variety of species using several neurobiological measures of serotonergic functioning. MDMA has been found to be a selective neurotoxin for serotonin axons and neurochemical studies have documented resulting decrements in concentrations of CNS serotonin metabolites. Moreover MDMA-induced axonal damage is prolonged with long-term reductions in the density of serotonin axons evident in non-human primates. The most severe deficits in serotonergic functioning have been observed in the neocortex, striatum and

hippocampus, and neurotoxicity is related to both dose and frequency of administration. Importantly, when administered at doses and in the mode commonly employed by recreational users, MDMA is neurotoxic in animals. In accordance with concerns raised by animal data, biological assessments of serotonergic functioning in humans, including examination of concentrations of serotonergic metabolites in CSF and neuroendocrine challenges, have indicated that similar patterns, consistent with MDMA-induced serotonergic neurotoxicity, are found in recreational users of 'Ecstasy'. Neuroimaging techniques have confirmed the presence of MDMA-induced serotonergic neural injury and reduced density of serotonin uptake sites in humans. Each of these research fields converges to support the hypothesis that recreational use of MDMA produces prolonged damage to CNS serotonergic functioning in humans. The functional consequences of the resulting neurochemical and anatomical alterations will be examined in the following section.

1.4 MEMORY AND COGNITIVE IMPAIRMENT AS A FUNCTIONAL CONSEQUENCE OF MDMA-INDUCED SEROTONERGIC NEUROTOXICITY

Animal studies of MDMA-induced neurotoxicity have demonstrated that the long-term effects of MDMA are most evident in those areas of the brain rich in serotonin terminals such as the cerebral cortex, hippocampus and striatum (Steele et al., 1994; Boot et al., 2000). Notably, the hippocampus is densely innervated by serotonergic axons and terminals and it has been postulated that this region is particularly vulnerable to MDMA's neurotoxic effects (Boot et al., 2000). Of the little that is known of the structural basis of cognitive functioning, the hippocampus and cerebral cortex have been strongly implicated in memory functioning and general cognition, respectively (Martinez & Kesner, 1986). Therefore, when considering the functional consequences of serotonergic neurotoxicity it can be inferred that MDMA-induced damage has

potential implications for memory and cognition. Additional justification for an examination of memory in MDMA-users can be gleaned from neuropharmacological studies of the biochemical basis of memory and learning, which have implicated a role for serotonin in mnemonic functioning (Cooper, Bloom & Roth, 1978). Serotonin's involvement in memory has been consolidated further through the study of neurodegenerative illnesses such as dementia, which feature memory dysfunction (Cross, 1990). In support of these hypotheses, deficits in memory functioning have been identified as one of the more pervasive and enduring consequences of MDMA use. In addition to studies of immediate and short-term memory, investigations of attention and concentration, executive functioning and processing speed have demonstrated that the implications of recreational MDMA use also include more pervasive impairment in cognitive functioning. Observations of impairment in general cognition suggest that the neurotoxic effects of MDMA are widespread, implicating neuronal damage in other brain regions. The following review of the literature will examine these findings and discuss the case for a causal relationship between MDMA use and memory and cognitive impairment.

1.4.1 Memory Functioning in MDMA-users

The term memory has been defined in numerous different ways but customarily refers to the storage and retrieval of information. Human memory is conceptualised in terms of both the structure of the memory system and the processes operating within that system. While structure refers to the way in which the memory system is organised, processes refer to the activities occurring within the system (Eysenck & Keane, 1990). The structure of memory is commonly described in terms of stages, including short-term and long-term memory. The first stage of short-term memory is referred to as immediate memory. It serves as a limited capacity store from which information is

transferred to a more permanent store and typically lasts from 30 seconds to several minutes. The restricted capacity of immediate memory imposes limitations on the amount of information able to be processed and remembered. The second stage of short-term memory, labeled delayed memory in some assessment batteries, has duration of up to one hour (Lezak, 1995), but is more typically measured 25 to 35 minutes after the presentation of stimuli (Wechsler, 1997). Finally, long-term memory is a store of essentially unlimited capacity, which can hold information over extremely long periods of time (Eysenck & Keane, 1990).

Important distinctions can also be drawn between the different stages of memory processing. The process whereby information is transformed into a memory is referred to as encoding. Encoding occurs during the presentation of information and determines which stimuli are stored within memory (Eysenck & Keane, 1990). Encoding processes are essential for transferring information from the temporary memory store, which lasts only seconds and which is believed to be governed by the working memory system, to more durable memory stores. The "depth of processing effect" has been studied to differentiate between superficial encoding, where information is only fleetingly stored, and deep encoding, which results in more enduring memories. Superficial encoding occurs when information, such as a phone number, is rapidly repeated for several seconds in what is known as the phonological loop. Information recycled in this manner is encoded only superficially and therefore is readily forgotten after a few seconds. To establish a more durable memory, Schacter (1996) postulates that incoming information must be encoded more thoroughly, or deeply, by associating it meaningfully with knowledge that already exists in memory. Information encoded deeply is recalled more accurately and remembered for longer periods of time than information encoded superficially. These two levels of encoding processes are thought

to depend on different networks of brain structures (Schacter, 1996). The process of recalling stored information is referred to as retrieval (Eysenck & Keane, 1990). It is thought that the brain engages in an act of construction during the retrieval process, whereby a complex combination of past encodings and pre-existing knowledge are triggered (Schacter, 1996).

Finally, those memory functions that mediate information in the verbal modality are differentiated from those that deal with information that cannot be communicated in words or symbols such as complex visual patterns. These memory modalities differ from one another in their neuroanatomical organisation (Lezak, 1995). The following sections will review the literature examining immediate and delayed memory functioning in MDMA-users for both the verbal and non-verbal modalities.

Verbal Memory

Verbal memory dysfunction has consistently been observed in recreational MDMA-users, however, the pattern of impairment evident in this population has varied across studies. The use of different assessment batteries and study designs, in addition to variations across cohorts of MDMA-users, have contributed to these discrepancies. Immediate verbal memory dysfunction in MDMA-users has been observed in several of the studies reviewed below, and the case for a causal relationship between MDMA use and immediate memory impairment is supported by observations of a dose-response relationship between different features of MDMA exposure and immediate memory performance. Delayed verbal memory dysfunction has also been observed in MDMA users, however, a dose-response relationship has been found with less consistency. A possible explanation for the inconsistency evident across the studies reviewed below in their observation of a dose-response relationship is discussed in a later section.

In an early study of cognitive functioning in MDMA-users, Krystal, Price, Opsahl, Ricaurte et al. (1992) examined the clinical significance of verbal memory dysfunction by administering a comprehensive standardised neuropsychological battery to 9 three week abstinent MDMA-users. Although the researchers did not compare MDMA-users' performances with controls they evaluated the clinical significance of the subjects' neuropsychological profiles in relation to normative data on measures of frontal executive functioning, memory, verbal and non-verbal cognitive functioning, and intelligence. The authors found no clinical impairment in cognitive functioning amongst MDMA-users after conducting preliminary mental status examinations. More extensive neuropsychological assessment revealed group patterns of impairment on the Wechsler Memory Scale (WMS). The examination of memory functioning identified mild impairment in performances on the WMS initial and delayed paragraphs, which assess immediate and short-term verbal memory, in 5 of the 9 subjects. Profiles were labeled as mildly impaired if they fell one standard deviation below age-matched normative values. The researchers concluded that their results indicated that individuals with histories of extensive MDMA use exhibited sub-clinical impairment in verbal memory, while other cognitive functioning remained intact. However these subtle memory impairments were not of sufficient magnitude to be evident upon examination of general mental status.

In a controlled study of memory in MDMA-users, Bolla et al. (1998) compared the memory performances of two week abstinent MDMA-users with controls matched for age, gender and verbal intelligence. The researchers used a composite measure of immediate and delayed verbal memory which was comprised of raw scores from the

logical memory and verbal paired associates subtests of the Wechsler Memory Scale (WMS), the digit span subtest of the Wechsler Adult Intelligence Scale Revised (WAIS-R) and the Rey Auditory Verbal Learning Test (RAVLT). The logical memory subtest of the WMS assesses subjects' memory for contextual material presented in story format while the verbal paired associates subtest of the WMS requires subjects to remember a list of eight unrelated word pairs over four presentations. The RAVLT is a test of verbal learning requiring subjects to recall a list of 15 unrelated words over 5 successive presentations. Recall after the first presentation of the word list provides a measure of immediate memory span, while consecutive presentations provide a measure of learning. Subjects are then presented with an interference list of 15 different words, followed by free recall of the original list, to assess any decrement in performance after interference. Delayed memory is assessed with free recall of the original list after a thirty minute delay and the recognition component requires subjects to identify words from the original list from either a story or word list.

The immediate verbal memory factor was computed from test scores on the RAVLT, the digit span subtest of the WAIS-R, and the verbal paired associates subtest of the WMS. Although the researchers claim that this factor was a measure of immediate verbal memory, the inclusion of the digit span subtest, which requires subjects to recall number spans both forwards and backwards, suggests that this factor also comprised measures of attention and working memory. The delayed verbal memory factor was computed from raw scores on both the recall and recognition component of the RAVLT and the 30 minute delay of the logical memory and verbal paired associate subtests of the WMS.

Statistical analyses revealed that MDMA-users manifested impaired visual and verbal memory performance when compared to controls. Regression analyses examining the association between MDMA use and memory performance revealed that the estimated monthly dose of MDMA was associated with impaired immediate verbal memory. No association between estimated monthly dose of MDMA and delayed verbal memory was found. However, the combination of free recall and recognition performances in the delayed verbal factor may have masked the nature of memory impairment and prevented the relationship from becoming apparent. A composite measure of delayed free recall scores alone may have revealed an association. Thus, Bolla et al. (1998) found that more extensive MDMA use was associated with greater impairment in immediate verbal memory in a dose-response fashion. Although Bolla et al. (1998) matched participants for age, intelligence and sex, the researchers did not control for the effects of polydrug use, depression or anxiety, factors also known to influence memory functioning (Lezak, 1995). Although the observed relationship must be interpreted with caution, the evidence for a dose-response relationship between MDMA-exposure and immediate memory dysfunction is consistent with the hypothesis that MDMA-use causes memory impairment.

In an attempt to demonstrate a dose-response effect for MDMA consumption and cognitive impairment, Parrott, Lees, Garnham, Jones et al. (1998) examined the consequences of different levels of MDMA consumption on memory. Parrott et al. (1998) compared the verbal memory performances of novice MDMA-users (less than 10 occasions of use) with regular MDMA-users (more than 10 occasions of use) and non-drug using controls to determine if regular MDMA use resulted in greater impairment. The three groups were not matched for age, intelligence, sex depression, anxiety or other drug use, and the researchers did not statistically control for these

variables. The researchers used measures taken from the Cognitive Drug Research computerised test battery to assess memory. The verbal memory assessment consisted of a word recall task, where subjects were visually presented with 15 words at a rate of one every two seconds and were then required to write down recalled words. The delayed recall task was conducted at the end of the assessment battery when subjects were instructed to write down words recalled from the original list.

Both novice and regular MDMA-users performed significantly worse than controls for immediate and delayed recall, indicating a comparative deficit in memory functioning. However, the observed differences in memory performance between both MDMA groups and controls must be interpreted with caution because the researchers' did not control for the confounding effects of age, sex, depression, anxiety, polydrug use, and intelligence. Despite previous findings of a dose-response relationship between MDMA use and memory deficits, there was no difference between the performance of regular and novice users on the verbal memory task. However, a detailed assessment of the amount of MDMA consumed by participants was not conducted, and subjects were classified into novice and regular users on the basis of an arbitrary cut-off point of MDMA consumption. Thus the researchers did not determine in a precise fashion the level of MDMA consumption in participants. It is therefore possible that the two user groups did not differ sufficiently in their consumption of MDMA to manifest differences in memory impairment. Furthermore, the researchers did not control for residual effects of recent MDMA use on memory performance, which potentially may have masked any differences between novice and regular MDMA-users. Despite these methodological limitations, Parrott et al. (1998) demonstrated both immediate and delayed memory dysfunction when compared to controls.

A valid methodological criticism of earlier studies of memory impairment in MDMA-users was made by Morgan (1998) who claimed that because these studies did not compare MDMA-users with other polydrug users who had never taken MDMA, it was possible that the memory deficits observed in MDMA-users were in fact associated with a history of other illicit drug use. To address this problem Morgan (1999) assessed cognitive functioning in MDMA-users in comparison to polydrug users who had never taken MDMA and non-drug using controls. The polydrug using controls and MDMA-users were matched for consumption of amphetamine, LSD, hallucinogenic mushrooms, inhalants, and cocaine in the previous year. The three groups were not matched for pre-morbid intelligence, however, correlational analyses revealed that intelligence did not correlate with either immediate or delayed recall performance. Immediate and delayed verbal memory was assessed using the story recall test from the Rivermead Behavioural Memory Test. Participants were played an audiotaped news story and were required to recall the story both immediately and after a 40 minute delay. The MDMA-users were found to have significantly poorer performances on both the immediate and delayed recall than polydrug using and non-drug using controls, which is consistent with the findings of the Parrott et al. (1998) study reported above. These results suggest that MDMA use is uniquely associated with immediate and delayed memory impairment rather than polydrug use per se, which lends further support to the hypothesis that MDMA causes memory impairment. Immediate and delayed recall performances were not correlated with estimated total lifetime consumption of MDMA, however a combined measure of frequency of use and estimated dose per session was correlated with immediate recall in a dose-response fashion. There was no association between this indicator of MDMA consumption and delayed recall, which is consistent with the Bolla et al. (1998) study reported above. These results provide further evidence for a

causal relationship between consumption of MDMA and the severity of impairment of immediate recall performance.

In accordance with observations of neuronal recovery in animals with MDMA-induced neurotoxicity, Morgan (1999) attempted to determine whether MDMA-users regained memory functioning after a period of abstinence. The relationship between the period of time since MDMA was last used and memory impairment was examined by dividing the MDMA cohort into three groups, representing those who had taken MDMA within the last month, those who had last used between 1 to 6 months prior to testing and those who had not used for over 6 months. Analyses revealed that recall performance of individuals who had not taken MDMA within the past six months was better than those who had used MDMA. Morgan claims that these results provide tentative evidence for the recovery of memory after a period of abstinence from MDMA. However, there were only three individuals in the six-month abstinence group thus this finding must be regarded with caution. The study of neuronal recovery in animals suggests that this period of abstinence is not sufficient to examine the implications of potential neuronal recovery for memory performance in humans (Hatzidimitriou et al., 1999). These issues are addressed in the study of the long-term effects of MDMA reported in Chapter three.

Evidence for delayed verbal memory dysfunction was replicated in a more recent study. Reneman et al. (2000) found significant deficits in delayed verbal memory, as measured by the delayed free recall task from the RAVLT, in five abstinent MDMA-users compared to controls. The small sample size of this study and the researchers' failure to control for the effects of intelligence, sex, anxiety, depression and other drug use,

prevents definitive conclusions from being drawn, however, this result is consistent with other reported findings.

In another recent highly controlled study, Gouzoulis-Mayfrank, Daumann, Tuchtenhagen, Pelz et al. (2000) compared the memory performance of MDMA-users who had no regular use of other psychotropic drugs, with the exception of cannabis, to matched controls with a history of cannabis use and drug-naïve controls. The three groups were similar in terms of age, sex and education level and the investigators statistically controlled for intelligence. Memory was assessed using a German equivalent of the RAVLT, the standardised measure of verbal memory and learning described earlier.

The authors found that MDMA-users recalled fewer words after the first presentation of the word list than drug-naïve controls, indicating a comparative deficit in immediate verbal memory in MDMA-users when compared to non-drug users. MDMA-users' performance on this task did not differ significantly from cannabis using controls indicating comparative performances in immediate verbal memory, while the cannabis users' performance on this task did not differ significantly from drug-naïve controls. MDMA-users required a greater number of repetitions to learn the word list than both control groups and forgot more words after interference than drug-naïve controls. Moreover, verbal memory performance was associated with several different characteristics of MDMA use. Specifically, poorer immediate recall performance was associated with estimated cumulative dose of MDMA, a greater decrement in performance after interference was associated with frequency of use and greater number of repetitions required for learning was associated with average dose. Despite the variability in the observations of a dose-response relationship, collectively the findings

of the Gouzoulis-Mayfrank et al. study lend further support to the existence of a dose-response relationship and are consistent with both the Bolla et al. (1998) and Morgan (1999) studies. Finally, there was no difference between the three groups' performance on the recognition task. Although the authors did not examine this aspect of their data, a clinical interpretation of these results suggests that MDMA-users have comparative learning deficits and require greater exposure to information than non-users and cannabis users to effectively commit information to memory, which may be indicative of encoding difficulties. Furthermore, these individuals have greater difficulty consolidating information in memory, and interference stimuli result in a greater decrement in performance than non-MDMA-users.

Despite the customary pattern of polydrug use reported in surveys of MDMA-users (Topp et al., 1999), the non-polydrug using sample of MDMA-users in the Gouzoulis-Mayfrank et al. study rules out the cumulative effects of polydrug use in conjunction with MDMA as a likely alternative explanation for memory impairment in MDMA-users. These findings, in addition to Morgan's (1999) observation of memory impairment in polydrug-using MDMA-users when compared to polydrug-using controls, further strengthens the argument for a specific causal relationship between MDMA-use and verbal memory impairment.

Non-Verbal Memory

The body of literature documenting evidence supporting the presence of non-verbal memory deficits in MDMA-users is less comprehensive than for verbal deficits. Of the few studies that have examined non-verbal memory some indications of impairments in MDMA-users when compared to non-users have emerged, however, many of these findings are limited by the methodological problems discussed earlier. In their

previously described study of three week abstinent MDMA-users and controls matched for age, sex, and intelligence, Bolla et al. (1998) computed a visual memory factor from raw scores on the Rey Complex Figure and the visual reproduction, figural memory and visual paired associates subtests of the WMS. The Rey Complex Figure is a test of visual memory requiring subjects to copy a geometric figure, then reproduce it after either a 3 or 30 minute delay. The figural memory subtest of the WMS assesses immediate visual recognition where the subject is presented with three abstract rectangular target designs and is then required to identify them from an array of similar designs. On the visual paired associates subtest the subject is presented with nonsense line drawings paired with a coloured square. The subject is subsequently presented with the shapes in a different order and is required to recognise the colour that previously accompanied them. This is repeated after a thirty-minute delay. Finally, on the visual memory subtest, geometric shapes are exposed to subjects for 5 seconds, which they then reproduce. Subjects are then required to freely recall these shapes after a delay of thirty minutes. Regression analyses revealed that higher average monthly doses of MDMA were associated with greater decrements in delayed visual memory function. However, the inclusion of both free recall and recognition tasks in the researchers' visual memory factor makes it difficult to determine the exact nature of any visual memory impairment observed.

In a more recent study of non-verbal memory, McCann et al. (1999) compared the performance of 3 week abstinent MDMA-users and controls on an incidental learning task taken from the computerised Walter Reed Army Institute of Research Performance Battery over three test days. Subjects were matched for age, however the study failed to control for sex, intelligence, depression, anxiety and other drug use. Subjects were initially presented with a key of letter-digit pairings and were simultaneously required to

indicate which digit corresponded to a series of displayed letters. This exercise results in incidental learning of the letter-digit pairings. The code key is then removed and subjects are required to continue to match the pairs from memory to receive full points for each task. Subjects are able to view the code key if necessary, and thus continue to learn the stimuli pairings. After a delay of approximately 20 minutes, subjects are then required to complete one block of the task without the code key or feedback. The researchers reported that when memory performance was averaged over the three days MDMA-users performed significantly worse than controls. Although MDMA-users performed significantly worse than controls on the delayed recall task on the first day of testing, this discrepancy between the groups was not evident on the second and third days of testing. McCann et al. did not consider the clinical implications of these data, however, this pattern of results may suggest encoding difficulties in MDMA-users similar to those evidenced on verbal memory tasks. An evaluation of subjects' speed and accuracy on this task revealed that the MDMA-users were less accurate than controls but there was no difference in the two groups' speed of performance. Regression analyses revealed a dose-response relationship between extent of exposure to MDMA and memory performance indicating that greater exposure to MDMA was associated with poorer non-verbal memory functioning.

In their German study outlined earlier, Gouzoulis-Mayfrank et al. (2000) examined both memory and learning in the non-verbal modality in MDMA-users. The researchers compared MDMA-users with cannabis using controls and non-drug using controls on a standardised measure of non-verbal memory which assessed immediate memory span and learning for visuo-spatial material. Subjects were presented with complex visual arrangements consisting of geometric figures in the same format outlined for the RAVLT. The researchers found that MDMA-users recalled fewer figures after the first presentation than both non-users and cannabis users, indicating a relative deficit in

immediate recall and single-trial learning, however, there were no differences between the three groups on the number of repetitions required for learning. Although Gouzoulis-Mayfrank et al. did not consider the clinical implications of these data, the pattern of results is suggestive of encoding problems for non-verbal stimuli, but an intact learning curve.

In summary, although the evidence for comparative deficits in non-verbal memory in MDMA-users is less comprehensive than that for verbal memory, it is apparent that a similar pattern of disturbance is evident in both modalities. While acknowledging the methodological shortcomings in the literature, it can be cautiously inferred that MDMA-users have poorer immediate memory for both verbal and non-verbal material than non-users. The pattern of memory performance evidenced in several of the studies demonstrates MDMA-users have problems with single trial learning and require greater exposure to material before it is committed to memory and this may be indicative of encoding problems. Furthermore, interference results in a greater decrement in verbal memory performance in MDMA-users suggesting they have greater difficulty consolidating information in memory. Additionally, MDMA-users display poorer performance on delayed memory tasks indicating deficits in either storage or retrieval of information from memory. Finally, MDMA exposure is related to poorer memory performance in a dose-response fashion indicating that heavier MDMA-use is associated with greater impairment in memory functioning. This dose-response relationship supports the inference of a causal relationship between MDMA-use and memory impairment. The argument for a causal relationship is further strengthened by the observation that non-polydrug-using MDMA-users also manifest memory impairment and polydrug-using MDMA-users display impairment when compared to polydrug-using controls. These two lines of evidence suggest that the cumulative

effects of the polydrug use, commonly reported among this population, do not account for the memory impairment observed in MDMA-users. Importantly, although comparative memory deficits are evident in MDMA-users it is unclear whether these impairments are of sufficient magnitude to be clinically significant, however, there is some indication that MDMA-users manifest sub-clinical memory impairment.

1.4.2 Information Processing in MDMA-users

Attention

The concept of attention can refer to several different capacities or processes. Lezak (1995) proposes that the different processes involved in attention relate to aspects of how the individual is receptive to stimuli in the environment and how they initially process incoming information. Lezak (1995) differentiates between four aspects of attention. Selective attention refers to the ability to highlight important stimuli in the environment while suppressing awareness of competing distractions. Sustained attention involves the capacity to maintain attention over a period of time. Divided attention is described as the capacity to attend to multiple elements within a task with competing demands and alternating attention involves a shift in focus between tasks.

Attentional deficits can impede an individual in almost every area of cognitive functioning, including the ability to learn and remember. Several researchers have examined attention and concentration in MDMA-users and have found evidence of impairment when compared to individuals who have not used MDMA. McCann et al. (1999) administered a computerised psychological battery to assess attention and concentration in 3-week abstinent MDMA-users over three days of testing. The researchers found deficits in MDMA-users when compared to unmatched controls on a mental arithmetic task involving sustained attention on the second and third days of

testing. The poorer performance by the MDMA-users on this task may be indicative of relative deficits in higher order attention and concentration skills. Interestingly, there was no difference between the two groups at the baseline measurement on the first day of testing. However, while both groups' performance improved over the three days of testing, controls' performance improved more dramatically and the disparity between the two groups increased over progressive days. Moreover, MDMA-users exhibited slower reaction times for this task on the second and third days of testing, but did not differ from controls at the baseline measurement. The clinical interpretation of this pattern of results suggests that MDMA-users did not benefit from repeated exposure to the same degree as non-users and this may reflect some limitations in learning.

In the German study described earlier, Gouzoulis-Mayfrank et al. (2000) compared MDMA-users with non-drug using and cannabis using controls on measures of selective visual attention requiring response inhibition, divided attention and an attentional task requiring intermodal integration of both visual and auditory information. Each of these attention tasks measured subjects' reaction time in response to relatively complex stimuli or stimuli involving competing cognitive demands. The authors found that MDMA-users exhibited slower reaction times than non-drug users and cannabis users on the selective visual attention task and MDMA-users had longer reaction times than cannabis users on the tests of divided attention and intermodal integration. Moreover, longer reaction times on the divided attention task were associated with regular MDMA use over a long period, but not with estimated total dose or frequency of use. Significantly, however, there were no differences between MDMA-users and controls on the less complex reaction time tasks, which measured responses to simple visual stimuli. The clinical interpretation of the results of this study suggests that MDMA-users exhibit problems with more complex tasks requiring sophisticated attention and

concentration skills when compared to controls, however, they have similar performances to non-users on measures of basic attention and concentration.

In their attempt to establish a dose-response relationship between MDMA exposure and attention deficits, Parrott et al. (1998) compared the performance of regular and novice MDMA-users with unmatched controls on three measures of basic attention. Subjects were administered a forced choice reaction time task, where individuals were required to press a button when a target stimulus randomly appeared; a number vigilance task, where subjects were required to respond when the presented number matched a target number; and a number recognition task, where subjects indicated if a number string was identical to a previously presented string of digits. No difference in performance between the three groups was found. These results, in conjunction with the Gouzoulis-Mayfrank et al. (2000) study, lend further support to the hypothesis that MDMA-users only begin to display comparative deficits in attention when the task is of sufficient complexity to require higher order or more sophisticated attention and concentration skills.

Working Memory

Lezak (1995) refers to working memory as a process by which information is held in the mind, internalised, then used to guide behaviour in the absence of reliable external cues. In more practical terms, the concept of working memory refers to situations in which the individual must hold, manipulate, and transform cognitive material before generating a response (Squire & Butters, 1984). In their study outlined in the previous sections, Gouzoulis-Mayfrank et al. (2000) assessed verbal working memory in MDMA-users using the digits backward sub-scale from the Wechsler Adult Intelligence Scale-Revised. This task requires subjects to recall number spans in the reverse of the presented order. The authors found that MDMA-users performed significantly worse

than non-MDMA-users, indicating a comparative deficit in working memory. Moreover, poorer performance on this working memory task was associated with heavier MDMA use. There was no difference between the two groups on the less complex digits forward task, which does not require the same degree of mental manipulation. These results are consistent with the clinical interpretation of the findings described previously, which propose that MDMA-users have difficulties when more sophisticated attention and concentration skills are required to process more complex information. This pattern was replicated for information presented in the non-verbal modality. The visuo-spatial assessment of basic attention also yielded no differences between MDMA-users and controls. The block-tapping task used by the authors to assess visuo-spatial attention skills does not place competing cognitive demands on the individual and thus requires less sophisticated concentration skills to complete successfully.

In their study described in earlier sections, McCann et al. (1999) compared the performance of 3 week abstinent MDMA-users with unmatched controls on a visual discrimination task, which the authors claim to be a measure of working memory. The task required subjects to memorize standard visual stimuli, which consisted of matrices of random coloured cells. Subjects were then presented with two comparison stimuli, one of which was identical to the first matrix. Subjects were then required to identify the matching stimuli. The researchers found that MDMA-users performed significantly worse than controls and concluded that MDMA-users exhibited deficits in working memory. Although the researchers claim that this task assesses working memory, it can be argued that the task involves visual recognition memory. Therefore the researchers' conclusions regarding working memory functioning in MDMA-users are problematic.

These results do, however, suggest MDMA-users have impairment in non-verbal memory, when compared to non-users.

Speed of Information Processing

Slowed mental processing impacts on an individual's ability to grasp complex information involving competing cognitive demands or to process larger quantities of material (Lezak, 1995). Deficits in this area, therefore, are likely to impact on attention and learning, and consequently, memory functioning.

Wareing, Fisk and Murphy (2000) compared current and 6 month abstinent MDMA-users with non-MDMA using controls, matched for age and sex, on a measure of processing speed. Subjects were required to complete a time-limited letter discrimination task with three levels of complexity. The researchers found that controls and MDMA-users completed a similar number of sets within the time frame, however, the controls were more accurate than the two MDMA groups at the highest level of complexity. This indicates that both current and 6 month abstinent MDMA-users process complex information less accurately than non-MDMA-users within a limited time frame. The authors propose that these results are indicative of MDMA-users being unable to cope with high levels of cognitive demands.

In summary, research has demonstrated that MDMA-users exhibit comparative deficits in attention when required to invoke higher order attentional capacities, such as when responding to competing cognitive demands in the case of divided attention, and when manipulating and transforming information in the case of working memory. Moreover, in support of a causal relationship between MDMA-use and impairment in information processing, deficits in both divided attention and working memory were associated with heavier MDMA-use in a dose-response fashion. The clinical examination of the literature in terms of the nature of attentional impairment indicates that MDMA-users

have intact basic attentional capacities and only begin to display deficits when challenged sufficiently. Consistent with this pattern of results is the observation that divided attention is a sensitive indicator for any condition that reduces attentional capacity (Lezak, 1995). Finally, comparative deficits in speed of mental processing for complex information provides further evidence for MDMA-users' difficulties in coping with high levels of cognitive demands.

1.4.3 Executive Functioning in MDMA-users

Executive functioning refers to the higher-level cognitive processes involved in planning and executing action, as well as adapting behaviour as required. They consist of those capacities that enable individuals to engage in independent, purposive, self-serving behaviours. Impaired executive functioning may affect cognitive processing by compromising an individual's ability to devise strategies in planning, initiating and completing cognitive tasks. Executive functioning has its neuroanatomical basis in the frontal lobes of the brain (Lezak, 1995). Therefore, it is plausible that MDMA-induced neurotoxicity has implications for executive functioning as a consequence of the serotonergic projections that innervate the frontal lobes (Kandel, Schwartz & Jessell, 1991). Executive functioning in MDMA-users has been investigated by researchers with varying results.

Wareing et al. (2000) assessed executive functioning in both current and 6 month abstinent MDMA-users compared to controls matched for age and sex, using a random letter generating task where subjects were asked to speak aloud consonants (no vowels) in a random sequence, whilst avoiding redundant responses and adhering to several rules. The level of difficulty of the task was increased as the speed at which the subjects' responded was increased. Successful performance on this task is thought to be

indicative of efficient central executive performance. The researchers found that MDMA-users generated fewer letters and exhibited a greater degree of redundancy and broke more rules than controls at the highest level of difficulty. These results suggest that MDMA-users exhibit comparative deficits in central executive functioning when compared to non-MDMA-users when faced with a task of sufficient complexity to place demand on cognitive resources.

Further evidence for executive impairment was reported by McCann et al. (1999) who assessed logical reasoning skills in MDMA-users via a self-paced task of semantic recognition and transformational grammar in which the subject was required to indicate true or false to statements regarding letter pairings. When the researchers averaged subjects' responses over three days of testing they found MDMA-users performed significantly worse than controls. However, in their more adequately controlled study, Gouzoulis-Mayfrank et al. (2000) assessed executive functioning in MDMA-users with a word fluency task and found no evidence of executive impairment. Subjects were required to generate as many words as possible within a minute whilst adhering to specific rules. This task is designed to assess frontal lobe functioning, which is involved in the generation of ideas. The researchers found no difference between the two MDMA-using groups and controls. It can therefore be concluded that of the few studies examining executive functioning in MDMA-users, inconsistent results prevent definitive conclusions from being drawn regarding the existence or nature of any deficits, however, some indications of relative impairment are evident.

In summary, it is apparent from the review of the literature in the previous sections, that recreational MDMA use is associated with comparative deficits in verbal and non-verbal memory, higher order attentional capacity and working memory. Indications of

deficits in mental processing speed and executive functioning have also been identified, though inconclusively. It can therefore be proposed that recreational MDMA use results in cognitive disturbance. A summary of the studies reviewed in the previous sections is represented in Table 1.3.

Table 1.3: Summary of the Studies of Cognitive Disturbance in MDMA-Users.

Study	Verbal Mem.	Non-verbal Mem.	Work Mem.	Atten-tion	Proc. Speed	Exec. Funct.	Dose-Response relation-ship
Parrott et al. (1998)	×						-
Bolla et al. (1998)							×
McCann et al. (1999)		×		×		×	×
Morgan (1999)	×	×					×
Gouzoulis-Mayfrank et al. (2000)	×	×	×	×		-	×
Reneman et al. (2000)	×						
Wareing et al. (2000)		-	×		×	×	

Note: × Significant results; - non-significant results.

1.4.4 Methodological Considerations Regarding the Validity of Studies of Cognitive Impairment Among MDMA-Users

Several methodological issues must be considered when evaluating the validity of the studies examining cognitive dysfunction in MDMA-users, described in the previous review of the literature. Clearly, it is unethical to randomise participants and expose individuals to a potential toxin, thus a retrospective cohort design is commonly employed when studying the effects of MDMA on memory (Hennekens & Buring, 1987). Within this design individuals who have previously been exposed to MDMA are matched with controls and their memory performances are compared. For a valid study, the groups being compared should be matched with respect to all other factors that may

be related to memory functioning. As this is often difficult, potential confounding factors, which may contribute to differences in memory performance, can be measured and statistically controlled for. Intelligence, sex, age, depression, anxiety and drug use are either known or are potentially related to memory functioning (Lezak, 1995). Thus an appropriate method of studying the effects of MDMA on memory would involve matching the MDMA-exposed group and controls on these factors, or controlling for the confounding effects of these factors statistically. Of the eight published studies reviewed in the previous sections, only two have adequately controlled for the influence of the potential confounders age, sex, intelligence, and other drug use. None of the studies reviewed have controlled for depression or anxiety, despite the impact of both of these conditions on memory and attentional functioning (Lezak, 1995). Table 1.4 presents the methodological limitations of these studies by indicating whether they have adequately controlled for the potentially confounding effects of age, intelligence (IQ), sex and other drug use on memory and cognitive performance.

Table 1.4: Potential Confounders Adequately Controlled for in Present Studies of Cognitive Functioning in MDMA-Users.

Study	Design	Confounders			
		Age	IQ	Sex	Other drugs
Krystal et al. (1992)	No control group				
Parrott et al. (1998)	Retrospective cohort				
Bolla et al. (1998)	Retrospective cohort	×	×	×	
McCann et al. (1999)	Retrospective cohort			×	
Morgan (1999)	Retrospective cohort (matched for age, sex and IQ)	×	×	×	×
Gouzoulis-Mayfrank et al. (2000)	Retrospective cohort	×	×	×	×
Reneman et al. (2000)	Retrospective cohort (matched for age and education)	×			
Wareing et al. (2000)	Retrospective cohort (matched for sex)	×		×	

Note: × indicates where confounders were adequately controlled for in the study.

Although some investigators screened for potential confounds during the preliminary stages of the study, it is apparent from Table 1.4 that in the majority of cases neither matching nor statistical adjustment was employed to control for the effects of age, sex, intelligence and other drug use on memory performance. Furthermore, as mentioned above, none of the studies reviewed have controlled for the confounding effects of depression and anxiety. Consequently, the validity of many of the studies demonstrating a relationship between MDMA use and memory disturbance is questionable. However, the comparative cognitive impairment evident in MDMA-users in the two well controlled studies lends more weight to the view that MDMA-use is associated with memory dysfunction and general cognitive impairment.

1.4.5 Studies Examining the Relationship Between Memory Impairment and Serotonin Concentrations through Examination of Metabolites

There is one other literature relevant to the consideration of the role of MDMA in memory impairment, namely the metabolic examination of the relationship between memory impairment and serotonin concentrations. The functional consequences of MDMA-induced serotonergic neurotoxicity have been researched from a metabolic perspective in an attempt to establish a relationship between reduced central serotonergic functioning and impaired cognition. Studies examining memory and metabolic concentrations of serotonin in MDMA-users have provided tentative evidence to support an association between serotonin levels and memory performance, however, to date this evidence is inconclusive. Bolla et al. (1998) found that lower levels of serotonergic metabolites in CSF were associated with poorer memory performance in MDMA-users. Conversely, however, a similar study of attention and memory in MDMA-users failed to reveal any correlation between CSF serotonergic metabolites and cognitive performance (McCann et al., 1999).

Through the study of receptor density in MDMA-users, Reneman et al. (2000) have attempted to consolidate the relationship between serotonergic functioning and memory impairment. The researchers compared memory functioning and brain cortical postsynaptic serotonergic receptor density in five abstinent MDMA-users, to controls. It is known that severe serotonin depletion causes upregulation of postsynaptic serotonergic receptors. The researchers found a correlation between memory performance and density of postsynaptic serotonergic receptors in the MDMA-users, however the small sample size of this study prevents any definitive conclusions from being drawn. Despite the inconclusive nature of these results, the fact that cognitive studies have consistently found evidence of impairment in MDMA-users suggests MDMA-use is associated with memory dysfunction.

1.4.6 Is There a Causal Relationship Between MDMA-Use and Memory Dysfunction?

Despite the methodological limitations of the memory and cognitive literature reviewed above, the collective body of evidence as a whole suggests that MDMA-use is associated with memory impairment and general cognitive dysfunction. The question of whether MDMA-use *causes* cognitive dysfunction and memory impairment is addressed in the following discussion.

As it is ethically impossible to examine the causal relationship between MDMA-use and memory and cognitive impairment through experimental means, this hypothesis will instead be assessed by drawing on the converging lines of evidence from the literature. The hypothesis that recreational MDMA-use causes memory and cognitive dysfunction will be evaluated in terms of the set of criteria developed by Hill (1965) as a guideline for making inferences about disease aetiology from observational data. These criteria

were used by Hall, Ward and Mattick (1998) to evaluate the evidence pertaining to the question of whether methadone maintenance treatment causes reductions in heroin use and crime among opioid dependent individuals. These criteria have been adapted to evaluate the legitimacy of making causal inferences regarding MDMA-use and memory and cognitive dysfunction from the quasi-experimental and observational studies reviewed above. The extent to which the literature satisfies the following criteria will determine whether the hypothesis that MDMA-use causes cognitive dysfunction can be substantiated.

Consistency: A relationship is deemed consistent if it is replicated in studies conducted by different investigators, using different assessment measures. A consistently observed relationship is less likely to be due to sampling errors or bias. The review of the literature in the previous sections has demonstrated that the relationship between MDMA-use and cognitive dysfunction has been observed by several different investigators using a variety of cognitive and biological measures. Although some studies have not reported significant relationships, the majority of studies indicate that this relationship has been consistently observed.

Specificity: Specificity exists when the relationship between exposure to the drug and outcome is such that if the drug is given, the outcome occurs. This criterion suggests a strong relationship between the two, which increases confidence in causality. The animal literature reviewed in previous sections demonstrates specificity, where neurotoxicity occurs after administration of MDMA. Neurotoxicity has additionally been demonstrated in human recreational MDMA-users through metabolic and neuroimaging techniques. However, the specificity of the relationship between MDMA-use and cognitive dysfunction is variable as a function of the numerous factors

mediating cognitive functioning, such as intelligence, and the individual effects of different dose regimens in recreational users. It has, however, been established that the memory impairment evident in MDMA-users is specific to MDMA use and not cannabis or polydrug use.

A dose-response relationship: A dose-response relationship between exposure to a substance and an outcome increases confidence in the assumption that the substance is responsible for the outcome. A dose-response relationship between exposure to MDMA and memory dysfunction has been demonstrated in several of the studies reviewed in earlier sections, suggesting that more extensive use of MDMA is associated with greater impairment, however this relationship has not been consistently observed. Evidence for a dose-response relationship is variable within the literature as a result of the complexity of the concept of 'dose' in the case of MDMA. Animal studies have established that frequency of administration, total exposure and highest blood concentration each mediate the neurotoxic process. Thus it is difficult to construct a simplistic linear dose-response equation. Furthermore, measurement of these exposure factors is unreliable due to the problematic nature of self-report of drug use, the unknown composition of the drug sold as 'Ecstasy', the highly variable dose regimens of users, and the unknown interactive effects of polydrug use on the neurotoxic process. Finally, the possibility of a threshold effect for neurotoxicity, in addition to individual differences in premorbid cognitive functioning, complicate the relationship further. It is therefore not surprising that evidence for a dose-response relationship between MDMA-use and cognitive dysfunction is not always consistent, however, this relationship has been observed in some form in the majority of studies.

Plausibility: A relationship is plausible if it is consistent with other relevant knowledge. The causal relationship between memory dysfunction and MDMA-use is plausible because it is consistent with our knowledge of the mechanism of MDMA-induced serotonergic neurotoxicity and the role of serotonin in memory and cognition.

Coherence: A relationship is coherent if it makes sense of other information about the condition. The observed serotonergic neurotoxic effects of MDMA and resulting cognitive impairment are consistent with our knowledge regarding the high density of serotonergic receptors in the hippocampal region and our understanding of the role of the hippocampus in memory functioning (Steele et al., 1994; Martinez & Kesner, 1986). The study of neurodegenerative disorders featuring memory dysfunction, which have been found to be associated with the degeneration of the serotonergic system, offers further support to the coherence argument (Cross, 1990).

Experiment: It is not possible to experimentally establish whether MDMA use results in memory dysfunction in humans, however, it is possible to demonstrate MDMA's neurotoxicity in animals. Experimental evidence of MDMA-induced neurotoxicity has been demonstrated in those species most closely related to humans (primates), using oral administration and similar dose regimens to those employed in recreational users.

In summary, the examination of the nature of the relationship between MDMA-use and memory and cognitive dysfunction in response to these criteria, suggests that when the literature is taken as a whole, there is a strong case for the recreational use of MDMA causing memory impairment and cognitive dysfunction.

CHAPTER 2

Encoding Deficits in Recreational MDMA-Users: A clinical examination of the nature of MDMA-induced memory dysfunction

The previous chapter has reviewed the literature examining the neurotoxicity of MDMA and the functional implications of MDMA-induced serotonergic damage. Several lines of evidence have converged to support a causal relationship between recreational MDMA use and memory impairment. First, the review of the animal literature established that MDMA is selectively toxic to serotonergic neurons in non-human primates when administered orally, the manner typically employed by human recreational users, and when given in doses comparable to human use. Second, human studies of CSF serotonin metabolite concentrations and neuroimaging techniques have confirmed the presence of degeneration in the serotonergic system in the brains of recreational MDMA-users. Third, studies in non-human primates have found that the hippocampus, an area strongly implicated in memory functioning, is particularly vulnerable to MDMA's neurotoxic effects, as a function of the area's dense innervation by serotonin terminals (Steele et al, 1994; Boot et al, 2000; Martinez & Kesner, 1986). Finally, examinations of the biochemical basis of memory and neurodegenerative illnesses featuring memory impairment have suggested an integral role for serotonin in mnemonic functioning (Cooper, Bloom & Roth, 1978; Cross, 1990). Collectively these research findings support the hypothesis that recreational MDMA-use causes memory dysfunction. Indeed, while acknowledging the methodological shortcomings outlined in the previous chapter, the collective body of literature to date indicates that MDMA-users manifest impairment in both verbal and non-verbal immediate and short-term

memory when compared to non-users. Additionally, evidence for a dose-response relationship between MDMA exposure and memory performance has been demonstrated, lending further support to there being a causal relationship between MDMA-use and memory deficits.

Despite the evidence supporting the existence of memory dysfunction in MDMA-users, of the eight memory studies reviewed in the previous chapter, only two adequately controlled for the influence of possible covariates. Furthermore, neither of these studies controlled for the influence of depression and anxiety, two factors known to interfere with cognitive functioning (Lezak, 1995). It has been hypothesised that individuals with serotonin depletion, who are likely to be suffering from depression and / or anxiety, are attracted to recreational use of MDMA, as a result of its mood enhancing and serotonin releasing properties. Thus, these factors may be significant confounders in the study of cognition in recreational MDMA-users. It is therefore the intention of the study reported in this chapter to investigate whether MDMA-users exhibit comparative memory deficits after controlling for the influence of age, sex, intelligence, the use of other drugs and anxiety and depression. All of these variables are either known to be or may plausibly be associated with cognitive impairment (Lezak, 1995).

While the current literature indicates the presence of memory dysfunction in MDMA-users, research to date has failed to present a revealing clinical picture of the pattern of impairment evident, beyond simplistic modality and storage distinctions. The haphazard use of assessment batteries, as opposed to a hypothesis testing approach to the assessment of memory, has impeded any attempts to extricate a meaningful representation of memory dysfunction in MDMA-users. This failure to examine the *nature* of any memory dysfunction has prevented researchers from determining whether

encoding, storage or retrieval problems are responsible for the impairment evident in MDMA-users. In contrast, the present study was designed to discover a meaningful clinical picture of memory dysfunction in MDMA-users through the neuropsychological examination of the different memory modalities and mechanisms involved in memory functioning.

In summary, this study has two aims:

1. To determine whether there are differences in memory performance between MDMA-users and controls after adjusting for the effects of age, sex, intelligence, depression, anxiety and other drug use.

2. If differences in memory performance are found, to ascertain the nature of the dysfunction. Therefore to determine whether memory dysfunction in MDMA-users is due to encoding, storage or retrieval difficulties.

2.1 METHOD

2.1.1 Participants

A total of sixty-two individuals, thirty-one MDMA-users and thirty-one controls, participated in the study. The MDMA group comprised thirty-one recreational MDMA-users who had used 'Ecstasy' within the previous six months and at least ten times in their lives. All MDMA-users abstained from use for at least 7 days before the assessment to control for residual effects of the drug. MDMA is an illicit drug and MDMA-users are consequently a hidden population of unknown size and composition. It is therefore impossible to systematically sample this population. Thus subjects were recruited via peer networks using the snowball technique, in which participants

introduced the researcher to MDMA-using friends. Initial contacts were generated by MDMA-users already known to the experimenter. Thirty-one control subjects were recruited from university students and graduates. MDMA-users were paid $20 for participation in the study. Controls completed the study to obtain credit points as a component of their undergraduate degree in psychology. There was no mean difference between the two groups in intelligence, age, sex, depression and anxiety. Exclusionary criteria for the study included: past or present psychotic illness, previous incidence of serious head injury, and English as a second language. Neither depression nor anxiety was accepted as grounds for exclusion because both conditions were measured and controlled statistically. One control subject was excluded as an outlier after presenting an amnestic memory profile, leaving thirty valid control subjects.

2.1.2 Study Design

A retrospective cohort study design was employed to examine the effects of MDMA use on memory functioning. Within this design, individuals who have previously been exposed to MDMA are compared with controls and statistical adjustment is used to control for the influence of potentially confounding variables on memory functioning. This is an accepted method for studying the effects of a potential toxin on cognitive functioning, while controlling for potential confounders (Hennekens & Buring, 1987).

2.1.3 Procedure

Participants were screened through a telephone interview to assess their suitability for inclusion in the study. Assessment schedules were arranged to ensure at least 7 days of abstinence from MDMA at the time of testing. Written consent was obtained from subjects before commencing the assessment. A consent form outlining the nature of the study informed participants of their right to withdraw from the study at any time and

included an assurance of anonymity and confidentiality (a copy of the consent form can be found in Appendix I). In order to protect the anonymity and confidentiality of participants, no identifying information was recorded, completed assessment profiles were catalogued under subject numbers and signed consent forms were stored separately from profiles. The study was granted approval by the Australian National University Human Research Ethics Committee.

Participants were assessed individually by the candidate. Demographic information such as age, sex, and education level was obtained, in addition to information regarding MDMA use, including age of first use, highest frequency of use over one month, and highest ever dose administered at the one time, using a questionnaire designed for this purpose (a copy of the questionnaire can be found in Appendix II). A detailed history of MDMA use was attained through the use of the time line method to ensure as accurate an estimation as possible of the total number of 'Ecstasy' pills consumed. This method involves a detailed examination of each year of drug taking, using landmarks and events to map the changing frequency and pattern of MDMA use over time. This method was adapted from the procedure described by Anglin, Hser and Chou (1993) which has reasonable reliability and validity. A detailed history of concurrent drug use was taken, including the frequency of amphetamine, cocaine, LSD, heroin, inhalant, cannabis, benzodiazepine and alcohol use whilst under the influence of MDMA. An assessment of general drug use was then conducted, examining previous and current consumption of amphetamine, cocaine, LSD, heroin, benzodiazepines, inhalants, cannabis and alcohol.

Participants were administered a battery of standardised assessment measures to obtain an estimate of intellectual functioning, memory functioning, depression, and anxiety.

Each of these measures is described in detail in the following section. On average, the entire assessment was completed in an hour.

2.1.4 Measures

Intelligence

An estimate of intellectual functioning was obtained by administering the National Adult Reading Test (NART; Nelson, 1982). The NART comprises of a list of 50 phonetically irregular words, which examinees are required to read aloud. Correct pronunciation of the words is credited. General word knowledge, which is required for correct pronunciation of the irregular words, was used to estimate pre-morbid intellectual functioning because it correlates highly with overall ability and tends to be more resilient to the effects of toxins or dementing processes than other intellectual capacities (Lezak, 1995). The NART has been identified as one of the most reliable methods for estimating pre-morbid intelligence because it has greater resistance to the effects of a number of psychiatric and neurological conditions than other vocabulary measures (Lynch & McCaffrey, 1997).

Depression

Depression was assessed using the Beck Depression Inventory Second Edition (BDI-II; Beck, Steer & Brown, 1996). The BDI-II is a 21 item self-report inventory designed to measure the severity of depression that has well established reliability and validity. It assesses typical depressive symptoms including mood, pessimism, guilt, self-punishment, irritability, social withdrawal, sleep disturbance, appetite disturbance, loss of libido, agitation, worthlessness, concentration difficulty, and loss of energy. Each item is rated on a 4 point scale ranging from 0 to 3. The BDI-II requires between 5 and 10 minutes to complete.

Anxiety

Anxiety was assessed using the Beck Anxiety Inventory (BAI; Beck & Steer, 1993). The BAI is a self-report instrument designed to measure the severity of anxiety. It has well established reliability and validity. It consists of 21 descriptive statements of anxiety symptoms, which are listed on a 4-point scale. Both cognitive and somatic symptoms of anxiety are represented and the scale was constructed to measure symptoms that are minimally shared with depression. The BAI requires between 5 – 10 minutes to complete.

Memory

Memory was assessed using the Wechsler Memory Scale Third Edition (WMS-III) (Wechsler, 1997). The WMS-III is an individually administered neuropsychological battery, which assesses clinically relevant aspects of learning and memory in both the verbal and non-verbal modalities, in addition to evaluating working memory. The WMS-III is a standardised battery with normative data derived from a stratified nationally represented US sample of over 12 000 healthy adults aged from 16 to 89 years. It has well established reliability and validity and is a widely used psychometric tool (Wechsler, 1997).

The WMS-III consists of 6 primary subtests and 5 optional subtests, however, only the primary subtests and the optional digit span subtest were administered in the present study. The following description of each of the subtests outlines the nature of each task.

Auditory (Verbal) Subtests

Auditory subtests are presented orally. Memory performance both immediately after presentation, or following a 25 –35 minute delay, is believed to be indicative of immediate and delayed verbal memory functioning respectively.

Logical Memory I: Two short stories, Story A and B, are orally presented to examinees. The second story is presented twice and examinees are required to retell the stories via free recall immediately after each presentation. A total of 25 chunks of information are present in each story.

Logical Memory II: Examinees are required to freely recall both stories from Logical Memory I after the delay.

Logical Memory Recognition: Examinees are required to answer a series of questions about the two Logical Memory stories requiring a yes / no response.

Verbal Paired Associates I: This task requires examinees to learn novel word associations. Eight pairs of illogically associated words are presented orally. The first word in each pair is then provided and examinees are required to recall the word with which it was paired. Four repeat presentations of the set of word pairs, in 4 differing orders, are administered with examinees receiving feedback over successive trials.

Verbal Paired Associates II: The examinee is provided with the first word in each pair after the delay and required to recall the word with which it was paired. No feedback is given.

Verbal Paired Associates Recognition: Examinees are read a list of 24 word pairs and asked to identify the original word pairs.

Visual Subtests

These subtests are presented in the visual modality and performance is believed to be indicative of nonverbal memory functioning. As in the case of the auditory subtests, memory is examined immediately after presentation of stimuli and following a delay of 25 - 35 minutes.

Faces I: Examinees are shown a series of 24 faces for 3 seconds each. A set of 48 photographs, including the 24 previously exposed faces, is presented immediately afterwards and the examinee is required to identify the 24 original faces. The Faces subtest is a recognition task involving cued recall.

Faces II: The examinee is presented with a set of 48 photographs after the delay, including 24 different distraction faces, and is asked to identify the original set of 24 faces.

Family Pictures I: A family portrait is initially presented to familiarise examinees with the family members. Examinees are then shown four successive scenes depicting members of the family engaging in everyday activities in four different environments for ten seconds each. After all

four scenes are shown the examinee is required to recall which members were present in each scene, where they were situated and what activities they were engaged in.

Family Pictures II: After the delay, the examinee is asked to recall the details described above in Family Pictures I about each scene.

Attention and Working Memory Subtests

Letter - Number Sequence: A string of alternating letters and numbers are presented orally to the examinee, who is required to repeat the string, recalling the numbers in ascending order, followed by the letters in alphabetical order. The length of the string is increased by one after every two trials and the task is discontinued after two consecutive errors are made on the same string length. The letter-number sequence subtest is a measure of working memory as it requires the examinee to manipulate information in immediate memory.

Spatial Span - Forwards and Backwards: There are two components to this task: a forward component, which is believed to provide a measure of basic attention and concentration, and a backward component, which is believed to be a measure of working memory. In both, a series of spatial patterns are visually presented on a three dimensional board. The examiner taps a pattern on a set of blocks at a rate of one per second and the examinee is required to copy either the exact pattern in the forwards component, or the pattern in reverse order for the backwards component. The length of the pattern is increased by one block after every two trials.

The task is discontinued after two consecutive errors on a pattern of the same length.

Digit Span - Forwards and Backwards: The forwards component to Digit span is believed to be a measure of basic attention and concentration, while the backwards component is believed to provide a measure of working memory. The examinee is read a series of digits at a rate of one every second and is required to repeat the numbers immediately after the presentation in either the same order or in the reverse order to that presented by the examiner. The span is increased by one every two trials and the examinee is discontinued after two consecutive errors on a span of the same length.

Raw scores from the 6 primary subtests of the WMS-III yield 8 primary indexes: the Immediate Memory Index, a composite measure of verbal and visual immediate memory; the General Memory Index, a composite measure of delayed and recognition verbal and visual memory; the Auditory and Visual Immediate Indexes, providing a measure of immediate memory in the two modalities; the Auditory and Visual Delayed Index providing a measure of the ability to retain information over time in the two modalities; the Auditory Recognition Index providing a measure of the ability to remember information via cued recall after a delay; and the Working Memory Index.

2.1.5 Data Analysis

The data were analysed using the software package SPSS for Windows Version 9.0. The procedures recommended by Tabachnick and Fidell (1989) were used to screen the data prior to conducting statistical analyses.

For discrete variables, comparisons between groups were performed using Pearson's chi-square test and Fisher's exact test, where expected cell frequencies in two by two tables were less than five. For continuous variables with approximate normal distributions, comparisons between groups were made using Student's t-test for independent samples. All statistical tests employed a two-tailed alpha criterion of 0.05.

Comparisons between the two groups' performances, while adjusting for possible confounding variables, were made by developing multiple linear regression models. The assumptions of linearity and normality of the error distribution were assessed by graphical analysis of the residuals, while outliers were also assessed graphically. In order to maximise power and precision, each of the regression models was reduced using the backward elimination method recommended by Kleinbaum, Kupper and Muller, (1988). This method involves the elimination of variables when they are not statistically significant in the model, providing that they do not substantially alter the estimates of the remaining variables. This method results in the most parsimonious model that is able to explain the data. The results of these statistical analyses are presented in the following section.

2.2 RESULTS

The results of the statistical analyses are reported in the following sections. Firstly, demographic information describing general characteristics of the sample is presented, along with the results of assessments of current intellectual and psychological functioning. Secondly, patterns of recreational drug use are reported for both MDMA-users and controls, followed by an examination of the characteristics of MDMA use amongst the MDMA-using cohort. The results of comparisons between MDMA-users and controls for memory performance are then presented, followed by analyses of dose-response relationships between MDMA-exposure and memory performance.

2.2.1 Demographic Information

The demographic characteristics of the sample are presented in Tables 2.1 to 2.3. As discussed in previous sections, age, sex, intellectual functioning, depression and anxiety may have an influence on memory functioning (Lezak, 1995). Thus possible differences between the MDMA-using cohort and controls on these variables have been examined.

Table 2.1: Means and Standard Deviations for Age, Education and Estimated Intelligence (IQ).

	Age (years)	Education (years)	IQ (NART)
Controls	23.33 (6.59)	14.67 (1.94)	106.97 (7.17)
MDMA	24.00 (4.66)	13.77 (2.22)	103.39 (7.64)

It can be seen from Table 2.1 that the cohort of MDMA-users was well matched with controls. Independent sample t-tests revealed no significant difference between the two groups for age, $t(59) = -.046$, $p>.05$, years of education, $t(59) = 1.67$, $p>.05$ and estimated pre-morbid intelligence, as measured by the NART, $t(59) = 1.89$, $p>.05$.

Table 2.2: Sex Distribution for Controls and MDMA-Users

	Sex		
	Female (%)	Male (%)	Total
Control	20 (66.7)	10 (33.3)	30
MDMA	19 (61.3)	12 (38.7)	31
Total	39 (63.9)	22 (36.1)	

The two groups were also well matched in terms of sex. There was no significant difference in the distribution of males and females in each of the groups, $\chi^2(1, \underline{N} = 61) = .191$, $p>.05$ (see Table 2.2).

Table 2.3: Means and Standard Deviations for Depression and Anxiety

	Depression (BDI)	Anxiety (BAI)
Controls	8.07 (8.72)	8.03 (8.30)
MDMA	10.53 (10.37)	10.10 (8.88)

Finally, as can be seen from Table 2.3, there were no significant differences between controls and MDMA-users on measures of depression, $t(58) = -.10$, $p>.05$ or anxiety, $t(58) = -.93$, $p>.05$. An examination of the clinically relevant categories of severity for the BDI and BAI indicated that the means for both groups were within the 'Minimal' range for depression and the 'Mild' range for anxiety. The distributions of depression and anxiety scores in terms of these clinically relevant categories of severity were also analysed in order to rule out the possibility that the mean scores for depression and anxiety underestimated group differences by masking variances in the distribution of severity on these measures (see Tables 2.4 and 2.5).

Table 2.4: Distribution of Depression Scores for Categories of Severity on BDI

	Depression – BDI Categories		
	Minimal to Mild (%)	Moderate to Severe (%)	Total
Control	27 (90.0)	3 (10.0)	30
MDMA	25 (80.6)	6 (19.4)	31
Total	52 (85.2)	9 (14.8)	

Table 2.5: Distribution of Anxiety Scores for Categories of Severity on BAI

	Anxiety – BAI Categories		
	Minimal to Mild (%)	Moderate to Severe (%)	Total
Control	25 (83.3)	5 (16.7)	30
MDMA	22 (71.0)	9 (29.0)	31
Total	47 (77.0)	14 (23.0)	

The two groups were also well matched in terms of depression and anxiety (see Table 2.5). There were no significant differences between the two groups in the distribution of either depression, Fisher's exact test, $p>.05$, or anxiety scores, χ^2 (1, $\underline{N}$ = 61) = 1.32, $p>.05$.

2.2.2 Patterns of Other Recreational Drug Use

Alcohol consumption and illicit drug use may also impact on general cognitive functioning (Lezak, 1995). To address this, estimates of recreational drug use other than MDMA were obtained and differences between the two groups were statistically controlled for in later comparative analyses. The analyses of lifetime use and current use of recreational drugs other than MDMA are presented in Table 2.6. For the purposes of the present study, lifetime use was defined as reporting ever taking the drug,

and current use was defined as reporting present use of the drug once a month or more frequently.

Table 2.6: Patterns of Other Recreational Drug Use

	Lifetime Use (i.e. ever used) (%)	Current Use (i.e. once a month or more) (%)
Alcohol		
Control	25 (83.3)	24 (80.0)
MDMA	31 (100)*	27 (87.1)
Cannabis		
Control	17 (56.7)	6 (20.0)
MDMA	21 (67.7)	19 (61.3)**
Benzodiazepine		
Control	1 (3.3)	0 (0)
MDMA	9 (29.0)*	2 (6.5)
Amphetamine		
Control	2 (6.7)	2 (6.7)
MDMA	26 (83.9)**	14 (45.2)**
Heroin		
Control	0 (0)	0 (0)
MDMA	2 (6.5)	1 (3.2)
Cocaine		
Control	1 (3.3)	0 (0)
MDMA	18 (58.1)**	6 (19.4)*
LSD		
Control	2 (6.7)	2 (6.7)
MDMA	19 (61.3)**	6 (19.4)
Inhalants		
Control	2 (6.7)	0 (0)
MDMA	8 (25.8)	0 (0)

*p< .05, **p<.01.

As might be expected, there were a number of differences between the MDMA-users and controls in both the lifetime and current use of recreational drugs. As shown in Table 2.6, MDMA-users had significantly greater lifetime use of alcohol, Fisher's exact test, $p<.05$, benzodiazepines, Fisher's exact test, $p<.05$, amphetamine, $\chi^2(1, N = 61) = 36.60$, $p<.01$, cocaine, $\chi^2(1, N = 61) = 21.30$, $p<.05$, and LSD, $\chi^2(1, N = 61) = 20.15$, $p<.05$. Additionally, a greater number of MDMA-users currently used cannabis, $\chi^2(1, N = 61) = 10.75$, $p<.05$, amphetamine, $\chi^2(1, N = 61) = 11.68$, $p<.01$, and cocaine, Fisher's exact test, $p<.05$. These differences in drug use were controlled for statistically in the comparative analyses.

2.2.3 Patterns of Recreational MDMA-Use Within MDMA-Using Cohort

A comprehensive analysis of recreational MDMA use was conducted for the MDMA-using cohort to obtain a thorough representation of their pattern of use. The estimated total lifetime dose of MDMA, the highest frequency of MDMA use in one month and the highest number of pills swallowed at the same time, as reported by subjects, were examined. These characteristics were measured as a result of the animal literature, which has shown that total exposure, frequency of exposure and absolute concentrations of MDMA in the bloodstream each mediate the neurotoxic process (Steele et al., 1994). These three characteristics of MDMA use were then combined to create a composite measure of MDMA exposure. This representation of MDMA exposure was subsequently used to examine the dose-response relationship between MDMA use and cognitive dysfunction. Similar MDMA exposure variables have been computed in other studies of MDMA-use and cognitive dysfunction to examine a dose-response relationship (Bolla et al., 1998).

Table 2.7: Pattern of MDMA Use in MDMA-Users (n=31)

	Minimum	Maximum	Mean (SD)
Estimated Total Dose (no. of MDMA pills)	11	680	166 (171)
Highest Frequency of Use[a]	0.5	16	5 (4)
Highest Dose[b]	0.5	5	2 (1)
Time since last MDMA use (days)	7	168	37 (33)
Duration of use (months)	5	156	50 (36)
Age of first use	14	30	20 (4)
Polydrug Use[c]	0	184	44 (60)

[a]Highest number of occasions of MDMA use in one month.
[b]Highest number of MDMA pills swallowed at one time.
[c]Number of occasions cocaine and/or amphetamine were taken concurrently.

Table 2.7 summarises the pattern of recreational use in MDMA-users. There was a wide range in exposure to MDMA in the sample, ranging from 11 to 680 pills consumed in a lifetime, ($\underline{M}$ = 166). The frequency of use was highly variable, ranging from less than one occasion of use per month to sixteen occasions in one month. The mean for the highest frequency of use was 5 occasions per month, which is greater than every weekend in the month. The number of pills swallowed at the one time ranged from a half to 5 pills ($\underline{M}$ = 2). The time since last use within the cohort was also highly variable, ranging from 7 days to 5 months, with a mean period of abstinence of 37 days. The duration of MDMA use ranged from 5 months to 13 years, with a mean duration of approximately 4 years of use. Finally, the mean age of first use, being 19 years (range 14 to 30), in this cohort is not dissimilar to other Australian cohorts (Topp et al., 1999).

The polydrug measure of concurrent amphetamine and / or cocaine use was collected to examine whether a relationship existed between MDMA-use, concurrent amphetamine and / or cocaine use, and memory dysfunction. Knowledge of the neurochemical actions involved in the MDMA-induced neurotoxic process suggests that the dopamine releasing properties of amphetamine and cocaine may potentially increase the neurotoxicity of MDMA (Sprague et al., 1998). However, correlational analyses revealed no significant relationship between these variables.

2.2.4 Memory Functioning in MDMA-Users and Controls

The results of analyses comparing memory performance in MDMA-users and controls are presented in the following sections. Firstly, comparisons between MDMA-users and controls on the WMS-III memory indexes are presented. As outlined in greater detail in the method section, the memory indexes are composite measures of memory functioning. The summary indexes, representing immediate, delayed and working memory functioning, are examined, followed by the indexes representing immediate and delayed memory functioning for both the auditory (verbal) and visual modalities. Secondly, comparisons between MDMA-users and controls are made for performance on each of the verbal memory subtests, followed by comparisons for performance on each of the visual memory subtests. Finally, MDMA-users and controls are compared in terms of their performance on the subtests assessing attention and working memory.

Memory Indexes

Both adjusted and unadjusted comparisons between MDMA-users and controls were conducted for each of the WMS-III memory indexes. The unadjusted differences were calculated using independent samples t-tests, while multiple linear regression models

were constructed to examine the differences between the two groups while adjusting for the potentially confounding effects of sex, age, intelligence, depression, anxiety, and other drug use. These regression models were reduced using the backward elimination method described in the method section and the adjusted means and t-values were derived from the final reduced models. The results of these analyses are summarised in Tables 2.8 to 2.13. (The final regression models, for significant comparisons, can be found in Appendix III).

Table 2.8: WMS-III Memory Index Means and Comparisons for MDMA-Users (n = 31) and Controls (n = 30).

WMS-III Memory Index	Mean	Unadjusted Mean Difference	Adjusted Mean Difference	Unadjusted t	Adjusted t
Immediate Memory					
Control	112.83	11.87	10.30	4.09***	-3.57**
MDMA	100.97				
General Memory (delayed)					
Control	110.23	8.62	6.60	3.12**	-2.45**
MDMA	101.61				
Working Memory					
Control	111.47	5.66	4.19	1.67	-1.30
MDMA	105.81				

**p<.01, ***p<.001

Table 2.8 shows the results for the unadjusted and adjusted comparisons involving the memory indexes. It is evident that MDMA-users displayed significantly poorer immediate and general (delayed) memory functioning, as measured by the WMS-III composite memory indexes. The differences between the two groups in memory function remained after adjusting for the effects of potential confounders. Estimated intelligence was a significant covariate for the immediate memory index, while intelligence and sex were significant in the case of the general memory index. There was no significant difference between MDMA-users and controls on the WMS-III composite measure of working memory functioning.

Given a significant difference was found in the immediate memory index, it is pertinent to examine the measures contributing to this in greater detail. Table 2.9 shows the results of analyses for the visual and auditory memory indexes, which constitute the immediate memory index.

Table: 2.9 WMS-III Immediate Memory Index Means and Comparisons for MDMA-Users (n = 31) and Controls (n = 30).

WMS-III Memory Index	Mean	Unadjusted Mean Difference	Adjusted Mean Difference	Unadjusted t	Adjusted t
Auditory (verbal) Immediate					
Controls	118.87	11.90	9.73	4.27***	-3.60**
MDMA	106.97				
Visual Immediate					
Controls	102.07	7.87	7.87	2.51*	-2.51*
MDMA	94.19				

*p<.05, **p<.01, ***p<.001

As can be seen in Table 2.9, the unadjusted comparisons between MDMA-users and controls for the immediate memory indexes indicated that MDMA-users displayed significantly poorer verbal and visual immediate memory functioning than controls. These group differences in immediate memory functioning remained apparent after adjusting for the effects of potential confounders. Both intelligence and sex were significant covariates within the final regression model. In the case of the visual immediate memory index, the unadjusted model was retained because none of the potential confounding variables were significant within the final model or significantly altered the estimate of the difference when removed.

The measures contributing to the significant difference in the delayed memory index were also examined in greater detail. Table 2.10 shows the results of comparisons

between the two groups for auditory and visual delayed memory, and the auditory recognition performance, which constitute the delayed memory index.

Table 2.10: WMS-III Delayed Memory Index Means and Comparisons for MDMA-Users (n = 31) and Controls (n = 30).

WMS-III Memory Index	Mean	Unadjusted Mean Difference	Adjusted Mean Difference	Unadjusted t	Adjusted t
Auditory (verbal) Delayed					
Controls	111.70	5.09	3.57	1.92	-1.36
MDMA	106.61				
Visual Delayed					
Controls	101.63	8.41	6.94	2.57*	-2.11*
MDMA	93.23				
Auditory Recognition					
Controls	113.83	8.03	7.67	2.76**	-2.73**
MDMA	105.81				

*p<.05, **p<.01

It is evident from Table 2.10 that MDMA-users were significantly worse than controls on the WMS-III composite measures of visual delayed memory. Both the unadjusted and adjusted comparisons were statistically significant and intelligence was a significant covariate. No significant differences between the two groups' memory functioning in the verbal modality, as measured by the WMS-III auditory delayed index, was evident from either the unadjusted or adjusted comparisons. Finally, it is also apparent from Table 2.10 that MDMA-users' cued recall performance, as measured by the WMS-III verbal recognition index, was significantly poorer than controls and this group difference endured after controlling for the effects of potential confounders. Sex was a significant covariate for this measure.

Verbal Memory Subtests

In the following section, both the adjusted and unadjusted analyses comparing performances of MDMA-users and controls on the verbal memory subtests are presented. Tables 2.11 and 2.12 summarise performance on each of the verbal memory subtests, both before and after controlling for the potential confounding effects of sex, age, intelligence, depression, anxiety and other drug use. (Final regression models for significant analyses and analyses where group differences were no longer significant after controlling for possible confounders can be found in Appendix III).

The total Logical Memory subtest performance for the immediate (I) and delayed (II) conditions were compared for MDMA-users and controls, in addition to an examination of group performance on each of the individual stories (A and B), including the two trials of B in the immediate condition (Bi and Bii). Finally, performance on the recognition trial of Logical Memory, a measure of cued recall, was compared. The results of these analyses are presented in Table 2.11.

Table 2.11: WMS-III Logical Memory Subtest Means and Comparisons for MDMA-Users (n = 31) and Controls (n = 30).

Subtest	Mean	Unadjusted Mean Difference	Adjusted Mean Difference	Unadjusted t	Adjusted t
Logical Memory I Total					
Control	49.80	8.19	6.98	4.05***	-3.55**
MDMA	41.61				
Logical Memory I Story A					
Control	16.97	3.48	3.88	4.10***	-3.91***
MDMA	13.48				
Logical Memory I Story B i					
Control	13.87	2.54	2.14	3.16**	-2.65*
MDMA	11.32				
Logical Memory I Story B ii					
Control	18.97	2.16	1.71	2.61*	-2.08*
MDMA	16.81				
Logical Memory II Total					
Control	31.40	5.14	3.93	3.11**	-2.45*
MDMA	26.26				
Logical Memory II Story A					
Control	14.07	3.00	2.48	3.00**	-2.57*
MDMA	11.07				
Logical Memory II Story B					
Control	17.27	2.07	1.58	2.24*	-1.72
MDMA	15.19				
Logical Memory Recognition					
Control	27.80	1.09	.865	2.20*	-1.78
MDMA	26.71				

*p<.05, **p<.01, ***p<.001

Table 2.11 shows that MDMA-users recalled significantly less information than controls on the total Logical Memory I subtest, a measure of immediate contextual

verbal memory. Both the unadjusted and adjusted analyses were significant and intelligence, depression and anxiety were significant covariates for this measure. The unadjusted and adjusted analyses, represented in Table 2.11, indicate that MDMA-users recalled significantly less information than controls from Story A and after both the first presentation and second presentation of Story B. Intelligence and depression, were significant covariates in the case of Story A, and intelligence was a significant covariate in the case of the first and second presentations of Story B.

It is also apparent from Table 2.11 that after a delay of 25 to 35 minutes, MDMA-users recalled significantly less information than controls on the total Logical Memory II subtest, as evidenced by the adjusted and unadjusted comparisons (sex, depression and anxiety were significant covariates). An examination of the amount of information recalled from the two stories after the delay revealed that MDMA-users recalled significantly less from both Story A and B. In the case of Story A, this group difference in verbal memory performance remained after controlling for potential confounders (sex, intelligence, depression, and anxiety were significant covariates). Group differences in delayed verbal memory performance on Story B were no longer significant after controlling for the effects of intelligence, however, a trend was apparent ($p=.09$). Finally, MDMA-users performed significantly worse than controls on the Logical Memory recognition subtest, a measure of cued recall. This difference in recognition performance did not remain after controlling for the effects of intelligence and sex, however again a trend was observed ($p=.08$).

The recognition performance for the two groups on the Logical Memory subtest was broken down by story to determine if differences between the two groups were masked by the combined measure of cued recall for both single and repeated presentations of

verbal material. Distinguishing between the recognition performance for Story A and B allows further examination of the nature of memory impairment. In the case of Story A, controls' cued recall performance ($\underline{M}$ = 13.13, $\underline{SD}$ = 1.59) was comparable to MDMA-users ($\underline{M}$ = 12.48, $\underline{SD}$ = 1.69), $\underline{t}(59)$ = 1.54, $\underline{p}>.05$. However, controls correctly recognised significantly more information from Story B ($\underline{M}$ = 14.67, $\underline{SD}$ = 0.55) than MDMA-users ($\underline{M}$ = 14.22, $\underline{SD}$ = 0.10), $\underline{t}(59)$ = 2.33, $\underline{p}<.05$) and this difference was not influenced by any of the potential confounders and no covariates remained in the final regression model.

Group performance was then compared for the total Verbal Paired Associates (VPA) subtest, in addition to comparisons for each of the four recall trials (a – d). Recall performance after the delay of 25 to 35 minutes (VPA II) was also compared for the two groups. The recognition subtest was not included in the analysis because it became apparent that the task was not sufficiently challenging when every subject obtained a perfect score.

Table 2.12: WMS-III Verbal Paired Associates (VPA) Subtest Means and Comparisons for MDMA-Users (n = 31) and Controls (n = 30).

Subtest	Mean	Unadjusted Mean Difference	Adjusted Mean Difference	Unadjusted t	Adjusted t
VPA I Total					
Control	29.23	3.69	3.28	2.66*	-2.56*
MDMA	25.55				
VPA I List a					
Control	6.27	2.04	2.24	3.40**	-4.01***
MDMA	4.23				
VPA I List b					
Control	7.47	0.95	.652	2.12*	-1.51
MDMA	6.52				
VPA I List c					
Control	7.77	0.51	.320	1.81	-1.16
MDMA	7.26				
VPA I List d					
Control	7.73	0.19	0.08	0.77	-0.42
MDMA	7.55				
VPA II					
Control	7.60	0.25	0.07	0.71	-0.28
MDMA	7.36				

*p<.05, **p<.01, ***p<.001

It can be seen from the unadjusted and adjusted analyses in Table 2.12 that MDMA-users performed significantly worse than controls on the total VPA subtest, a measure of immediate verbal memory and learning (intelligence, age, sex, and anxiety were significant covariates). MDMA-users recalled significantly fewer word pairs than controls after the first presentation of the list (List 'a') (sex and anxiety were significant covariates). The unadjusted analysis for List 'b', presented in Table 2.12, reveals that MDMA-users recalled significantly fewer word pairs than controls after the second presentation of the list, however, this group difference was no longer apparent after controlling for the effects of intelligence, age, and sex. Finally, there was no difference between the two groups in the number of pairs recalled after subsequent presentations of

the list (list 'c' and 'd') or after the delay of 25 to 35 minutes. The pattern of results recorded over the four trials of this subtest is represented in Figure 2.1.

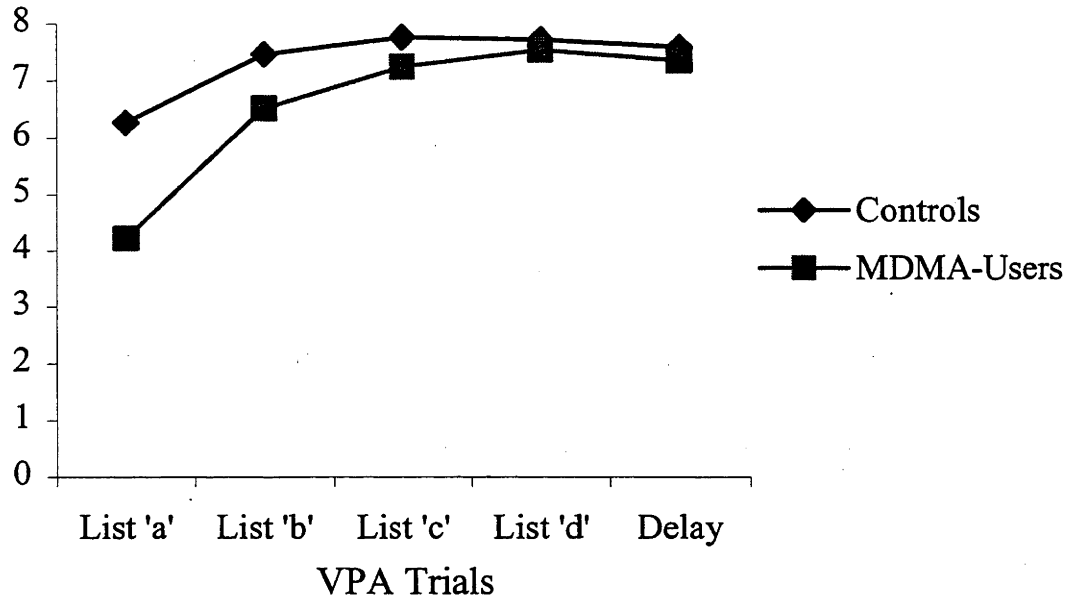

Figure 2.1: Verbal Paired Associates Learning Curve

The pattern of results for the VPA subtest evident in Figure 2.1, indicates that the difference between MDMA-users and controls' performance is quite marked on the first trial, but recovers to be comparable to controls over successive trials. While MDMA-users' performance improves after the second presentation of the word pairs to become equivalent to that of the controls, the controls' performance improves from the first to the second trial and subsequently levels out.

Visual Memory Subtests

In the following section both the unadjusted and adjusted comparisons between MDMA-users and controls' performance in the visual memory subtests are presented. The performance of controls and MDMA-users on the immediate (I) and delayed (II) conditions of the Faces subtest, a measure of cued visual recall, and the Family Pictures subtest, a measure of memory for contextual visual material, were compared using the aforementioned analyses. The results of these analyses are presented in Table 2.13.

Table 2.13: WMS-III Faces and Family Pictures Subtest Means and Comparisons for MDMA-Users (n = 31) and Controls (n = 30).

Subtest	Mean	Unadjusted Mean Difference	Adjusted Mean Difference	Unadjusted t	Adjusted t
Faces I					
Control	39.43	2.21	2.21	2.17*	-2.17*
MDMA	37.23				
Faces II					
Control	39.13	2.46	2.46	1.95	-1.95
MDMA	36.68				
Family Pictures I					
Control	49.40	4.21	3.31	2.26*	-1.78
MDMA	45.19				
Family Pictures II					
Control	49.10	4.07	3.14	2.29*	-1.75
MDMA	45.03				

*p<.05

It is evident from Table 2.13 that MDMA-users recognised fewer faces than controls in the immediate condition of the Faces subtest. There were no significant covariates, thus the unadjusted analysis was retained. There was no significant difference between the performance of MDMA-users and controls on the Faces subtest in the delayed condition, however a trend was evident (p=.06). Again the unadjusted regression model was retained since there were no significant covariates. An examination of the unadjusted and adjusted analyses for the Family pictures subtest, presented in Table

2.13, indicates that MDMA-users recalled significantly less information than controls from the family pictures in both the immediate (I) and delayed (II) conditions, however, these group differences did not remain after controlling for the effects of age and intelligence. A trend was evident, however, for recall performance on both the immediate (p=.08) and delayed (p=.09) conditions.

Attention and Working Memory Subtests

In the following section, comparisons between MDMA-users and controls' performance on the WMS-III attention and working memory subtests are presented. The results of these analyses are presented in Table 2.14. As demonstrated earlier, controls and MDMA-users were comparable in terms of potential confounding variables, apart from other drug use. As it is unlikely that the more extensive recreational drug use amongst MDMA-users would have a beneficial effect on attention or working memory functioning, it was perceived that group differences would not be masked and become evident after the adjusted analysis. Thus it was determined that the unadjusted analyses were sufficient to conclude that no significant differences between the two groups were evident.

Table 2.14: WMS-III Letter-Number Sequencing, Spatial Span and Digit Span Subtest Means and Unadjusted t values for MDMA-Users (n = 31) and Controls (n= 30).

Subtest	Mean	Unadjusted Mean Difference	Unadjusted t
Letter Number Sequencing			
Control	13.33	1.04	1.59
MDMA	12.29		
Spatial Span Total			
Control	18.16	0.65	0.87
MDMA	17.52		
Spatial Span Forward			
Control	9.10	0.33	0.68
MDMA	8.77		
Spatial Span Backward			
Control	8.93	0.19	0.52
MDMA	8.74		
Digit Span Total			
Control	20.37	1.40	1.28
MDMA	18.97		
Digit Span Forward			
Control	11.60	0.54	0.92
MDMA	11.07		
Digit Span Backward			
Control	8.77	0.86	1.37
MDMA	7.90		

It can be seen in Table 2.14 that there were no significant differences between MDMA-users and controls' performances on the attention and working memory subtests.

2.2.5 Examination of a Dose-Response Relationship Between MDMA Exposure and Verbal Memory Performance

The possibility of a dose-response relationship between MDMA use and memory dysfunction was examined in the cohort of MDMA-users. As outlined in a previous section, the estimated total lifetime dose of MDMA, the highest frequency of MDMA use in one month and the highest number of pills swallowed at the same time were

combined to create a composite measure of MDMA exposure. This measure of MDMA exposure was then included in regression analyses to examine the relationship between exposure and memory performance on each of the WMS-III memory indexes and subtests, while controlling for the effects of age, sex, intelligence, anxiety, depression and other drug use. Significant regression analyses suggesting a dose-response relationship between the extent of MDMA exposure and memory dysfunction are presented in Tables 2.15 to 2.17. There was no dose-response relationship observed for the general, immediate and working memory indexes, the auditory immediate and delayed indexes, the visual immediate and delayed indexes, the auditory recognition index, the Logical Memory subtests, the faces and family pictures subtests, or the subtests assessing attention and concentration.

Table 2.15: Multiple Linear Regression Model Examining Dose-Response Relationship Between MDMA Use and VPA I Total Performance While Adjusting for Potential Confounders (n = 31).

Variable	**B**	**SE**	**T**	**p[a]**
MDMA Exposure[b]	-.001	.000	-2.17	.040
IQ	.334	.124	2.70	.012
Anxiety	.277	.107	2.58	.016
Age	-.471	.198	-2.38	.025
F=6.21, p=.001				
Adjusted R Square=.418				

Note: B = unstandardised regression coefficient

[a]Two-tailed

[b]MDMA Exposure = highest frequency of use per month × estimated total dose × highest dose

It can be seen in Table 2.15 that a dose-response relationship between MDMA-exposure and VPA Total performance was evident after controlling for the effects of potential confounders. This relationship suggests that the greater the exposure to MDMA, the poorer the total performance on the VPA subtest, a measure of immediate verbal memory and learning.

Table 2.16: Multiple Linear Regression Model Examining Dose-Response Relationship Between MDMA Use and VPA I List 'a' Performance While Adjusting for Potential Confounders (n=31).

Variable	B	SE	T	p[a]
MDMA Exposure[b]	-.000	.000	-3.18	.050
IQ	.139	.054	2.55	.017
Anxiety	.122	.047	2.58	.016
F=5.66, p=.004				
Adjusted R Square=.325				

Note: B = unstandardised regression coefficient
[a]Two-tailed
[b]MDMA Exposure = highest frequency of use per month × estimated total dose × highest dose

An examination of a dose-response relationship between MDMA-exposure and each of the VPA subtest trials revealed significant relationships between exposure and performance on the first and third trials, but not the second or final trials. It can be seen in Table 2.16 that a dose-response relationship between MDMA-exposure and recall after the first presentation of the VPA word pairs (List 'a') was evident after controlling for the effects of potential confounders. This relationship again suggests that the greater the exposure to MDMA, the poorer the immediate verbal memory performance.

Table 2.17: Multiple Linear Regression Model Examining Dose-Response Relationship Between MDMA Use and VPA I List 'c' Performance While Adjusting for Potential Confounders (n=31).

Variable	B	SE	T	p[a]
MDMA Exposure[b]	-.000	.000	-2.08	.048
IQ	.066	.033	2.04	.052
Anxiety	.049	.028	1.73	.097
Age	-.074	.052	-1.41	.170
F=3.27, p=.028				
Adjusted R Square=.238				

Note: B = unstandardised regression coefficient
[a]Two-tailed
[b]MDMA Exposure = highest frequency of use per month × estimated total dose × highest dose

A dose-response relationship between MDMA-exposure and memory performance after the third presentation of the VPA word pairs (List 'c') was evident after controlling for the effects of potential confounders (see table 2.17). As in the case of List 'a', this relationship suggests that the greater the exposure to MDMA, the poorer the recall performance of the word pairs on the third trial.

2.3 DISCUSSION

This study set out to ascertain whether recreational MDMA-users manifest memory dysfunction, after controlling for the influence of potentially confounding variables on memory performance. More importantly, in light of the failure to date to present a meaningful clinical picture of memory dysfunction in MDMA-users, it was intended that the present study would explore the nature of memory impairment in MDMA-users. Several conclusions can be drawn from the comparative examination of memory functioning in recreational MDMA-users and controls presented in the previous section. First, MDMA-users manifested comparative deficits in immediate and delayed memory functioning, after controlling for the effects of intelligence, age, sex, depression, anxiety and other drug use. Dysfunction was evident in both the verbal and visual modalities for immediate memory and the visual modality for delayed memory. Working memory, attentional capacity, and delayed memory functioning in the verbal modality remained intact. Second, the clinical examination of verbal memory functioning in MDMA-users revealed a pattern of dysfunction that was consistent with encoding rather than retrieval deficits. Furthermore, the impact of encoding problems in MDMA-users was more apparent on tasks of greater complexity. Third, observations of comparable rates of forgetting for controls and MDMA-users indicated intact storage of information in the MDMA using cohort, ruling out a rapid rate of decay as a possible explanation for memory dysfunction. Finally, a dose-response relationship was evident between MDMA exposure and verbal memory performance.

A discussion of the comparative analyses for the WMS-III memory indexes is presented in the following section to address the question of whether MDMA-users manifest memory dysfunction. A clinical examination of the individual subtest performances is

then carried out to determine the nature of memory dysfunction and evidence supporting the hypothesis that encoding dysfunction was responsible for the memory impairment evident in MDMA-users is presented. Finally, the observation of a dose-response relationship between MDMA exposure and verbal memory functioning is addressed.

2.3.1 Memory Dysfunction in MDMA-Users

An examination of immediate and delayed memory functioning, in both the verbal and visual modalities, was carried out through comparative analyses of the WMS-III composite memory indexes for MDMA-users and controls, while controlling for the effects of age, sex, intelligence, depression, anxiety and other drug use. It was apparent that MDMA-users manifested significantly poorer functioning for both immediate and delayed memory. Working memory functioning, however, was intact. The examination of immediate memory functioning by modality revealed MDMA-users demonstrated impairment in both verbal and visual memory when compared to controls. Comparative deficits in delayed memory functioning were also evident in the visual modality, however, delayed verbal memory remained intact. The auditory recognition index of the WMS-III revealed significant differences between the two groups' cued memory functioning, however, this index was interpreted with caution because it is comprised of performances on the recognition tasks for both the word pairs and story subtests. The word pairs recognition task was overly simplistic and was not independently examined in the analysis because every subject obtained a perfect score on this measure. Consequently, the observed difference between the two groups on the recognition index could only be attributed to recognition performance on the story subtest. Recognition functioning was therefore examined through performances on this subtest alone, and is described in detail below.

It can be concluded from the comparative analyses of the WMS-III memory indexes that MDMA-users manifest memory dysfunction which cannot be attributed to the effects of age, sex, intelligence, other drug use, depression or anxiety. Indeed the construction of the regression analyses revealed that many of these factors do significantly influence memory performance in MDMA-users. Therefore, failure to control for these factors in the existing literature and in future studies is problematic. The observation of memory dysfunction in the cohort of MDMA-users in the present study is consistent with the two other well controlled studies in the literature. Gouzoulis-Mayfrank et al. (2000) found that MDMA-users, without a history of polydrug use, were impaired in immediate verbal and visual memory functioning when compared to cannabis users and non-drug using controls. Importantly, the non-polydrug using sample of MDMA-users in this study rules out the cumulative effects of polydrug use, in conjunction with MDMA, as an alternative explanation for memory impairment in this population. The unique association between memory impairment and MDMA use was further consolidated by Morgan (1999), who found that MDMA-users had poorer immediate and delayed verbal memory when compared to polydrug-using and non-drug using controls. The results of the present study confirm that MDMA-use is associated with memory impairment. In the following section, the pattern of memory impairment observed in the MDMA-using cohort is examined from a clinical perspective to ascertain a meaningful picture of the nature of memory impairment in MDMA-users.

2.3.2 The Nature of Memory Dysfunction in MDMA-Users

Lezak (1995) postulates that memory dysfunction may result from a variety of sources, including compromised learning due to defective encoding, the rapid loss of newly required information (forgetting) due to storage deficits, and retrieval problems. Retrieval problems are evident when recognition or cueing techniques indicate that more learning has occurred than free recall performance indicates. A clinical examination of the comparative memory performances on each of the WMS-III subtests for controls and MDMA-users was carried out to ascertain whether the memory impairment identified by the WMS-III indexes resulted from defective encoding, retrieval or rapid forgetting. Total subtest performance scores were considered a crude indication of functioning and therefore were not interpreted. Instead individual subtests and subtest trials were examined to gain an in depth understanding of the pattern of memory impairment. This investigation revealed a pattern of impairment, across several subtests, that was consistent with encoding problems. Furthermore, rapid forgetting was ruled out as a possible explanation for the memory dysfunction observed in MDMA-users and the observed pattern of impairment was not consistent with retrieval problems.

MDMA-users consistently manifested comparative deficits in recall performance after a single presentation of verbal material. A plausible explanation for this dysfunction in single trial learning is that MDMA-users do not encode information as efficiently as controls and require repeat exposure to stimuli before effective recall is possible. As shown in Figure 2.1, MDMA-users' recall of simple verbal information (VPA word pairs) recovered to levels comparable to controls after the second presentation of the stimuli (List 'b'), and their recall performance was equivalent to controls on the remaining trials (Lists 'c' and 'd'). After the delay, MDMA-users' recall continued to

be comparable to controls, indicating that once encoded, the information was retained in the memory store and effectively retrieved. This pattern of dysfunction suggests inadequate or inefficient encoding processes, which initially impede effective learning, but which are overcome after repeat exposure. On the Logical Memory subtest, which required the recall of more complex contextual verbal information, single trial learning in MDMA-users was similarly impaired when compared to controls. MDMA-users recalled significantly less information than controls immediately after exposure to the two separate stories (Story A and B). Furthermore, they failed to recover to levels comparable to controls after being exposed to Story B a second time. An examination of the adjusted mean differences revealed that MDMA-users improved their recall performance at a rate similar to controls after the second exposure to Story B, however, they remained impaired in comparison to controls. It is likely that MDMA-users' performance would have eventually equaled controls, if given the opportunity of repeated exposure to the story. However, unlike their performance on the word pairs task, they failed to benefit immediately from repeat exposure due to the complexity of the material. This pattern of dysfunction is consistent with the hypothesis that MDMA-users manifest problems with encoding processes, which prevent them from learning information as efficiently as non-users. Consequently, they require greater exposure to information before being able to recall comparable amounts as non-users. Furthermore, this effect becomes more apparent as the complexity of the information to be recalled is increased.

MDMA-users' story recall remained impaired after the delay in the case of Story A. Despite the finding that MDMA-users recalled significantly less from Story B than controls in the immediate condition, the difference between the two groups' delayed recall of Story B failed to reach statistical significance after controlling for potential

confounders. However, a definite trend was observed. The failure to find a statistically significant difference for the delayed recall of Story B, may be interpreted as indicative of comparable memory performance for controls and MDMA-users after the delay, perhaps as a result of consolidation of information in memory in MDMA-users or greater decay in the controls' performance. However, an examination of the adjusted mean differences revealed that MDMA-users recalled approximately two items less than controls from Story B, on both the immediate and delayed condition of this task. This similarity in the adjusted mean differences, in addition to the observed trend, indicates that the difference between the Story B recall for the two groups after the delay may not have reached statistical significance as a result of the small size of the sample. This conclusion is supported by findings of delayed verbal memory impairment in the existing literature (Morgan, 1999)

Indications of encoding problems were further supported through an examination of the recognition subtests for the two stories. In the assessment of memory functioning, unimpaired free recall performance is indicative of intact encoding and retrieval processes. Problematic free recall and intact recognition are indicative of retrieval processes dysfunction but intact encoding, whereas problematic recognition is indicative of encoding processes dysfunction (Lezak, 1995). Recognition performance from the Logical Memory subtest was therefore used, in the present study, to further examine whether memory dysfunction in MDMA-users occurred as a result of problematic encoding or retrieval processes. An explanation of retrieval dysfunction would be plausible, if recognition performances were equivalent for controls and MDMA-users, in light of the impaired free recall performance for MDMA-users on both Story A and B. This would suggest that although MDMA-users had effectively encoded similar amounts of information as controls, retrieval problems prevented them from freely

recalling as much information. Alternatively, if MDMA-users failed to recognise comparable amounts of information as controls, problems in encoding would be apparent. It was evident that MDMA-users' cued recognition performance for Story B was significantly poorer than controls, indicating that an encoding rather than a retrieval problem was responsible for the memory dysfunction observed in MDMA-users. The difference between the cued recognition performance for MDMA-users and controls on Story A, however, failed to reach statistical significance. In the context of the pattern of results already presented, this result was not deemed to be indicative of a retrieval problem, because suggestions of retrieval dysfunction were not justified by performances on other subtests, such as the VPA word pairs. It should be noted that Story B is more complex than Story A, because it contains specific information regarding times, temperature, and numerical values, as opposed to general contextual information. It is therefore plausible that encoding problems in MDMA-users were more readily apparent on Story B as a result of the complexity of this task. Recognition tasks are generally considered to be less cognitively demanding than free recall, and thus it is possible that the difficulty of the recognition task for the less complex Story A was not of a sufficient magnitude to differentiate between controls and MDMA-users. A similar ceiling effect was evident on the overly simplistic recognition task for the word pairs subtest, which was excluded from the analysis after every subject obtained a perfect score.

Finally, an examination of the adjusted mean differences for each of the immediate and delayed story trials revealed that a comparable rate of forgetting was evident from the immediate presentation to the delayed recall for both groups. Therefore it was apparent that storage in MDMA-users was intact and the rapid loss of newly required information was ruled out as a possible explanation for memory dysfunction in MDMA-users.

It has been hypothesised that a plausible explanation for the observed deficit in single trial learning in MDMA-users, in conjunction with their recovery after repeated exposure to simple verbal information but failure to recover after repeated exposure to complex verbal information, is that MDMA-users do not encode information as effectively as controls. This hypothesis is supported by the recognition dysfunction evident in MDMA-users for more complex material, and the comparable rates of forgetting for the two groups, which do not support retrieval dysfunction or rapid forgetting as possible explanations for memory dysfunction in MDMA-users. Further support is to be found in the clinical interpretation of the existing literature on memory dysfunction in MDMA-users, developed in Chapter 1. This examination confirms that when presented with tasks of sufficient complexity, MDMA-users manifest problems with single trial learning and require greater exposure to material before it is committed to memory, when compared to non-users (Gouzoulis-Mayfrank et al., 2000; McCann et al., 1999). This pattern of dysfunction observed in the existing studies of memory in MDMA-users is consistent with problems in encoding processes and lends further support to the argument that memory impairment in MDMA-users occurs as a result of encoding dysfunction.

However, several criticisms regarding the encoding dysfunction hypothesis need to be considered. First, indications of recognition impairment were only evident on one of the two stories. Comparable recognition performance on the single presentation story is inconsistent with encoding problems in light of MDMA-users' impaired free recall on this task. However, when considered in the context of the pattern of findings, this result was not deemed sufficient to contradict the indications of encoding problems in MDMA-users. It is evident, however, that further studies need to be carried out to rule

out concurrent retrieval problems. Second, the examination of the attention and working memory subtests revealed no indications of impairment in MDMA-users, a finding that is inconsistent with other studies in the literature (Wareing et al., 2000; Gouzoulis-Mayfrank et al., 2000). It may be argued that encoding dysfunction would also be apparent on these tasks, and the present study's failure to find evidence of impairment is inconsistent with the encoding hypothesis. However, upon consideration of the nature of the attention and working memory subtests, it can be argued that they were not of a sufficient complexity for MDMA-users to manifest encoding difficulties. It has consistently been observed, both in the present study and in the existing literature, that MDMA-users maintain comparable levels of memory and attentional functioning until challenged by more complex tasks, requiring manipulation and recall of greater amounts of information (Gouzoulis-Mayfrank et al., 2000; Wareing et al., 2000). Alternatively, the high functioning status of the MDMA-using cohort in the present study may account for the failure to replicate comparative deficits in working memory functioning observed in other studies. Gouzoulis-Mayfrank et al. (2000) found that MDMA-users performed significantly worse on the digits span backwards subtest of the Wechsler Adult Intelligence Scale-Revised, which is an identical task to the digits span backwards task of the WMS-III performed in the present study. However, only one subject in the Gouzoulis-Mayfrank et al. study had completed a university degree, whereas, 17 MDMA-users in the present study had completed a university degree at either the undergraduate or postgraduate level. It is plausible that the MDMA-users in the present study were able to employ alternative cognitive strategies to compensate for compromised working memory functioning. Finally, it is also possible that the failure to control for depression and anxiety in the Gouzoulis-Mayfrank et al. study may have contributed to the inconsistencies between the two studies, since both depression and anxiety are known to adversely affect attention and concentration (Lezak, 1995). In

conclusion, encoding dysfunction in MDMA-users remains a plausible explanation for the comparative memory deficits evident in this cohort.

An examination of the comparative analyses of the visual memory subtests revealed a significant deficit in MDMA-users' immediate memory for faces. The difference between the two groups' performance on this subtest after the delay did not reach statistical significance, however, a definite trend was evident. Similar trends were observed for the immediate and delayed conditions of the family pictures subtest, involving memory of contextual visual information, which failed to reach statistical significance after controlling for covariates. The composite measures of immediate and delayed visual memory functioning, which are comprised of performances on both visual subtests, indicated visual memory dysfunction in MDMA-users, suggesting that power might have been a problem when considering the subtests in isolation. Alternatively, evidence for visual memory impairment in the Gouzoulis-Mayfrank et al. (2000) study, which had a similar sample size to the present study, suggests that the failure to find a significant difference on measures of visual memory performance might also be attributed to the high functioning status of the present study's cohort of MDMA-users.

The apparent inconsistencies between the findings of the present study and the two other highly controlled studies in the literature highlight several methodological limitations in the study of cognitive dysfunction in MDMA-users. As outlined earlier, sampling problems are evident because of the illicit nature of MDMA use, and the fact that MDMA-users are therefore a hidden population. As a result, it is impossible to randomly sample this population and differences between cohorts of MDMA-users prevent confident generalisations from being made to the MDMA-using population at

large. However, despite differences between cohorts, memory dysfunction has consistently been demonstrated using a diverse range of assessment batteries across samples drawn in several different countries. Furthermore, alternative explanations for differences in memory and cognitive functioning between MDMA-users and non-users, such as intelligence, sex, age, and other drug use, have been statistically controlled for in two published studies, and the present study's results are consistent with these after further controlling for the effects of anxiety and depression. Additionally, the present study's findings of patterns of impairment that are indicative of encoding dysfunction are consistent with a clinical interpretation of the results of existing studies in the literature. Thus, although inconsistencies in the patterns of cognitive impairment are evident between different MDMA-using cohorts, the body of evidence as a whole suggests that memory dysfunction is a feature of MDMA use, and this dysfunction appears to result from encoding problems.

2.3.3 Dose-Response Relationship Between Memory Functioning and MDMA-Exposure

The observation of a dose-response relationship between MDMA exposure and verbal memory performance on the word pairs subtest suggests that greater exposure to MDMA is associated with greater impairment in verbal memory and learning. It is evident, however, that the pattern of results for the word pairs trials is inconsistent. Indications of encoding problems in the present study and the existing literature suggest that a dose-response relationship between the initial recall trial of the word pairs subtest ('List a') and MDMA-exposure is expected. Indeed, decrements in performance on this trial were apparent in the MDMA-using group. However, the significant dose-response relationship between MDMA-exposure and the third recall trial, in the absence of a significant relationship for the second trial, is not consistent with what is known of

encoding problems in MDMA-users. The failure to find a significant dose-response relationship between MDMA exposure and memory performance on other verbal and visual subtests, in addition to the inconsistent results apparent in the current literature, raises the question of whether the concept of a dose-response relationship is appropriate in the case of MDMA use. Firstly, measurement problems regarding the assessment of exposure to MDMA are inherent as a result of the unknown dose and composition of MDMA pills, and the problematic nature of self-report of drug using behaviour. The present study's use of a valid and reliable measurement technique attempted to minimise measurement error, however, it is likely that problems with reliability persist. Secondly, animal studies have demonstrated factors such as frequency of administration, absolute concentrations of MDMA in the bloodstream and total exposure, influence the neurotoxic process. The cumulative and multiplicative effects of variations in these dose regimens are unknown in humans and consequently, it is questionable as to whether a linear dose-response equation is appropriate. Moreover a threshold effect may also be apparent. Finally, the multiplicative effects of polydrug use on the neurotoxic process are also unknown, further challenging the capacity to detect any dose-response relationship that might exist. The examination of concurrent cocaine and amphetamine use in the present study failed to shed light on this question and no significant relationship between concurrent polydrug use and memory functioning was found. In conclusion, drawing meaningful conclusions from the relationship between MDMA-exposure and memory functioning is problematic as a result of measurement problems and the unknown nature of the neurotoxic process in recreational users, in addition to the numerous other factors and individual differences that influence memory and cognitive functioning. The inconsistent pattern evident in the results of the examination of a dose-response relationship in the present study is therefore not surprising.

In conclusion, it has been established by the present study that MDMA-users manifest memory impairment. Furthermore, the clinical examination of the nature of memory impairment revealed that MDMA-users demonstrated a pattern of impairment that was consistent with encoding deficits. The present study highlights the need for future research to confirm the existence of inefficient encoding processes in other samples of MDMA-users, and to rule out the possibility of concurrent retrieval deficits. Finally the observation of memory impairment in the present study raises the question of whether impairment persists after abstinence from MDMA. This question is particularly pertinent in light of observations of neuronal regeneration in animal studies (Steele et al., 1994). The study presented in the following chapter will address this question and examine memory dysfunction in previous MDMA-users who have been abstinent from the drug for two years.

CHAPTER 3

Memory Dysfunction in Two Year Abstinent MDMA-Users: A clinical examination of the long-term cognitive effects of recreational MDMA use.

As has been discussed in Chapter 1, the possible neurotoxic consequences of recreational MDMA use were first raised by animal studies, which demonstrated that MDMA is a selective neurotoxin to serotonergic pathways in the brains of experimental animals and non-human primates. The observation of serotonergic neurotoxicity in non-human primates after oral administration of MDMA in doses comparable to recreational use of the drug consolidated concerns that similar patterns of toxicity were occurring in humans. Investigations of serotonergic integrity in the brains of human recreational users have confirmed indications of neurotoxicity. Neuroimaging, neuroendocrine, and CSF studies suggest that recreational MDMA-users manifest indicators consistent with serotonergic degeneration and that these effects are dose-related. It is evident from the existing literature and the study reported in the previous chapter that one of the functional implications of MDMA-induced neurotoxicity is memory dysfunction. The evidence presented in Chapter 2 suggests that the nature of this memory dysfunction is consistent with impaired encoding processes. The review of the literature in the first chapter indicates that general cognitive impairment has also been associated with recreational MDMA-use. These findings are consistent with what is known of the dense serotonergic innervation of the hippocampus and cortex, the areas of the brain implicated in memory and general cognitive functioning respectively, suggesting that these brain regions are particularly vulnerable to the neurotoxic effects of MDMA. The observation of memory dysfunction in current recreational MDMA-users presented in the previous study poses the question of whether memory impairment

is a permanent consequence of MDMA use, or whether axonal regeneration and consequently, cognitive recovery occurs over time.

On the basis of the animal literature investigating the long-term effects of MDMA, it can be hypothesised that MDMA-induced neurotoxicity in humans may also be enduring. It has been observed that MDMA-induced neural damage in primates is prolonged and possibly permanent. However, indications of neuronal recovery are also evident. An examination of serotonergic functioning in MDMA-treated monkeys 18 months after administration found evidence to suggest persistent serotonergic degeneration in some brain regions and reinnervation in other areas (Insel et al., 1989). Similar patterns of neuronal reinnervation were found in MDMA-treated primates seven years after administration of MDMA (Hatzidimitriou et al., 1999). In this study, ten squirrel monkeys were injected with MDMA twice daily (5mg/kg) on four consecutive days, while control monkeys received injections of saline at the same dose regimen. Post-mortem analyses of half of the sample, two weeks after administration, revealed pronounced reductions in serotonergic axon density in the cerebral cortex, hippocampus, striatum, amygdala and thalamus, and slight to moderate reductions in the hypothalamus of MDMA-treated monkeys when compared to controls. Post-mortem analyses of the remaining monkeys, seven years after administration of MDMA, revealed that serotonergic axon density remained decreased in the neocortex, although significant recovery relative to the two-week survivors was evident. Recovery in one field of the hippocampal region also occurred in the seven year survivors, however, significant decreases in serotonin axon density remained apparent in the remaining fields. Similar indications of partial recovery were apparent in the striatum of the seven year survivors, while complete recovery was evident in the thalamus and hypothalamus and some areas of the amygdala. The researchers concluded from their findings that

monkeys treated with MDMA continue to show altered brain serotonin innervation patterns seven years after administration, suggesting that some MDMA-induced alterations in serotonergic innervation may be permanent (Hatzidimitriou et al., 1999). The study findings suggest that although some serotonergic recovery does take place over a seven year period, this recovery is not always complete and does not occur in a number of regions. Of particular significance to the study of memory and cognitive dysfunction in human recreational users is the observation that those areas of the brain that do not completely recover include the neocortex and hippocampus.

The pattern of partial recovery and prolonged MDMA-induced damage in primates leads to the question of whether similar patterns of deinnervation persist in humans, after discontinuation of use. The effects of MDMA-use on serotonergic functioning in humans has not been investigated after long periods of abstinence to date. However, a neuroendocrine study of MDMA-users 12 months after discontinuation of MDMA use has demonstrated that indications of long-lasting serotonergic system impairment are also evident in humans (Gerra et al., 2000). Fifteen male recreational MDMA-users with a history of at least 25 occasions of use were administered a d-fenfluramine challenge (a specific serotonergic agonist) after both three weeks and 12 months of abstinence from MDMA. Blunted prolactin and cortisol responses to d-flenfluramine in comparison to controls were observed after three weeks of abstinence, indicating an overall reduction of serotonergic transmission in MDMA users. Blunted prolactin responses remained unchanged after 12 months of abstinence, and were significantly reduced in comparison to controls, suggesting that the overall reduction in serotonergic transmission observed after three weeks of abstinence had endured. In contrast, cortisol responses were restored after 12 months discontinuation of MDMA. Comparisons revealed that cortisol responses for 12 month abstinent MDMA-users did not differ

significantly from controls, and had improved significantly when compared to responses recorded three weeks after discontinuation. It was argued by the researchers that the restored responses of cortisol in the 12 month abstinent MDMA users may represent an expression of initial recovery in the serotonergic system. Furthermore, the recovery of the cortisol responses after 12 months, in comparison to the enduring reduction in prolactin responses, suggests that MDMA-induced neurotoxicity may differently affect distinct areas of the serotonergic system (Gerra et al., 2000).

Observations of prolonged and possibly permanent serotonergic degeneration in monkeys seven years after administration of MDMA, in addition to indications of enduring serotonergic system damage in humans 12 months after discontinuation of use, suggest that long-term cognitive consequences of recreational MDMA-use are also probable. It was the purpose of the study reported in this chapter to determine if functional implications of MDMA-induced serotonergic neurotoxicity were apparent after two years of abstinence and, specifically, if the memory and cognitive dysfunction observed in current MDMA-users was evident two years after discontinuation of MDMA use.

3.1 METHOD

3.1.1 Participants

A total of sixty individuals, thirty abstinent MDMA-users and thirty controls, participated in the study. The MDMA group was comprised of thirty abstinent recreational MDMA-users who had used MDMA at least 10 times in their lives and who had not used the drug within the previous two years. As mentioned in the previous study, MDMA-users are a hidden population of unknown size and composition and it is therefore impossible to systematically sample from this population. Thus subjects were

recruited via peer networks using the snowball technique. Initial contacts were generated through abstinent MDMA-users already known to the experimenter and leaflets and posters distributed in music stores throughout Canberra city. The abstinent MDMA-users were compared to the 30 control subjects described in the previous study. Comparisons between abstinent MDMA-users and the 31 current MDMA-users recruited for the previous study were also conducted. Abstinent MDMA-users were paid $20 for their participation in the study. Controls completed the study to obtain credit points as a component of their undergraduate degree in psychology. There was no mean difference between the two groups in age, depression and anxiety. The two groups differed significantly in mean intelligence and sex distribution. Exclusion criteria for the study included: past or present psychotic illness, previous incidence of serious head injury, and English as a second language. Neither depression nor anxiety were grounds for exclusion because both conditions were measured and controlled for statistically.

Three cases in the abstinent MDMA-users cohort were current heroin users. There were too few cases to control for the possible confounding effects of heroin use through regression analyses, thus a sensitivity analysis was conducted, where the regression analyses were re-run with the exclusion of these cases. No differences in the outcome of the results were evident, thus these cases were retained in the analyses.

3.1.2 Study Design

The retrospective cohort study design described in the previous chapter was employed to examine the long-term effects of MDMA use on memory functioning.

3.1.3 Procedure

The procedure outlined in the previous study was replicated to study the long-term effects of MDMA-use on memory functioning. The identical screening process, consent form, questionnaire and time line interview method were implemented and the assessment battery described in the previous chapter was administered. Completed profiles were stored under the same restricted conditions to protect the confidentiality and anonymity of participants and the study was granted approval by the Australian National University Human Research Ethics Committee.

3.1.4 Data Analysis

The data were analysed using the software package SPSS for Windows Version 9.0. The procedures recommended by Tabachnick and Fidell (1989) were used to screen the data prior to statistical analyses.

Two sets of comparative analyses in memory functioning were conducted: comparisons between controls and abstinent MDMA-users, and comparisons between current and abstinent MDMA-users. For discrete variables, comparisons between groups were performed using Pearson's chi-square test and Fisher's exact test, where expected cell frequencies in two by two tables were less than five. For continuous variables with approximate normal distributions, comparisons between groups were made using student's t-test for independent samples. For variables not conforming to a normal distribution, comparisons between groups were made using the non-parametric Mann-Whitney U-test. All statistical tests employed a two-tailed alpha criterion of 0.05.

As outlined in the previous study, comparisons between the groups' memory performances were made while adjusting for possible confounding variables by developing multiple linear regression models. In order to maximise power and precision, each of these models was reduced using the backward elimination method (Kleinbaum, Kupper & Muller, 1988). As described previously, variables were removed from the model when they were not statistically significant, providing that they did not substantially alter the estimates of the variables remaining in the model. This method results in the most parsimonious model that is able to explain the data, while increasing the precision of the estimates of interest. The adjusted mean differences and t-values were derived from the final regression models. The assumptions of linearity and normality of the error distribution were assessed by graphical analysis of the residuals, while outliers were also assessed graphically. The results of these statistical analyses are presented in the following section.

3.2 RESULTS

The outcomes of the aforementioned comparative analyses are reported in the following sections. The results of the comparisons between abstinent MDMA-users and controls are presented first, followed by the results of the comparisons between the two MDMA-using cohorts. In each set of analyses, demographic information, estimations of current psychological and intellectual functioning, recreational drug use and memory functioning are compared. In the second set of analyses the pattern of MDMA use for the two cohorts is also compared, in addition to an examination of the dose-response relationship between past MDMA-exposure and memory performance.

COMPARATIVE ANALYSES BETWEEN ABSTINENT MDMA-USERS AND CONTROLS

3.2.1 Demographic Information

The demographic characteristics of the sample are presented in Tables 3.1 to 3.3. As discussed in the previous chapter, age, sex, intellectual functioning, depression and anxiety influence memory functioning (Lezak, 1995). Thus differences between the abstinent MDMA-using cohort and controls on these variables were assessed to establish whether the two groups were well matched.

Table 3.1: Means, Standard Deviations for Age, Education and Estimated Intelligence (IQ). (N = 60)

	Age (years)	Education (years)	IQ (NART)
Controls	23.33 (6.59)	14.67 (1.94)	106.97 (7.17)
Abstinent MDMA	24.80 (6.84)	12.88 (2.47)**	100.53 (10.51)**

**p<.01

As can be seen from Table 3.1, the cohort of abstinent MDMA-users was well matched with controls for age, $t(58) = -.846$, $p>.05$, however significant differences between the two groups were apparent in years of education and estimated intelligence, as measured by the NART. Controls had completed significantly more years of education than abstinent MDMA-users, $t(58) = 3.11$, $p<.01$ and had higher estimated intelligence than abstinent MDMA-users, $t(58) = 2.78$, $p<.01$. In past studies of memory dysfunction in MDMA-users, years of education has been used as an indicator of intellectual functioning in place of more concise measures (e.g. Wareing et al, 2000). It was perceived that estimated IQ would be a more genuine estimation of intellectual functioning, thus education was not controlled for statistically.

Table 3.2: Sex Distribution for Controls and Abstinent MDMA-Users

	Sex		
	Female (%)	Male (%)	Total
Control	20 (66.7)	10 (33.3)	30
Abstinent MDMA	9 (30.0)	21 (70.0)	30
Total	29 (48.3)	31 (51.7)	

As shown in Table 3.2, there was a significant difference between the two groups in terms of the distribution of males and females in each group, $\chi^2(1, \underline{N} = 60) = 8.08$, $\underline{p}<.01$. This group difference was controlled for statistically in subsequent comparative analyses for memory functioning.

Table 3.3: Means and Standard Deviations for Depression and Anxiety

	Depression (BDI)	Anxiety (BAI)
Controls	8.07 (8.72)	8.03 (8.30)
Abstinent MDMA	11.80 (11.17)	11.87 (12.21)

It is evident from Table 3.3 that there were no significant differences between controls and MDMA-users on measures of depression, $\underline{t}(58) = -1.44$, $\underline{p}>.05$ and anxiety, $\underline{t}(58) = -1.42$, $\underline{p}>.05$. As was the case in the previous study, an examination of the clinically relevant categories of severity for the BDI and BAI indicated that the means for both groups were within the 'Minimal' range for depression and the 'Mild' range for anxiety. The distribution of depression and anxiety scores in terms of these clinically relevant categories of severity were also analysed (see Tables 3.4 and 3.5). As described in the previous chapter, it was perceived that the mean scores of depression and anxiety could potentially underestimate group differences by masking variance in the distribution of severity on these measures.

Table 3.4: Distribution of Depression Scores for Categories of Severity on BDI

	Depression – BDI Categories		Total
	Minimal to Mild (%)	Moderate to Severe (%)	
Control	27 (90.0)	3 (10.0)	30
Abstinent MDMA	24 (80.0)	6 (20.0)	30
Total	51 (85.0)	9 (15.0)	

Table 3.5: Distribution of Anxiety Scores for Categories of Severity on BAI

	Anxiety – BAI Categories		Total
	Minimal to Mild (%)	Moderate to Severe (%)	
Control	25 (83.3)	5 (16.7)	30
Abstinent MDMA	21 (70.0)	9 (30.0)	30
Total	46 (76.7)	14 (23.3)	

However, the two groups were also well matched in terms of depression and anxiety, as measured by the BDI and BAI respectively (see Tables 3.4 and 3.5). There were no significant differences between the two groups in the distribution of either depression, Fisher's exact test, $p>.05$, or anxiety scores, χ^2 (1, $\underline{N}$ = 60) = 1.49, $p>.05$.

3.2.2 Patterns of Recreational Drug Use

As mentioned in the previous chapter, alcohol consumption and illicit drug use have potential consequences for general cognitive functioning (Lezak, 1995), therefore an estimate of recreational drug use was obtained to control for group differences. Differences in the lifetime use and current use of recreational drugs other than MDMA were analysed and are presented in Table 3.6. As described earlier, for the purposes of

this study, lifetime use was defined as reporting having ever taken the drug, and current use was operationalised as reporting use of the drug once a month or more frequently.

Table 3.6: Patterns of Other Recreational Drug Use

	Lifetime Use (ie. ever used) (%)	Current Use (ie. once a month or more) (%)
Alcohol		
Control	25 (83.3)	24 (80.0)
Abstinent MDMA	30 (100.0)	23 (76.7)
Cannabis		
Control	17 (56.7)	6 (20.0)
Abstinent MDMA	26 (86.7)*	19 (63.3)**
Benzodiazapine		
Control	1 (3.3)	0 (0)
Abstinent MDMA	14 (46.7)***	2 (6.7)
Amphetamine		
Control	2 (6.7)	2 (6.7)
Abstinent MDMA	25 (83.3)***	6 (20.0)
Heroin		
Control	0 (0)	0 (0)
Abstinent MDMA	13 (43.3)***	3 (10.0)
Cocaine		
Control	1 (3.3)	0 (0)
Abstinent MDMA	20 (66.7)***	4 (13.3)
LSD		
Control	2 (6.7)	2 (6.7)
Abstinent MDMA	28 (93.3)***	2 (6.7)
Inhalants		
Control	2 (6.7)	1 (3.3)
Abstinent MDMA	17 (56.7)***	0 (0)

*p< .05, **p<.01 ***p<.001

As might be expected, there were a number of differences between the abstinent MDMA-users and controls in the lifetime use of recreational drugs. As shown in Table 3.6 MDMA-users had significantly greater lifetime use of cannabis, $\chi^2(1, \underline{N} = 60) = 6.65$, $\underline{p}<.05$, benzodiazapines, $\chi^2(1, \underline{N} = 60) = 15.02$, $\underline{p}<.001$, amphetamine, $\chi^2 (1, \underline{N} = 60) = 35.62$, $\underline{p}<.001$, cocaine, $\chi^2(1, \underline{N} = 60) = 26.44$, $\underline{p}<.001$, heroin, $\chi^2(1, \underline{N} = 60) = 16.60$, $\underline{p}<.001$, LSD, $\chi^2(1, \underline{N} = 60) = 45.07$, $\underline{p}<.001$ and inhalants, $\chi^2(1, \underline{N} = 60) = 17.33$, $\underline{p}<.001$. These differences were statistically controlled for in later comparative analyses for memory functioning. Despite the marked differences in lifetime use of other drugs,

the two groups were well matched in terms of current drug use, with the exception of cannabis consumption. A greater number of MDMA-users currently used cannabis once a month or more frequently, $\chi^2(1, \underline{N} = 60) = 11.59$, $p<.01$ and this difference was controlled for in later comparative analyses.

3.2.3 Memory Functioning in Abstinent MDMA-Users and Controls

The results of the analyses comparing the memory performance of abstinent MDMA-users and controls follow the same format as the previous study and are presented in the following sections. Firstly, comparisons between abstinent MDMA-users and controls on the WMS-III memory indexes are presented. Immediate, delayed and working memory functioning are examined, followed by the indexes representing immediate and delayed memory functioning for both the auditory (verbal) and visual modalities. Secondly, comparisons between abstinent MDMA-users and controls are made for performances on each of the verbal and visual memory subtests. Finally, results of the comparison between abstinent MDMA-users and controls for attention and working memory performance are presented. Final regression models can be found in Appendix IV for significant comparisons and comparisons which were no longer significant after controlling for potential confounders.

Memory Indexes

Both adjusted and unadjusted comparisons between abstinent MDMA-users and controls for memory functioning, as measured by the WMS-III memory indexes, are presented in this section. The results of these analyses are summarised in Tables 3.7 to 3.9.

Table 3.7: WMS-III Memory Index Means and Comparisons for Abstinent MDMA-Users (n = 30) and Controls (n = 30).

WMS-III Memory Index	Mean	Unadjusted Mean Difference	Adjusted Mean Difference	Unadjusted t	Adjusted t
Immediate Memory					
Control	112.83	18.20	17.44	6.01***	-5.38***
Abstinent MDMA	94.63				
General Memory (delayed)					
Control	110.23	15.17	15.17	5.25***	-5.25***
Abstinent MDMA	95.07				
Working Memory					
Control	111.47	10.43	9.84	2.90**	-2.43*
Abstinent MDMA	101.03				

*p<.05, **p<.01, ***p<.001

It is evident from Table 3.7 that abstinent MDMA-users displayed significantly poorer immediate, general (delayed) and working memory functioning, as measured by the WMS-III composite memory indexes. The differences between the two groups' memory functioning remained after adjusting for the effects of potential confounders. Intelligence was a significant covariate for the immediate memory index, while intelligence and sex were significant covariates for the working memory index. No covariates were significant in the final regression model for the general memory index, thus the unadjusted analysis was retained.

An examination of the differences between abstinent MDMA-users and controls in terms of immediate memory functioning in the verbal and visual modalities, revealed statistical significant differences between the two groups.

Table: 3.8 WMS-III Immediate Memory Index Means and Comparisons for Abstinent MDMA-Users (n = 30) and Controls (n = 30).

WMS-III Memory Index	Mean	Unadjusted Mean Difference	Adjusted Mean Difference	Unadjusted t	Adjusted t
Auditory (verbal) **Immediate**					
Controls	118.87	17.10	12.68	5.61***	-4.09***
Abstinent MDMA	101.77				
Visual Immediate					
Controls					
Abstinent MDMA	102.07	13.40	14.87	4.14***	-4.73***
	88.67				

***p<.001

As can be seen from the unadjusted and adjusted comparisons presented in Table 3.8, MDMA-users displayed significantly poorer verbal and visual immediate memory functioning than controls. Intelligence and age were significant covariates for the verbal immediate memory index and anxiety was a significant covariate for the visual immediate memory index.

Table 3.9: WMS-III Delayed Memory Index Means and Comparisons for Abstinent MDMA-Users (n = 30) and Controls (n = 30).

WMS-III Memory Index	Mean	Unadjusted Mean Difference	Adjusted Mean Difference	Unadjusted t	Adjusted t
Auditory (verbal) **Delayed**					
Controls	111.70	11.70	10.36	3.94***	-3.28**
Abstinent MDMA	100.00				
Visual Delayed					
Controls	101.63	14.30	14.30	4.22***	-4.22***
Abstinent MDMA	87.33				
Auditory Recognition					
Controls	113.83	10.50	10.50	3.63**	-3.63**
Abstinent MDMA	103.33				

**p<.01, ***p<.001

It is apparent from Table 3.9 that both the unadjusted and adjusted comparisons were also statistically significant for the WMS-III delayed memory indexes. Abstinent MDMA-users' delayed memory functioning was poorer than controls in the verbal modality, where intelligence was a significant covariate, and the visual modality, where there were no significant covariates. Finally, it is also apparent from Table 3.9 that abstinent MDMA-users' cued recall performance, as measured by the WMS-III verbal recognition index, was significantly poorer than controls. The unadjusted analysis was retained as no covariates were significant in the model.

Verbal Memory Subtests

In this section, abstinent MDMA-users and controls' performance on the verbal memory subtests are compared. Given significant differences were found between MDMA-users and controls on the WMS-III verbal memory indexes, individual subtest performances were examined to establish the nature of the verbal memory dysfunction in MDMA-users. Tables 3.10 and 3.11 represent the comparisons in performance on each of the verbal memory subtests, both before and after controlling for the potentially confounding effects of sex, age, intelligence, depression, anxiety and other drug use. As described in the previous study, the total logical memory subtest performance for the immediate (I) and delayed (II) conditions were compared for abstinent MDMA-users and controls, in addition to an examination of group performance on each of the individual stories (A and B), including the two trials of Story B in the immediate condition (Bi and Bii). Finally, performance on the recognition trial of logical memory, a measure of cued recall, was compared. The results of these analyses are presented in Table 3.10. Final regression models for significant comparisons, and comparisons that were no longer significant after controlling for the influence of potential confounders, can be found in Appendix IV.

Table 3.10: WMS-III Logical Memory Subtest Means and Comparisons for Abstinent MDMA-Users (n = 30) and Controls (n = 30).

Subtest	Mean	Unadjusted Mean Difference	Adjusted Mean Difference	Unadjusted t	Adjusted t
Logical Memory I Total					
Control	49.80	11.20	7.89	5.49***	-3.89***
Abstinent MDMA	38.60				
Logical Memory I Story A					
Control	16.97	3.93	-3.15	5.25***	-4.23***
Abstinent MDMA	13.03				
Logical Memory I Story B i					
Control	13.87	3.27	-3.15	3.93***	-3.28**
Abstinent MDMA	10.60				
Logical Memory I Story B ii					
Control	18.97	4.00	-2.51	4.55***	-2.95**
Abstinent MDMA	14.97				
Logical Memory II Total					
Control	31.40	8.63	-7.26	5.11***	-3.99***
Abstinent MDMA	22.77				
Logical Memory II Story A					
Control	14.07	4.73	-4.15	4.57***	-3.76***
Abstinent MDMA	9.33				
Logical Memory II Story B					
Control	17.27	3.83	-2.85	3.96***	-2.77**
Abstinent MDMA	13.43				
Logical Memory Recognition					
Control	27.80	1.60	-1.37	3.13**	-2.56*
Abstinent MDMA	26.20				

*p<.05, **p<.01, ***p<.001

The unadjusted and adjusted comparisons presented in Table 3.10 indicate that abstinent MDMA-users recalled significantly less information than controls on the total logical memory I subtest, a measure of immediate contextual verbal memory (intelligence and

age were significant covariates). A break down of the two logical memory stories, indicated that MDMA-users recalled significantly less information than controls from Story A and from both the first and second presentation of Story B. Intelligence was a significant covariate for Story A, while intelligence, age and sex were significant covariates for the first presentation of Story B. Intelligence and age were significant covariates for the second presentation of Story B.

The adjusted and unadjusted analyses presented in Table 3.10 reveal that after a delay of 25 to 35 minutes, abstinent MDMA-users recalled significantly less information than controls on the total logical memory II subtest, (age and intelligence were significant covariates). The analysis of the story recall performance of the two groups after the delay revealed that abstinent MDMA-users recalled significantly less information from both Story A and B. Sex was a significant covariate, in the case of Story A, and intelligence and age were significant covariates in the case of Story B. Finally, MDMA-users performed significantly worse than controls on the logical memory recognition subtest, a measure of cued recall, (age was a significant covariate).

As outlined in the previous study, the recognition performance for the two groups was broken down by story to determine if differences were apparent for both Story A and Story B. Controls' cued recall performance for Story A ($\underline{M}$ = 13.13, $\underline{SD}$ = 1.59) was comparable to abstinent MDMA-users ($\underline{M}$ = 12.40, $\underline{SD}$ = 1.73), $\underline{t}(58) = 1.71$, $\underline{p}>.05$. However, controls correctly recognised significantly more information from Story B ($\underline{M}$ = 14.67, $\underline{SD}$ = 0.55) than abstinent MDMA-users ($\underline{M}$ = 13.83, $\underline{SD}$ = 1.23), $\underline{t}(58) = 3.38$, $\underline{p}<.01$). This difference endured after controlling for the effects of potential confounders (age was a significant covariate).

Verbal memory performance was then compared for the two groups for the total Verbal Paired Associates (VPA) subtest, in addition to comparisons for each of the four recall trials (a – d). Recall performance after the delay of 25 to 35 minutes (VPA II) was also compared for controls and abstinent MDMA-users. As was the case in the previous study, the VPA recognition subtest was not included in the analysis because every participant obtained a perfect score on this measure.

Table 3.11: WMS-III Verbal Paired Associates (VPA) Subtest Means and Comparisons for Abstinent MDMA-Users (n = 30) and Controls (n = 30).

Subtest	Mean	Unadjusted Mean Difference	Adjusted Mean Difference	Unadjusted t	Adjusted t
VPA I Total					
Control	29.23	5.73	2.87	3.52**	-1.60
Abstinent MDMA	23.50				
VPA I List a					
Control	6.27	2.13	1.32	3.47**	-1.91
Abstinent MDMA	4.13				
VPA I List b					
Control	7.47	1.73	0.84	3.48**	-1.54
Abstinent MDMA	5.73				
VPA I List c					
Control	7.77	1.30	0.44	3.28**	-1.03
Abstinent MDMA	6.47				
VPA I List d					
Control	7.73	0.57	0.08	1.74	-0.42
Abstinent MDMA	7.17				
VPA II					
Control	7.60	0.25	0.07	0.71	-0.28
Abstinent MDMA	6.80				

**p<.01

As can be seen in Table 3.11, abstinent MDMA users performed significantly worse than controls on the total VPA subtest, a measure of immediate verbal memory and learning. However, this difference was no longer apparent after controlling for the effects of sex and intelligence. Abstinent MDMA-users recalled significantly fewer word pairs than controls after the first presentation of the word pairs (List 'a'). This

difference failed to reach statistical significance after controlling for the effects of intelligence and sex, however a trend was evident (p=.06). The unadjusted analysis for List 'b', presented in Table 3.11, reveals that MDMA-users recalled significantly fewer word pairs than controls after the second presentation of the word pairs, however, this group difference was again no longer apparent after controlling for the effects of intelligence and sex. Similarly, the unadjusted analysis of the third presentation of the word pairs (List 'c') indicates that abstinent MDMA-users recalled significantly fewer word pairs, but, this group difference was again no longer evident after controlling for the effects of sex, intelligence and age. Finally, there was no difference between the two groups in the number of word pairs recalled after the final presentation (List 'd') or after the delay of 25 to 35 minutes (VPA II).

Visual Memory Subtests

In the following section both the unadjusted and adjusted comparisons between abstinent MDMA-users and controls' performance in the visual memory subtests are presented (final regression models can be found in Appendix IV for significant comparisons and comparisons which were no longer significant after controlling for confounders). The performance of controls and abstinent MDMA-users on the immediate (I) and delayed (II) conditions of the Faces subtest, a measure of cued visual recall, and the Family Pictures subtest, a measure of memory for contextual visual material, were compared using the aforementioned analyses. The results of these analyses are presented in Table 3.12.

Table 3.12: WMS-III Faces and Family Pictures Subtest Means and Comparisons for Abstinent MDMA-Users (n = 30) and Controls (n = 30).

Subtest	Mean	Unadjusted Mean Difference	Adjusted Mean Difference	Unadjusted t	Adjusted t
Faces I					
Control	39.43	2.77	3.11	2.78**	-3.15**
Abstinent MDMA	36.67				
Faces II					
Control	39.13	3.03	3.03	2.85**	-2.85**
Abstinent MDMA	36.10				
Family Pictures I					
Control	49.40	10.07	12.31	4.16***	-5.02***
Abstinent MDMA	39.33				
Family Pictures II					
Control	49.10	10.43	10.59	4.24***	-4.04***
Abstinent MDMA	38.67				

**p<.01, ***p<.001

The unadjusted and adjusted comparisons presented in Table 3.12 indicate that abstinent MDMA-users recognised fewer faces than controls in both the immediate (I) and delayed (II) condition of the Faces subtest. Anxiety was a significant covariate for the immediate condition of the Faces subtest. No covariates were significant within the final model for the delayed condition, thus the unadjusted analysis was retained. An examination of the unadjusted and adjusted analyses for the family pictures subtest, presented in Table 3.12, indicates that abstinent MDMA-users recalled significantly less information than controls in both the immediate (I) and delayed (II) conditions. Significant covariates were intelligence and anxiety in the case of the immediate condition, and age and intelligence in the case of the delayed condition.

Attention and Working Memory Subtests

In this section, comparisons between abstinent MDMA-users and controls' performance on the WMS-III attention and working memory subtests are presented. The results of these analyses are summarised in Table 3.13.

Table 3.13: WMS-III Letter-Number Sequencing, Spatial Span and Digit Span Subtest Means and Comparisons for Abstinent MDMA-Users (n = 30) and Controls (n= 30).

Subtest	Mean	Unadjusted Mean Difference	Adjusted Mean Difference	Unadjusted t	Adjusted t
Letter Number Sequencing					
Control	13.33	2.23	1.78	3.24**	-2.48*
Abstinent MDMA	11.10				
Spatial Span Total					
Control	18.16	1.17	0.90	1.51	-1.09
Abstinent MDMA	17.00				
Spatial Span Forward					
Control					
Abstinent MDMA	9.10	0.47	0.39	0.93	-0.73
	8.63				
Spatial Span Backward					
Control	8.93	0.57	0.45	1.39	-1.02
Abstinent MDMA	8.37				
Digit Span Total					
Control	20.37	3.50	2.61	3.74***	-2.77**
Abstinent MDMA	16.87				
Digit Span Forward					
Control	11.60	0.97	0.41	1.81	-0.77
Abstinent MDMA	10.63				
Digit Span Backward					
Control					
Abstinent MDMA	8.77	2.43	2.12	4.71***	-3.92***
	6.33				

*p<.05, **p<.01, ***p<.001

As can be seen from Table 3.13, abstinent MDMA-users performed significantly worse than controls on the letter-number sequencing subtest, a measure of working memory intelligence was a significant covariate). There were no significant differences between abstinent MDMA-users and controls' performances on the spatial span subtests and this remained the case after adjusting for potential covariates. Abstinent MDMA-users' performance on the total digit span subtest, a measure of attention and working memory, was significantly poorer than controls, (intelligence was a significant covariate). There were no differences between the two groups' performance on the digit span forwards subtest, a measure of basic attention, for either the unadjusted or adjusted comparisons. However, significant differences between the two groups were evident on

the digit span backward subtest, a measure of working memory (intelligence was a significant covariate).

COMPARATIVE ANALYSES BETWEEN ABSTINENT MDMA-USERS AND CURRENT MDMA-USERS

Comparative analyses were conducted between the two MDMA-using cohorts to examine possible differences in memory functioning. In the following section, demographic information describing the two cohorts is reported, followed by an examination of the two groups' patterns of past and current MDMA-use. Comparisons between the two groups' memory functioning are then presented.

3.2.4 Demographic Information

The demographic characteristics of the two groups are presented in Tables 3.13 to 3.15. Potential differences in age, sex, estimated intelligence, depression and anxiety were examined for the two groups to determine whether the MDMA-using cohorts were well matched for potential confounding variables.

Table 3.13: Means, Standard Deviations for Age, Education and Estimated Intelligence (IQ) (N = 61).

	Age (years)	Education (years)	IQ (NART)
Current MDMA	24.00 (4.66)	13.77 (2.22)	103.39 (7.64)
Abstinent MDMA	24.80 (6.84)	12.88 (2.47)	100.53 (10.51)

As can be seen from Table 3.13, the cohort of abstinent MDMA-users was well matched with current MDMA-users in terms of age, $t(59) = -0.54$, $p>.05$, years of education $t(59) = 1.48$, $p>.05$ and estimated intelligence, as measured by the NART, $t(59) = 1.55$, $p>.05$.

Table 3.14: Sex Distribution for Current and Abstinent MDMA-Users.

	Sex		Total
	Female (%)	Male (%)	
Current MDMA	19 (61.3)	12 (38.7)	31
Abstinent MDMA	9 (30.0)	21 (70.0)	30
Total	28 (45.9)	33 (54.1)	

There was a significant difference between the two cohorts in terms of the distribution of males and females in each group, $\chi^2(1, \underline{N} = 61) = 6.01$, $\underline{p}<.05$ (Table 3.14). As described earlier, sex is a potential confounder for memory performance, therefore, this group difference was controlled for statistically using regression analysis.

Table 3.15: Means and Standard Deviations for Depression and Anxiety

	Depression (BDI)	Anxiety (BAI)
Current MDMA	10.53 (10.37)	10.10 (8.88)
Abstinent MDMA	11.80 (11.17)	11.87 (12.21)

Finally, as can be seen from Table 3.15, there were no significant differences between current and abstinent MDMA-users for measures of depression, $\underline{t}(58) = -0.46$, $\underline{p}>.05$ and anxiety, $\underline{t}(58) = -0.64$, $\underline{p}>.05$. Furthermore, the distribution of depression and anxiety scores, in terms of the BAI and BDI clinically relevant categories of severity, were comparable for the two groups (see Tables 3.16 and 3.17).

Table 3.16: Distribution of Depression Scores for Categories of Severity on BDI.

	Depression – BDI Categories		
	Minimal to Mild (%)	Moderate to Severe (%)	Total
Current MDMA	25 (80.6)	6 (19.4)	31
Abstinent MDMA	24 (80.0)	6 (20.0)	30
Total	49 (80.3)	12 (19.7)	

Table 3.17: Distribution of Anxiety Scores for Categories of Severity on BAI

	Anxiety – BAI Categories		
	Minimal to Mild (%)	Moderate to Severe (%)	Total
Current MDMA	22 (71.0)	9 (29.0)	31
Abstinent MDMA	21 (70.0)	9 (30.0)	30
Total	43 (70.5)	18 (29.5)	

3.2.5 Patterns of MDMA Use in Current and Abstinent MDMA-Users

A comprehensive analysis of past and current recreational MDMA use was conducted for the abstinent users and current users respectively. As outlined in the previous study, the estimated total lifetime dose of MDMA, the highest frequency of MDMA use in one month and the highest number of pills swallowed at the same time were examined on the basis of the animal literature, which suggests these characteristics of MDMA consumption mediate the neurotoxic process (Steele et al, 1994). The results of these analyses are presented in table 3.18.

Table 3.18: Patterns of MDMA Use in Current (n = 31) and Abstinent MDMA-Users (n = 30).

	Minimum	Maximum	Median	Mean (SD)
Estimated Total Dose (no. of pills)				
Current	11	680	104	166 (171)
Abstinent	12	7426	104	523 (1363)
Highest frequency of Use[a]				
Current	0.5	16	4	5 (4)*
Abstinent	0.5	300	8	20 (54)
Highest Dose[b]				
Current	0.5	5	1	2 (1)
Abstinent	0.5	12	2	2 (2)
Time Since Last Use (days)				
Current	7	168	28	37 (33)***
Abstinent	730	2920	730	977 (468)
Duration of Use (months)				
Current	5	156	36	50 (36)
Abstinent	2	120	42	43 (32)
Age of first Use (years)				
Current	14	30	19	20 (4)
Abstinent	13	35	18	19 (5)
Polydrug Use[c]				
Current	0	184	15	44 (60)
Abstinent	0	3713	6	251 (736)

*p<.05, ***p<.001

[a]Highest number of occasions of MDMA use in one month.

[b]Highest number of MDMA pills swallowed at one time.

[c]Number of occasions cocaine and/or amphetamine were taken concurrently.

It can be seen from Table 3.18 that the two cohorts of MDMA-users had comparable patterns of MDMA use in terms of estimated total exposure to MDMA, $t(59) = -2.20$, $p>.05$ and highest dose, $t(59) = -1.58$, $p>.05$. However, the abstinent cohort had previously used MDMA with a greater degree of regularity than current users, Mann-Whitney U-test, $z = -2.05$, $p<.05$. As was expected, there was a significant difference between the two groups for the length of time since last use of MDMA, $t(59) = -10.97$,

$p<.001$, however, the duration of use for the two groups was comparable, $t(59) = -0.70$, $p>.05$. Finally, the number of occasions of concurrent use of amphetamine and / or cocaine with MDMA was not significantly different for the two groups, $t(59) = -1.54$, $p>.05$.

It is also apparent from Table 3.18 that the cohort of abstinent MDMA-users manifested a diverse range of past MDMA use. The estimated extent of total exposure for the cohort was highly variable and ranged from 12 to 7426 pills consumed in a lifetime, (M = 523). The frequency of use ranged from less than one occasion of use per month, to 300 occasions in one month, which represented a high level of consumption on a daily basis. The mean for the highest frequency of use was 20 occasions per month, which is five occasions of use per week. The number of pills swallowed at the one time ranged from a half to 12 pills (M = 2). It is also evident from Table 3.18 that the period of abstinence within the cohort ranged from 2 to 8 years, (M = 3), and the duration of MDMA use ranged from 2 months to 10 years, with a mean duration of approximately 4 years of use. Finally, the mean age of first use of 19 in the abstinent cohort (range 13 to 35), was similar to the current users (M = 20), $t(59) = 0.85$, $p>.05$.

The possibility of a dose-response relationship between memory functioning and past MDMA exposure was examined for abstinent MDMA-users by constructing an exposure variable from the estimated total lifetime dose of MDMA, the highest frequency of use in one month and the highest number of pills swallowed at the same time. Correlational analyses between this measure of exposure and memory performance for each of the WMS-III indexes and subtests revealed no significant relationships. Correlational analyses also failed to reveal a significant relationship

between memory performance on any of the WMS-III indexes or subtests and polydrug exposure.

3.2.6 Lifetime and Current Patterns of Recreational Drug Use for Abstinent and Current MDMA-Users

Differences between current and abstinent MDMA-users in terms of lifetime use and current use of recreational drugs other than MDMA were examined using chi-squared analyses and are presented in Table 3.19.

Table 3.19: Patterns of Other Recreational Drug Use.

	Lifetime Use (ie. ever used) (%)	Current Use (ie. once a month or more) (%)
Alcohol		
Current MDMA	31 (100.0)	27 (87.1)
Abstinent MDMA	30 (100.0)	23 (76.7)
Cannabis		
Current MDMA	21 (67.7)	19 (61.3)
Abstinent MDMA	26 (86.7)	19 (63.3)
Benzodiazapine		
Current MDMA	9 (29.0)	2 (6.5)
Abstinent MDMA	14 (46.7)	2 (6.7)
Amphetamine		
Current MDMA	26 (83.9)	14 (45.2)
Abstinent MDMA	25 (83.3)	6 (20.0)*
Heroin		
Current MDMA	2 (6.5)	1 (3.2)
Abstinent MDMA	13 (43.3)**	3 (10.0)
Cocaine		
Current MDMA	18 (58.1)	6 (19.4)
Abstinent MDMA	20 (66.7)	4 (13.3)
LSD		
Current MDMA	19 (61.3)	6 (19.4)
Abstinent MDMA	28 (93.3)**	2 (6.7)
Inhalants		
Current MDMA	8 (25.8)	0 (0)
Abstinent MDMA	17 (56.7)*	0 (0)

*p< .05, **p<.01

It is evident from Table 3.19 that there were a number of differences between the abstinent and current MDMA-users in the lifetime use of recreational drugs. A greater

proportion of abstinent MDMA-users had a lifetime use of heroin, $\chi^2(1, \underline{N} = 61) = 11.18$, $\underline{p}<.01$, LSD, $\chi^2(1, \underline{N} = 61) = 8.85$, $\underline{p}<.01$, and inhalants, $\chi^2(1, \underline{N} = 61) = 6.00$, $\underline{p}<.05$. Despite these differences in lifetime use of other drugs, the two groups were well matched in terms of current drug use, with the exception of amphetamine consumption. A greater number of current MDMA-users used amphetamine once a month or more frequently, $\chi^2(1, \underline{N} = 61) = 4.38$, $\underline{p}<.05$.

3.2.7 Memory Functioning in Abstinent and Current MDMA-Users

The comparative analyses examining potential differences between current and abstinent MDMA-users' memory performance on the WMS-III indexes and subtests are reported in the following section. The final reduced regression models can be found in Appendix V in cases where significant differences between the two groups were apparent or differences were no longer apparent after controlling for the effects of potential confounders.

Memory Indexes

The adjusted and unadjusted comparisons between abstinent and current MDMA-users for memory functioning, as measured by the WMS-III memory indexes, are presented in Tables 3.20 to 3.22.

Table 3.20: WMS-III Memory Index Means and Comparisons for Abstinent (n = 30) and Current MDMA-Users (n = 31).

WMS-III Memory Index	Mean	Unadjusted Mean Difference	Adjusted Mean Difference	Unadjusted t	Adjusted t
Immediate Memory					
Current MDMA	100.97	6.33	3.85	2.08*	-1.19
Abstinent MDMA	94.63				
General Memory (delayed)					
Current MDMA	101.61	6.55	4.66	2.63*	-1.78
Abstinent MDMA	95.07				
Working Memory					
Current MDMA	105.81	4.77	3.87	1.51	-1.23
Abstinent MDMA	101.03				

*p<.05

It is evident from Table 3.20 that abstinent MDMA-users displayed significantly poorer immediate and general (delayed) memory than current users, as measured by the WMS-III composite indexes, however, these differences were no longer apparent after controlling for the effects of intelligence and sex. There was no difference between the two MDMA-using cohorts in terms of working memory functioning.

Table 3.21: WMS-III Immediate Memory Index Means and Comparisons for Abstinent (n = 30) and Current MDMA-Users (n = 31).

WMS-III Memory Index	Mean	Unadjusted Mean Difference	Adjusted Mean Difference	Unadjusted t	Adjusted t
Auditory (verbal) **Immediate**					
Current MDMA	106.97	5.20	1.22	1.62	-0.41
Abstinent MDMA	101.77				
Visual Immediate					
Current MDMA	94.19	5.53	5.31	1.66	-1.46
Abstinent MDMA	88.67				

The unadjusted and adjusted comparisons presented in Table 3.21 reveal that there were no significant differences between current and abstinent MDMA-users' verbal and visual memory functioning, as measured by the respective WMS-III indexes.

Table 3.22: WMS-III Delayed Memory Index Means and Comparisons for Abstinent (n= 30) and Current MDMA-Users (n = 31).

WMS-III Memory Index	Mean	Unadjusted Mean Difference	Adjusted Mean Difference	Unadjusted t	Adjusted t
Auditory (verbal) **Delayed**					
Current MDMA	106.61	6.61	4.12	2.45*	-1.45
Abstinent MDMA	100.00				
Visual Delayed					
Current MDMA	93.23	5.89	6.50	1.88	-1.96
Abstinent MDMA	87.33				
Auditory Recognition					
Current MDMA	105.81	5.81	1.05	1.29	-0.36
Abstinent MDMA	100.00				

*p<.05

Finally, it is evident from Table 3.22 that abstinent MDMA-users displayed significantly poorer delayed memory functioning than current users in the verbal modality. However, after controlling for the effects of intelligence and sex, these group differences were no longer apparent. There were no differences between the two MDMA-using cohorts in delayed memory functioning in the visual modality, or cued recall performance, as measured by the WMS-III verbal recognition index.

Verbal Memory Subtests

The adjusted and unadjusted analyses comparing performances of abstinent and current MDMA-users on the verbal memory subtests of the WMS-III are presented in this section. Comparisons between abstinent and current MDMA-users for the total logical memory subtest performances and individual story performances, in the immediate (I) and delayed (II) conditions, are presented in Table 3.23. Abstinent and current MDMA-

users' performances were then compared for the total Verbal Paired Associates (VPA) subtest and four recall trials (a – d), in addition to recall performance after the delay of 25 to 35 minutes (VPA II). The results of these analyses are presented in Table 3.24. As was the case in previous comparative analyses, the VPA recognition subtest was not reported because all participants obtained a perfect score.

Table 3.23: WMS-III Logical Memory Subtest Means and Comparisons for Current (n = 31) and Abstinent MDMA-Users (n = 30).

Subtest	Mean	Unadjusted Mean Difference	Adjusted Mean Difference	Unadjusted t	Adjusted t
Logical Memory I Total					
Current MDMA	41.61	3.01	1.63	1.39	-0.78
Abstinent MDMA	38.60				
Logical Memory I Story A					
Current MDMA	13.48	0.45	0.29	0.51	0.33
Abstinent MDMA	13.03				
Logical Memory I Story B i					
Current MDMA	11.32	0.72	0.76	0.93	-0.91
Abstinent MDMA	10.60				
Logical Memory I Story B ii					
Current MDMA	16.81	1.84	1.58	1.94	-1.68
Abstinent MDMA	14.97				
Logical Memory II Total					
Current MDMA	26.26	3.49	2.50	2.13*	-1.48
Abstinent MDMA	22.77				
Logical Memory II Story A					
Current MDMA	11.07	0.12	0.82	1.64	-0.74
Abstinent MDMA	9.33				
Logical Memory II Story B					
Current MDMA	15.19	1.76	1.29	2.08*	-1.56
Abstinent MDMA	13.43				
Logical Memory Recognition					
Current MDMA	26.71				
Abstinent MDMA	26.20	0.51	0.25	0.95	-0.49

*p<.05

The analyses presented in Table 3.23 reveal that abstinent MDMA-users recalled significantly less information than controls on the total logical memory II subtest, a measure of delayed contextual verbal memory. However this group difference did not remain after controlling for the effects of sex. A similar pattern was evident in the case of delayed recall for Story B. The unadjusted analyses indicate that the abstinent MDMA-users recalled significantly less information from Story B than current users after the delay, however, the two groups' performance on this subtest was comparable after controlling for the effects of age and intelligence. The unadjusted and adjusted analyses presented in Table 3.23 indicate that there were no differences between the two MDMA-using cohorts for performance on the remaining logical memory subtests. Further analysis of the recognition task for Story A and B revealed no significant differences in cued recall from Story A for current users ($\underline{M}$ = 12.48, $\underline{SD}$ = 1.69) and abstinent users ($\underline{M}$ = 12.40, $\underline{SD}$ = 1.73), $\underline{t}(59) = 0.19$, $\underline{p}>.05$. Similarly, current users' cued recall performance on Story B ($\underline{M}$ = 14.23, $\underline{SD}$ = 0.88) was comparable to abstinent users ($\underline{M}$ = 13.83, $\underline{SD}$ = 1.23), $\underline{t}(59) = 1.43$, $\underline{p}>.05$). Regression analyses revealed that the two groups' recognition performances remained comparable after controlling for the effects of potential confounders.

Table 3.24: WMS-III Verbal Paired Associates (VPA) Subtest Means and Comparisons for Abstinent (n = 30) and Current (n = 31) MDMA-Users.

Subtest	Mean	Unadjusted Mean Difference	Adjusted Mean Difference	Unadjusted t	Adjusted t
VPA I Total					
Current MDMA	25.55	2.05	0.33	1.13	0.20
Abstinent MDMA	23.50				
VPA I					
List a					
Current MDMA	4.23	0.09	0.73	0.14	1.18
Abstinent MDMA	4.13				
VPA I					
List b					
Current MDMA	6.52	0.78	0.05	1.35	-0.09
Abstinent MDMA	5.73				
VPA I					
List c					
Current MDMA	7.26	0.79	0.28	1.35	-0.64
Abstinent MDMA	6.47				
VPA I					
List d					
Current MDMA	7.55	0.38	0.07	1.17	-0.22
Abstinent MDMA	7.17				
VPA II					
Current MDMA	7.36	0.55	0.16	1.33	-0.37
Abstinent MDMA	6.80				

It evident from Table 3.24 that there were no significant differences between the two MDMA-using cohorts' performances on the VPA subtest, a measure of immediate verbal memory and learning. The pattern of results recorded over the four trials of this subtest for current and abstinent MDMA-users in comparison to controls is represented in Figure 3.1.

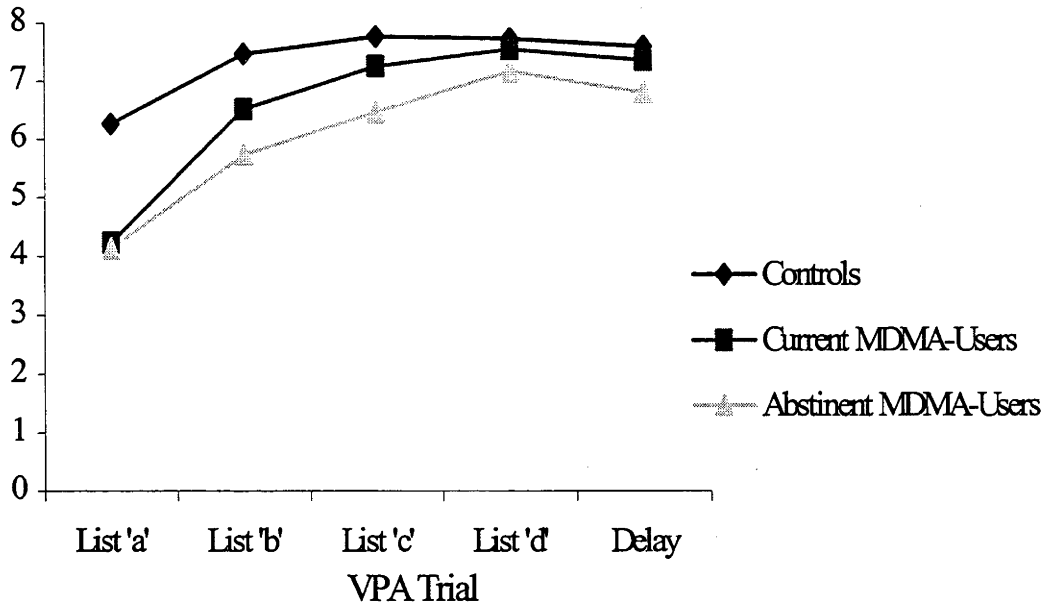

Figure 3.1: Verbal Paired Associates Learning Curve

It is apparent from Figure 3.1 that a similar pattern of learning was evident for the two MDMA cohorts. Performance on the first recall of the word pairs for the two groups is almost identical and is similarly impaired when compared to controls. Thus problems in single trial learning were apparent in both cohorts, when compared to controls. This difference did not reach statistical significance for abstinent users, however, a trend was evident (p=.06). Recall performance on the second presentation of the word pairs then recovered for MDMA-users and remained comparable to controls over subsequent trials.

Visual Memory Subtests

The performance of controls and abstinent MDMA-users on the immediate (I) and delayed (II) conditions of the Faces subtest, a measure of cued visual recall, and the Family Pictures subtest, a measure of memory for contextual visual material, are compared in this section. Both the unadjusted and adjusted comparisons between

current and abstinent MDMA-users' performances on these visual memory subtests are presented in Table 3.25.

Table 3.25: WMS-III Faces and Family Pictures Subtest Means and Comparisons for Abstinent MDMA-Users (n = 30) and Controls (n = 30).

Subtest	Mean	Unadjusted Mean Difference	Adjusted Mean Difference	Unadjusted t	Adjusted t
Faces I					
Current MDMA	37.23	0.56		0.53	
Abstinent MDMA	36.67				
Faces II					
Current MDMA	36.68	0.58		0.53	
Abstinent MDMA	36.10				
Family Pictures I					
Current MDMA	45.19	5.86	5.50	2.47*	-2.39*
Abstinent MDMA	39.33				
Family Pictures II					
Current MDMA	45.03	6.37	5.55	2.62*	-2.27*
Abstinent MDMA	38.67				

*p<.05

Note: Adjusted mean difference and t-value not reported for Faces I and II because regression model not significant.

It can be seen in Table 3.25 that abstinent MDMA-users recalled significantly less information than current users from the family pictures in both the immediate and delayed conditions. These group differences remained after controlling for the effects of potential confounders. Significant covariates included age, in the case of the immediate condition, and intelligence, sex and age, in the case of the delayed condition. There were no significant differences between the two MDMA-using cohorts in the number of faces recalled in the immediate (I) and delayed (II) condition.

Attention and Working Memory Subtests

Comparisons between abstinent and current MDMA-users performance on the WMS-III attention and working memory subtests are presented in Table 3.26.

Table 3.26: WMS-III Letter-Number Sequencing, Spatial Span and Digit Span Subtest Means and Unadjusted t values for Current (n = 31) and Abstinent MDMA-Users (n = 30).

Subtest	Mean	Unadjusted Mean Difference	Adjusted Mean Difference	Unadjusted t	Adjusted t
Letter Number Sequencing					
Current MDMA	12.29	1.19	0.74	2.19*	-1.45
Abstinent MDMA	11.10				
Spatial Span Total					
Current MDMA	17.52	0.52	0.23	0.61	-0.29
Abstinent MDMA	17.00				
Spatial Span Forward					
Current MDMA	8.77	0.14		0.25	
Abstinent MDMA	8.63				
Spatial Span Backward					
Current MDMA	8.74	0.38		0.95	
Abstinent MDMA	8.37				
Digit Span Total					
Current MDMA	18.97	2.10	1.76	2.01*	-1.67
Abstinent MDMA	16.87				
Digit Span Forward					
Current MDMA	11.07	0.43	0.46	0.75	-0.80
Abstinent MDMA	10.63				
Digit Span Backward					
Current MDMA	7.90	1.57	1.23	2.56*	-1.76
Abstinent MDMA	6.33				

*p<.05

Note: adjusted analyses for Spatial Span forwards and backwards not reported because regression models not significant

It can be seen in Table 3.26 that abstinent MDMA-users performed significantly worse than controls on the letter-number sequencing subtest, a measure of working memory. However, this group difference did not endure after controlling for the effects of age and intelligence. There were no significant differences between abstinent MDMA-users

and controls' performances on the spatial span subtests. Abstinent MDMA-users' performance on the total digit span subtest, a measure of attention and working memory, was significantly poorer than controls, however this difference was no longer apparent after adjusting for the effects of intelligence. No significant differences in performance on the digit span forwards task were apparent and the differences between current and abstinent users on the digits backward task was no longer significant after controlling for the effects of intelligence and lifetime use of heroin.

3.3 DISCUSSION

The study presented in this chapter set out to determine whether memory impairment in recreational MDMA-users endured after two years of abstinence from the drug. Several conclusions can be drawn from the comparative analyses between controls and abstinent MDMA-users presented in the previous section. First, it is evident that after two years of abstinence from MDMA, dysfunction in memory and cognitive functioning endures. Abstinent MDMA-users manifested dysfunction in immediate, delayed and working memory. Furthermore, comparative deficits were evident in both the verbal and visual modalities. Second, when compared to the previous study, it was evident that the cohort of abstinent MDMA-users demonstrated impairment in a wider range of memory and cognitive functioning, when compared to controls, than current users. Third, the cohort of abstinent MDMA-users manifested significantly poorer performances than the cohort of current MDMA-users, on a measure of visual memory for meaningful contextual material. The inconsistencies between the pattern of impairment evident in abstinent and current MDMA-users when compared to controls may be due to differences between the two cohorts' frequency of MDMA-use, a factor believed to mediate the neurotoxic process. Finally, similar patterns of dysfunction consistent with encoding

problems were evident in abstinent MDMA-users, however, indications of concurrent retrieval problems in this cohort cannot be ruled out.

A discussion of the comparative analyses between abstinent MDMA-users and controls and the two cohorts of MDMA-users is presented below. Firstly, comparative analyses between abstinent MDMA-users and controls on the WMS-III memory indexes will be discussed to address the question of whether past MDMA-users continue to manifest memory impairment after two years of abstinence from MDMA. The findings of the present study will then be discussed in comparison to the study presented in the previous chapter. Secondly, the comparative analyses between the two cohorts of MDMA-users will be discussed. Finally, the pattern of impairment evident in the abstinent cohort will be examined through the clinical examination of performance on the WMS-III subtests.

3.3.1 Enduring Memory Dysfunction in MDMA-Users After Two Years of Abstinence

Immediate, delayed and working memory functioning in abstinent MDMA-users was examined through comparative analyses of the WMS-III composite memory indexes for abstinent MDMA-users and controls, while controlling for the potentially confounding effects of sex, age, intelligence, depression, anxiety and other drug use. It was apparent that abstinent MDMA-users manifested dysfunction in immediate and delayed memory when compared to controls and these comparative deficits in memory functioning were evident in both the verbal and visual modality. Furthermore, abstinent MDMA-users demonstrated comparative deficits in working memory functioning. As outlined in the previous chapter, cued memory functioning was examined through the independent analysis of the story recognition subtest, rather than the auditory recognition index, and

is discussed in a later section. The recognition index is comprised of recognition performance on both the story subtest and the word pairs subtest, which was deemed invalid because every subject obtained a perfect score on this measure.

It can be concluded from the comparative analyses of the WMS-III memory indexes that recreational MDMA-users, who had been abstinent from the drug for two years, manifested dysfunction in immediate, delayed and working memory functioning. The differences in memory functioning between controls and abstinent MDMA users persisted after adjusting for the effects of intelligence, sex, age, anxiety, depression, and other drug use, suggesting that enduring cognitive dysfunction is a consequence of recreational MDMA-use. The results of the present study suggest that MDMA-induced cognitive dysfunction continues to be manifested two years after discontinuation of use. The cognitive dysfunction observed in the cohort of two-year abstinent users is largely consistent with the dysfunction observed in the current users participating in the study reported in the previous chapter and other studies of current users, providing support for the validity of the findings of the present study (Gouzoulis-Mayfrank et al., 2000; Morgan, 1999). Further studies of cognitive functioning in other cohorts of abstinent MDMA-users are needed to confirm these results and the question of whether some recovery in cognitive functioning occurs, as suggested by the observation of axonal regeneration in animal studies, needs to be addressed by long term studies of abstinent cohorts.

It is evident from the pattern of impairment observed in the present study that the cohort of abstinent MDMA-users manifested impairment in a more diverse range of cognitive functioning when compared to controls than was evident in the cohort of current users in the previous study. Abstinent MDMA-users demonstrated impairment in working

memory and delayed verbal memory when compared to controls, whereas the current users examined in the previous study displayed intact functioning on these measures. Furthermore, the differing patterns of cognitive dysfunction were apparent after controlling for factors that may potentially explain the difference between the two MDMA-using cohorts' cognitive performance, such as intelligence, sex, age, depression, anxiety and other drug use. The two MDMA-using cohorts were comparable in terms of total exposure to MDMA and highest dose of MDMA. However, a significant difference between the two cohorts' frequency of MDMA use was apparent. On average, abstinent MDMA-users' frequency of use was four times greater than current users. Moreover, the cohort of abstinent users' average frequency of MDMA use was five times per week, which constituted heavy consumption in comparison to studies of other Australian cohorts in the literature, which indicate the average frequency of use in MDMA-users is approximately once every 10 days (Topp et al., 1999). It is therefore hypothesised that the more diverse dysfunction evident in the abstinent MDMA-users may be due to their higher frequency of MDMA use, which could potentially have resulted in greater neurotoxicity. The absence of a dose-response relationship in the present study may be considered contradictory to this hypothesis, however, the possibility of a threshold effect for MDMA-induced neurotoxicity suggests that a dose-response relationship may not be observed in such a high use group.

Despite the differences in the pattern of impairment evident for the two groups when compared to controls, comparative analyses of the two MDMA-using cohorts revealed that the two groups' cognitive functioning was comparable on all memory indexes and subtests apart from the family pictures subtest, a measure of visual memory for contextual information. Impaired performance on this isolated test is not sufficient to

imply dysfunction, particularly in the absence of impairment in the remaining subtests and indexes.

In summary, the comparative analyses of memory functioning in abstinent MDMA-users and controls suggest that cognitive dysfunction is an enduring consequence of MDMA use. Additionally, the high frequency of use observed in the present study's cohort of abstinent MDMA-users may explain the more diverse manifestation of cognitive impairment observed in this cohort, when compared to the pattern of impairment observed in current users in the previous chapter. Finally, despite differences in the diversity of impairment in the two cohorts when compared to controls, memory performance was largely comparable for abstinent and current MDMA-users. The following section will examine the nature of the memory dysfunction evident in abstinent MDMA-users through a clinical examination of the WMS-III subtest performances.

3.3.2 The Nature of Memory Impairment in Two Year Abstinent MDMA-Users

As outlined in the previous chapter, memory dysfunction may potentially arise from defective encoding, storage deficits and retrieval problems (Lezak, 1995). A clinical examination of the comparative performances on the individual WMS-III subtests was conducted to determine whether the memory dysfunction evident in abstinent MDMA-users occurred as a result of defective encoding, retrieval or storage. Total subtest performances were not interpreted because they were considered to provide a nonspecific indication of dysfunction. The investigation of the nature of memory dysfunction revealed that abstinent MDMA-users manifested a pattern of impairment, across several subtests, that was consistent with encoding problems. In support of this hypothesis, comparable rates of decay in controls and abstinent users rule out rapid

forgetting as a possible explanation for memory dysfunction in the abstinent cohort. The pattern of impairment was inconsistent with retrieval problems, however, further studies need to be conducted before concurrent retrieval problems are definitively ruled out. Thus it was observed that indications of inefficient encoding processes, evident in the current users in the previous study, were also apparent in two-year abstinent users.

As was the case for the current users in the previous study, abstinent MDMA-users manifested comparative deficits in single trial learning. A definite trend was evident on the first trial of the Verbal Paired Associates (VPA) subtest, but recall performances over the remaining trials were comparable. Abstinent MDMA-users recalled fewer word pairs than controls from List 'a', however, this difference did not reach statistical significance after controlling for the effects of potential confounders. The trend observed suggests that the failure to reach statistical significance may be due to the small sample size. A plausible explanation for the dysfunction in single trial learning, suggested by abstinent MDMA-users' performance on the VPA subtest, is that abstinent MDMA-users do not encode information as efficiently as non-users and therefore require greater exposure to the stimuli before effective retrieval is possible. Recall performance was comparable after the delay, indicating that after repeat exposure, the information was encoded, retained in the memory store and effectively retrieved. On the more complex Logical Memory subtest, abstinent MDMA-users were similarly impaired after a single exposure to both Story A and B, and they failed to recover to recall performances comparable to controls after the second presentation of Story B. An examination of the mean differences revealed that abstinent MDMA-users improved their recall performance at a similar rate to controls after the second presentation of Story B, but remained comparatively impaired. Thus, unlike their performance on the less complex word pairs subtest, abstinent MDMA-users failed to recover to levels

comparable to controls after repeat exposure. This pattern of impairment is consistent with problematic encoding processes.

The encoding dysfunction hypothesis is consistent with the observation that abstinent MDMA-user's recall performance remained impaired after the delay for both Story A and B. Comparable rates of memory decay for both abstinent users and controls, from the immediate to the delayed condition, ruled out rapid forgetting as an alternative explanation for the observed memory dysfunction. Indications of encoding dysfunction were further verified through the examination of the recognition subtest for Story B. Abstinent MDMA-users recognised significantly less information from Story B than controls, suggesting that encoding, rather than retrieval problems were responsible for the comparative deficits observed in recall performance on this subtest. No significant difference between abstinent MDMA-users and controls' recognition performance for Story A was observed, which is consistent with the pattern of recognition performance reported in the previous study. As was outlined in the previous study, the significant difference observed between the two groups' recognition for Story B, but not Story A, can be attributed to the complexity of Story B when compared to Story A. It is suggested that the simplicity of the recognition task for Story A prevented differentiation between the two groups' performance. However, further studies need to be carried out to definitively rule out retrieval problems.

An examination of the visual memory subtests indicated that abstinent MDMA-users demonstrated impairment in their memory for faces and contextual meaningful visual material, when compared to controls. These observations of visual memory dysfunction are consistent with the evidence for visual memory problems in current MDMA-users (Gouzoulis-Mayfrank et al., 2000).

Examination of the WMS-III indexes for the two groups indicated that abstinent MDMA-users manifested dysfunction in working memory when compared to controls. The nature of working memory dysfunction was assessed through the clinical examination of the WMS-III subtests. The concept of working memory refers to the cognitive task of holding, manipulating and transforming cognitive material before generating a response. The WMS-III digits span backwards, letter-number sequencing and spatial span backwards subtests require the manipulation and transformation of letters and numbers in the memory and were therefore used in the present study to determine the nature of working memory functioning. Digits span forwards and spatial span forwards do not involve the same degree of manipulation of cognitive material in memory and thus were considered measures of simple attentional functioning. It was revealed that working memory dysfunction was only apparent in the auditory-verbal modality (digits span backwards and letter-number sequencing). Visual working memory, as assessed by the spatial span backwards subtest was intact. Furthermore, abstinent MDMA-users performances on measures of simple attention were comparable to controls (digits span forwards and spatial span forwards). The pattern of impairment evident in abstinent MDMA-users on the working memory and attention subtests is consistent with other studies of current users. Gouzoulis-Mayfrank et al. (2000) demonstrated that current MDMA-users manifested dysfunction on complex tasks requiring higher order attention and concentration skills, however, they displayed intact functioning on attentional tasks requiring a lesser degree of mental manipulation. The present study of abstinent users replicates the Gouzoulis-Mayfrank et al. study findings for current users on the digits span subtest. While performance on the digits span forwards was comparable for current users and controls subtest in the Gouzoulis-Mayfrank et al. study, performance on the more complex digit span backwards was

impaired. The similarity between this study of current users and the present study's findings in abstinent users suggests that the impairment evident in MDMA-users for working memory may endure after two years of abstinence from the drug. Further studies of long-term working memory dysfunction need to be conducted in abstinent MDMA-users to replicate these findings.

In summary, it is apparent that MDMA-induced immediate, delayed and working memory dysfunction is evident after two years of abstinence from the drug. The pattern of impairment is largely consistent with studies of current users and appears to result from problematic encoding processes, which are more readily apparent on tasks of greater complexity. Further long-term research of abstinent MDMA-users needs to be conducted to determine if axonal regeneration observed in animal studies, also occurs in humans, and if cognitive recovery is therefore possible. The sampling problems highlighted in the previous chapter were again evident in the present study's comparison between the two cohorts of current and abstinent users, which demonstrated that abstinent users had used MDMA with a greater degree of regularity. The effects of differing patterns of use on cognitive functioning in MDMA-users needs to be examined to determine if particular patterns of use place recreational users at a greater risk for cognitive dysfunction. The present investigation of abstinent users suggests that a higher frequency of administration may be a risk factor in the manifestation of long-term cognitive dysfunction.

CHAPTER 4

The review of the literature in Chapter 1 presents several lines of evidence which converge to support a causal relationship between recreational MDMA-use and memory and cognitive dysfunction. Animal studies have demonstrated that MDMA is a selective neurotoxin to serotonergic pathways in the brains of non-human primates, and this damage occurs when administered orally and in dose regimens comparable to human recreational use of the drug. The hippocampus and neocortex have been identified as particularly sensitive to MDMA's neurotoxic effects, as a result of their dense innervation by serotonergic neurons, and these brain regions are thought to be involved in memory and cognitive functioning. Neuroimaging, neuroendocrine and CSF serotonin metabolite studies have suggested similar patterns of neurotoxicity occur in recreational users (Steele et al., 2000; Boot et al., 2000). The study of long-term effects of MDMA in non-human primates has demonstrated that neurotoxicity is enduring in some brain regions, including the hippocampus and neocortex (Hatzidimitriou et al., 1999). Consistent with these findings is the study of neuroendocrine functioning in human recreational users, which has yielded indications of impairment in the serotonin system of users 12 months after discontinuation of use (Gerra et al., 2000). These collective findings indicate that MDMA-users risk inflicting enduring damage on brain serotonin pathways through their recreational use of the drug.

The study of the implications of MDMA-induced neurotoxicity has revealed that memory dysfunction and cognitive impairment are associated with recreational MDMA-use. As reviewed in Chapter 1, dysfunction in immediate, delayed and

working memory and attentional capacity have been identified as characteristics of recreational MDMA-users when compared to non-users (Gouzoulis-Mayfrank et al., 2000; Morgan, 1999). These findings are consistent with what is known of the function of the hippocampus and neocortex in memory and cognition and the probable impact of damage to these brain regions (Lezak, 1995). The study reported in Chapter 2 confirmed that MDMA-users continued to manifest memory dysfunction when compared to non-users, after controlling for the effects of potential confounders. Thus the memory impairment evident in the MDMA-users could not be attributed to differences in age, sex, intelligence, depression, anxiety and other recreational drug use. When taken with the current literature, this finding suggests that MDMA-users are at risk of incurring cognitive deficits through their recreational use of the drug.

The study of cognitive and memory dysfunction in MDMA-users to date has failed to present a revealing clinical picture of the nature of memory impairment. Therefore, the study reported in Chapter 2 set out to determine whether memory impairment in MDMA-users occurred as a result of encoding, storage or retrieval problems, while adequately controlling for confounding factors which may potentially influence memory functioning. This study revealed a pattern of memory impairment in MDMA-users that was consistent with encoding difficulties. The enduring nature of this memory dysfunction was revealed by the study presented in Chapter 3. The observation of enduring neurotoxicity in non-human primates in some brain regions, in addition to indications of reinnervation in other areas (Hatzidimitriou et al., 1999), raised the question of whether the cognitive impairment evident in current MDMA-users persisted after discontinuation of use. The study of the long-term consequences

of MDMA-use revealed that dysfunction in immediate, delayed and working memory endured after two years of abstinence from the drug.

In summary, the examination of memory functioning in MDMA-users in the studies presented in Chapters 2 and 3 has revealed that, when compared to non-users, MDMA-users manifest memory dysfunction, which cannot be attributed to other factors which influence memory functioning, such as age, sex, intelligence, anxiety, depression and other drug use, and the nature of this memory dysfunction is consistent with encoding difficulties. Moreover, memory dysfunction endures after two years of abstinence from MDMA.

These findings posit the question of whether the memory dysfunction evident in MDMA-users represents a clinically significant impairment with implications for everyday functioning. The examination of the WMS-III index scores, in comparison to normative data, revealed that on average, MDMA-users continued to function within the "average range" for memory performance when compared to their peers in the normal population, suggesting that their memory dysfunction has limited clinical significance. However, examination of index scores for individual cases suggested that a proportion of MDMA-users are functioning within the WMS-III "borderline range" and below, for memory performance. These clinical categories represent scores which lie two standard deviations below the mean for the normal population. In these cases, memory dysfunction may represent a significant clinical impairment, with potential implications for everyday functioning. This investigation was beyond the scope of the present studies, however, the pattern of results suggests that future studies are needed to determine what differentiates those individuals manifesting

more severe cognitive impairment from other recreational users. It is likely that larger sample sizes than those employed in the studies to date, will be needed to identify enough individuals to answer this question (Hall et al., 2000).

The comparison between the pattern of impairment evident in the two cohorts of MDMA-users studied in Chapters 2 and 3 revealed that frequent dose regimens may place recreational users at risk for more pervasive cognitive impairment. The abstinent cohort manifested a more pervasive pattern of memory impairment than the current using cohort, which could not be attributed to differences between the two cohorts in sex, age, intelligence, anxiety, depression or other drug use. The abstinent cohort did, however, use MDMA with greater frequency than current users, and in comparison to other Australian cohorts represented a very high frequency of use sample. It was cautiously concluded that the high frequency of MDMA use amongst this cohort may have contributed to their more pervasive pattern of cognitive impairment. This hypothesis is consistent with what is known of the neurotoxic process from animal studies, which suggest that higher frequency of administration results in greater neurotoxicity. These findings suggest that an important area for future research is the investigation of characteristics of recreational use, in conjunction with individual vulnerabilities, that place users at greater risk for cognitive impairment. It is proposed that recreational users who inject MDMA are also at a particularly high risk for neurotoxicity and cognitive impairment, as a result of being exposed to higher blood concentrations of the drug. In their survey of recreational patterns of use amongst MDMA-users in Sydney, Topp et al. (1999) reported that 16% of their sample had injected 'Ecstasy'. Future research of injecting

MDMA-users is needed to determine whether injecting MDMA-users represent a high-risk sample for cognitive impairment.

Criticisms regarding the conceptualisation of a linear dose-response relationship between MDMA-use and memory dysfunction have been raised in Chapter 2, suggesting the impact of differing dose regimens needs to be examined in greater detail to determine high risk patterns of use. The animal literature has indicated that total exposure, highest blood concentrations and frequency of administration each mediate the neurotoxic process (Steele et al., 1994). The present studies' attempts to establish a dose-response relationship while acknowledging these three factors yielded inconsistent results. These inconsistencies may be due to measurement limitations, the possibility of a threshold effect for MDMA-exposure and/or the numerous individual differences that influence cognitive functioning. Nevertheless, more sensitive measurement of these dose-response factors is needed to provide recreational users with information regarding harm minimisation practices. At present, harm minimisation for MDMA use appears to concentrate on the acute physiological and toxic effects of the drug (White et al., 1996). The results of the present studies indicate that recreational users also need to be informed of the short and long-term cognitive consequences of MDMA.

Several areas have been highlighted as appropriate starting points for future research. First, replication of encoding difficulties in MDMA-users are needed to confirm the hypothesis that memory dysfunction in MDMA-users occurs as a result of problems with encoding processes. Further studies examining the nature of memory impairment are required before concurrent retrieval dysfunction is ruled out as

contributing to the pattern of memory impairment in MDMA-users. Second, replication of memory dysfunction in other two year abstinent cohorts is needed to confirm that memory dysfunction in MDMA-users is enduring. Furthermore, the examination of memory functioning in users after longer periods of abstinence will determine whether memory disturbance continues. Third, long-term studies of MDMA-using cohorts are needed to examine whether recovery in cognitive functioning occurs over time, as suggested by the observation of reinnervation of the serotonergic system in non-human primates. The two-year abstinent cohort studied in the present study may potentially have recovered cognitive functioning relative to their memory performance while they were actively using MDMA. Alternatively, cognitive functioning may decline in MDMA-users over time. Damage to the serotonergic system may have implications for cognitive functioning in later life and the prospective study of recreational users as they age would determine whether these individuals were more adversely affected by the aging process than non-users. The study of neurodegenerative disorders which involve dysfunction in the serotonergic system, such as dementia, suggest that memory deficits are a feature of these conditions. Recreational MDMA-users may potentially be more adversely affected by memory dysfunction in old age.

In summary, the results of the studies reported in Chapters 2 and 3 indicate that recreational MDMA-users are at risk of incurring memory dysfunction, which may result from defective encoding processes, and that this pattern of memory impairment is enduring. Future studies of cognitive functioning in MDMA-users are needed to clarify high-risk patterns of use and the long-term consequences of recreational MDMA-use, to ensure that harm minimisation strategies regarding the use of MDMA

can be developed and recreational users are made aware of the long-term cognitive risks involved in the use of the drug.

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APPENDIX I: CONSENT FORM GIVEN TO PARTICIPANTS

THE AUSTRALIAN NATIONAL UNIVERSITY SURVEY OF "ECSTASY" USE

CONSENT FORM

You are invited to participate in the Australian National University Survey of "Ecstasy" Use. This study examines different characteristics of people who use "Ecstasy". The purpose of the survey is to find out what kind of people use "Ecstasy" and to look at different aspects of their functioning such as their mood and memory.

If you decide to participate, I will ask you a series of questions about your background, your drug use over the last few years, and how you have been feeling lately. I'll also ask you to complete several memory tasks which look at your short term memory for numbers, words or shapes.

Any information that is obtained in connection with this study will remain confidential. The information disclosed by you will be stored under a number, without names, to maintain your anonymity and confidentiality. The results of the study will be published in a way thatwill not identify you as having taken part. You are able to withdraw from the study at any time and you will be given a copy of this form to keep.

The interview will take about one hour.

Signed _____ Date___ / ___ /___

APPENDIX II:

DEMOGRAPHIC INFORMATION AND MDMA USE QUESTIONNAIRE

THE AUSTRALIAN NATIONAL UNIVERSITY
SURVEY OF ECSTASY USE

Subject No._____

Demographics

Age_____ years Sex M / F

Education_____ yrs

Primary / Year 10 / Year 12 / Tertiary / Postgraduate

Ecstasy Use

How old were you when you first started using "ecstasy"? _____years

How long has it been since you last used "ecstasy"? _____days

DURATION OF USE _____months

During this period, how often have you used "ecstasy"?_____times per month.

Can you estimate the total number of times you have used "ecstasy"? _____

How many "ecstasy" tablets do you usually take on the one occasion?_____

What is the most 'ecstasy' you have taken at the one time?_____

Other Drug Use

Do you usually take other drugs with 'ecstasy'?

Alcohol	
Cannabis	
Benzodiazapines	
Amphetamine (speed)	
Opiates (heroin)	
Cocaine	
Hallucinogens (LSD)	
Inhalents	

Others_____

_____

Do you regularly use any other recreational drugs?

Alcohol	
Cannabis	
Benzodiazapines	
Amphetamine (speed)	
Opiates (heroin)	
Cocaine	
Hallucinogens (LSD)	
Inhalents	

Others_____

_____

APPENDIX III:

SIGNIFICANT FINAL MULTIPLE REGRESSION MODELS FROM COMPARATIVE ANALYSES BETWEEN MDMA-USERS AND CONTROLS

Each of the final regression models presented in this appendix has been reduced using the backward elimination method where variables are removed from the model if they are not statistically significant (Kleinbaum et al., 1988). The process began with a full model, which included intelligence, sex, age, anxiety, depression, and other drug use. This method was employed to maximise the power and precision of the models. If none of the potential confounding variables were significant, the unadjusted model is presented.

1. Immediate Memory Index

Table 1: Multiple Linear Regression Model Predicting Immediate Memory Index While Adjusting For Potential Confounders (N=61).

Variable	B	SE	t	p[a]
Group	-10.30	2.89	-3.57	.001
IQ	0.44	0.19	2.27	.027
F=11.54, p=.000 Adjusted R Square=.260				

Note: B = unstandardised regression coefficient
[a]Two-tailed

2. General Memory Index

Table 2: Multiple Linear Regression Model Predicting General Memory Index While Adjusting For Potential Confounders (N=61).

Variable	B	SE	t	p[a]
Group	-6.60	2.70	-2.45	.018
IQ	0.48	0.18	2.63	.011
Sex	-5.47	2.78	-1.97	.054
F=6.66, p=.001 Adjusted R Square=.221				

Note: B = unstandardised regression coefficient
[a]Two-tailed

3. Auditory Immediate Index

Table 3: Multiple Linear Regression Model Predicting Auditory Immediate Index While Adjusting For Potential Confounders (N=61).

Variable	B	SE	t	p[a]
Group	-9.73	2.71	-3.60	.001
IQ	0.53	0.18	2.88	.006
Sex	-5.30	2.78	-1.90	.062
F=10.28, p=.000 Adjusted R Square=.317				

Note: B = unstandardised regression coefficient
[a]Two-tailed

4. Visual Immediate Index

Table 4: Multiple Linear Regression Model Predicting Visual Immediate Index While Adjusting For Potential Confounders (N=61).

Variable	B	SE	t	p[a]
Group	-7.87	3.14	-2.51	.015
F=6.30, p=.015 Adjusted R Square=.081				

Note: B = unstandardised regression coefficient
[a]Two-tailed

5. Visual Delayed Index

Table 5: Multiple Linear Regression Model Predicting Visual Delayed Index While Adjusting For Potential Confounders (N=61).

Variable	B	SE	t	p[a]
Group	-6.94	3.30	-2.11	.040
IQ	0.41	0.22	1.87	.067
F=5.20, p=.008 Adjusted R Square=.123				

Note: B = unstandardised regression coefficient
[a]Two-tailed

6. Auditory Recognition Index

Table 6: Multiple Linear Regression Model Predicting Auditory Recognition Index While Adjusting For Potential Confounders (N=61).

Variable	B	SE	t	p[a]
Group	-7.67	2.81	-2.73	.008
Sex	-6.63	2.93	-2.27	.027
F=6.65, p=.003 Adjusted R Square=.159				

Note: B = unstandardised regression coefficient
[a]Two-tailed

7. Logical Memory I Total

Table 7: Multiple Linear Regression Model Predicting Logical Memory I Total Performance While Adjusting For Potential Confounders (N=61).

Variable	B	SE	t	p[a]
Group	-6.98	1.97	-3.55	.001
IQ	0.40	0.13	3.08	.003
Depression	0.27	0.14	1.94	.058
Anxiety	-0.28	0.15	-1.79	.079
F=7.96, p=.000 Adjusted R Square=.321				

Note: B = unstandardised regression coefficient
[a]Two-tailed

8. Logical Memory I Story A

Table 8: Multiple Linear Regression Model Predicting Logical Memory I Story A Performance While Adjusting For Potential Confounders (N=61).

Variable	B	SE	t	p[a]
Group	3.88	6.20	0.63	.000
IQ	0.15	0.06	2.67	.010
Depression	8.39	0.04	1.97	.054
F=10.11, p=.000 Adjusted R Square=.317				

Note: B = unstandardised regression coefficient
[a]Two-tailed

9. Logical Memory I Story Bi (first presentation)

Table 9: Multiple Linear Regression Model Predicting Logical Memory I Story Bi Performance While Adjusting For Potential Confounders (N=61).

Variable	B	SE	t	p[a]
Group	-2.14	0.81	-2.65	.010
IQ	0.11	0.05	2.09	.041
F=7.45, p=.001 Adjusted R Square=.177				

Note: B = unstandardised regression coefficient
[a]Two-tailed

10. Logical Memory I Story Bii (second presentation)

Table 10: Multiple Linear Regression Model Predicting Logical Memory I Story Bii Performance While Adjusting For Potential Confounders (N=61).

Variable	B	SE	t	p[a]
Group	-1.71	0.83	-2.08	.042
IQ	0.13	0.06	2.27	.027
F=6.21, p=.004 Adjusted R Square=.148				

Note: B = unstandardised regression coefficient
[a]Two-tailed

11. Logical Memory II Total

Table 11: Multiple Linear Regression Model Predicting Logical Memory II Total Performance While Adjusting For Potential Confounders (N=61).

Variable	B	SE	t	p[a]
Group	-3.93	1.60	-2.45	.017
IQ	0.31	0.11	2.82	.007
Sex	-3.04	1.70	-1.78	.080
Depression	0.28	0.11	2.51	.015
Anxiety	-0.32	0.13	-2.55	.014
F=5.19, p=.001 Adjusted R Square=.262				

Note: B = unstandardised regression coefficient
[a]Two-tailed

12. Logical Memory II Story A

Table 12: Multiple Linear Regression Model Predicting Logical Memory II Story A Performance While Adjusting For Potential Confounders (N=61).

Variable	B	SE	t	p[a]
Group	-2.48	0.97	-2.57	.013
IQ	0.15	0.07	2.26	.028
Sex	-2.25	1.03	-2.19	.033
Depression	0.20	0.07	2.92	.005
Anxiety	-0.19	0.08	-2.50	.015
F=5.19, p=.001 Adjusted R Square=.262				

Note: B = unstandardised regression coefficient
[a]Two-tailed

13. Logical Memory II Story B

Table 13: Multiple Linear Regression Model Predicting Logical Memory II Story B Performance While Adjusting For Potential Confounders (N=61).

Variable	B	SE	t	p[a]
Group	-1.58	0.92	-1.72	.093
IQ	0.14	0.06	2.23	.029
F=5.17, p=.009 Adjusted R Square=.122				

Note: B = unstandardised regression coefficient
[a]Two-tailed

14. Logical Memory Recognition

Table 14: Multiple Linear Regression Model Predicting Logical Memory Recognition Performance While Adjusting For Potential Confounders (N=61).

Variable	B	SE	t	p[a]
Group	-0.87	0.49	-1.78	.080
IQ[b]	0.04	0.03	2.25	.215
Sex	-1.45	0.50	-2.90	.005
F=4.75, p=.005 Adjusted R Square=.158				

Note: B = unstandardised regression coefficient
[a]Two-tailed
[b]IQ retained in final model despite probability greater than 0.1 because estimates of variables remaining in the model altered substantially when removed (Kleinbaum et al., 1988).

15. Logical Memory Recognition Story B

Table 15: Multiple linear regression model predicting Logical Memory Recognition performance for Story B while adjusting for potential confounders (N=61).

Variable	B	SE	t	p[a]
Group	-0.44	0.19	-0.29	.023
F=5.45, p=.023 Adjusted R Square =.069				

Note: B = unstandardised regression coefficient
[a]Two-tailed

16. Verbal Paired Associates Total (over four trials)

Table 16: Multiple Linear Regression Model Predicting VPA Total Performance While Adjusting For Potential Confounders (N=61).

Variable	B	SE	t	p[a]
Group	-3.28	1.28	-2.56	.013
IQ	0.16	0.09	1.84	.071
Age	-0.26	0.11	-2.30	.026
Sex	-3.44	1.36	-2.53	.014
Anxiety	0.15	0.08	2.01	.050
F=6.50, p=.000 Adjusted R Square=.318				

Note: B = unstandardised regression coefficient
[a]Two-tailed

17. Verbal Paired Associates I List 'a' (first presentation)

Table 17: Multiple Linear Regression Model Predicting VPA I List 'a' Performance While Adjusting For Potential Confounders (N=61).

Variable	B	SE	t	p[a]
Group	-2.24	0.56	-4.01	.000
Sex	-1.24	0.59	-2.09	.041
Anxiety	8.56	0.03	2.56	.013
F=9.47, p=.000 Adjusted R Square =.301				

Note: B = unstandardised regression coefficient
[a]Two-tailed

18. Verbal Paired Associates I List 'b' (second presentation)

Table 18: Multiple Linear Regression Model Predicting VPA I List 'b' Performance While Adjusting For Potential Confounders (N=61).

Variable	B	SE	t	p[a]
Group	-0.65	0.43	-1.51	.137
IQ	0.05	0.03	1.70	.094
Sex	-1.07	0.44	-2.41	.019
Age	-0.09	0.04	-2.37	.021
F=9.47, p=.000 Adjusted R Square =.301				

Note: B = unstandardised regression coefficient
[a]Two-tailed

19. Faces I

Table 19: Multiple Linear Regression Model Predicting Faces I Performance While Adjusting For Potential Confounders (N=61).

Variable	B	SE	t	p[a]
Group	-2.21	1.02	-2.17	.034
F=4.72, p=.034 Adjusted R Square=.058				

Note: B = unstandardised regression coefficient
[a]Two-tailed

20. Family Pictures I

Table 20: Multiple Linear Regression Model Predicting Family Pictures I Performance While Adjusting For Potential Confounders (N=61).

Variable	B	SE	t	p[a]
Group	-3.31	1.86	-1.78	.081
IQ[b]	0.18	0.13	1.42	.161
Age	-0.37	0.17	-2.27	.027
F=3.83, p=.014 Adjusted R Square=.124				

Note: B = unstandardised regression coefficient
[a]Two-tailed
[b]IQ retained in final model despite probability greater than 0.1 because estimates of variables remaining in the model altered substantially when removed (Kleinbaum et al., 1988).

21. Family Pictures II

Table 21: Multiple Linear Regression Model Predicting Family Pictures II Performance While Adjusting For Potential Confounders (N=61).

Variable	B	SE	t	p[a]
Group	-3.14	1.80	-1.75	.086
IQ	0.21	0.12	1.69	.096
Age	-0.29	0.16	-1.83	.072
F=3.54, p=.020 Adjusted R Square=.113				

Note: B = unstandardised regression coefficient
[a]Two-tailed

APPENDIX IV:

SIGNIFICANT FINAL MULTIPLE REGRESSION MODELS FOR COMPARATIVE ANALYSES BETWEEN CONTROLS AND ABSTINENT MDMA-USERS

Each of the final regression models presented in this appendix has been reduced using the backward elimination method where variables are removed from the model if they are not statistically significant (Kleinbaum et al., 1988). The process began with a full model, which included intelligence, sex, age, anxiety, depression, and other drug use. This method was employed to maximise the power and precision of the models. If none of the potential confounding variables were significant, the unadjusted model is presented. The final regression models are also presented for cases where differences between the two groups were no longer apparent after controlling for potential confounders.

1. Immediate Memory Index

Table 1: Multiple Linear Regression Model Predicting Immediate Memory Index While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-17.44	3.24	-5.38	.000
IQ[b]	0.12	0.17	0.69	.495
F=18.10, p=.000				
Adjusted R Square=.367				

Note: B = unstandardised regression coefficient

[a]Two-tailed

[b]IQ retained in final model despite probability greater than 0.1 because estimates of variables remaining in the model altered substantially when removed (Kleinbaum et al., 1988).

2. General Memory Index

Table 2: Multiple Linear Regression Model Predicting General Memory Index While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-15.17	2.89	-5.25	.000
F=6.66, p=.001				
Adjusted R Square=.221				

Note: B = unstandardised regression coefficient

[a]Two-tailed

3. Working Memory Index

Table 3: Multiple Linear Regression Model Predicting General Memory Index While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-9.34	4.05	-2.43	.018
IQ	0.40	0.20	1.97	.054
Sex[b]	5.32	3.84	1.39	.171
F=5.70, p=.002				
Adjusted R Square=.193				

Note: B = unstandardised regression coefficient

[a]Two-tailed

[b]Sex retained in final model despite probability greater than 0.1 because estimates of variables remaining in the model altered substantially when removed (Kleinbaum et al., 1988).

4. Auditory Immediate Index

Table 4: Multiple Linear Regression Model Predicting Auditory Immediate Index While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-12.68	3.10	-4.09	.000
IQ	0.53	0.18	3.02	.004
Age	-0.69	0.24	-2.91	.005
F=16.47, p=.000				
Adjusted R Square=.440				

Note: B = unstandardised regression coefficient

[a]Two-tailed

5. Visual Immediate Index

Table 5: Multiple Linear Regression Model Predicting Visual Immediate Index While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-14.87	3.14	-4.73	.000
Anxiety	0.39	0.15	2.55	.013
F=6.30, p=.015				
Adjusted R Square=.081				

Note: B = unstandardised regression coefficient

[a]Two-tailed

6. Auditory Delayed Index

Table 6: Multiple Linear Regression Model Predicting Auditory Delayed Index While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-10.33	3.15	-3.28	.002
IQ	0.21	0.17	1.28	.207
F=8.64, p=.001 Adjusted R Square=.206				

Note: B = unstandardised regression coefficient
[a]Two-tailed

7. Visual Delayed Index

Table 7: Multiple Linear Regression Model Predicting Visual Delayed Index While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-14.30	3.39	-4.22	.000
F=17.77, p=.000 Adjusted R Square=.221				

Note: B = unstandardised regression coefficient
[a]Two-tailed

8. Auditory Recognition Index

Table 8: Multiple Linear Regression Model Predicting Auditory Recognition Index While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-10.50	2.90	-3.63	.001
F=13.14, p=.001 Adjusted R Square=.171				

Note: B = unstandardised regression coefficient
[a]Two-tailed

9. Logical Memory I Total

Table 9: Multiple Linear Regression Model Predicting Logical Memory I Total Performance While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-7.89	2.03	-3.89	.000
IQ	0.41	0.12	3.52	.001
Age	-0.48	0.15	-3.13	.003
F=17.60, p=.000 Adjusted R Square=.458				

Note: B = unstandardised regression coefficient
[a]Two-tailed

10. Logical Memory I Story A

Table 10: Multiple Linear Regression Model Predicting Logical Memory I Story A Performance While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-3.15	0.74	-4.23	.000
IQ	0.12	0.04	3.08	.003
F=20.54, p=.000 Adjusted R Square=.398				

Note: B = unstandardised regression coefficient
[a]Two-tailed

11. Logical Memory I Story Bi (first presentation)

Table 11: Multiple Linear Regression Model Predicting Logical Memory I Story Bi Performance While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-3.15	0.96	-3.28	.002
IQ[b]	0.06	0.05	1.28	.208
Age	-0.16	0.07	-2.33	.023
Sex[b]	1.46	0.91	1.61	.112
F=6.07, p=.000 Adjusted R Square=.256				

Note: B = unstandardised regression coefficient
[a]Two-tailed
[b]Sex and IQ retained in final model despite probability greater than 0.1 because estimates of variables remaining in the model altered substantially when removed (Kleinbaum et al., 1988).

12. Logical Memory I Story Bii (second presentation)

Table 12: Multiple Linear Regression Model Predicting Logical Memory I Story Bii Performance While Adjusting For Potential Confounders (N=60).

Variable	B	SE	T	p[a]
Group	-2.51	0.85	-2.95	.005
Age	-0.25	0.07	-3.87	.000
IQ	0.17	0.05	3.60	.001
F=15.51, p=.000 Adjusted R Square=.425				

Note: B = unstandardised regression coefficient
[a]Two-tailed

13. Logical Memory II Total

Table 13: Multiple Linear Regression Model Predicting Logical Memory II Total Performance While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-7.26	1.82	-3.99	.000
Age	-0.30	0.14	-2.18	.034
IQ[b]	0.15	0.10	1.40	.166
F=10.82, p=.000				
Adjusted R Square=.333				

Note: B = unstandardised regression coefficient
[a]Two-tailed
[b]Sex and IQ retained in final model despite probability greater than 0.1 because estimates of variables remaining in the model altered substantially when removed (Kleinbaum et al., 1988).

14. Logical Memory II Story A

Table 14: Multiple Linear Regression Model Predicting Logical Memory II Story A Performance While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-4.15	1.10	-3.76	.000
Sex[b]	-1.59	1.10	-1.44	.154
F=11.67, p=.000				
Adjusted R Square=.266				

Note: B = unstandardised regression coefficient
[a]Two-tailed
[b]Sex retained in final model despite probability greater than 0.1 because estimates of variables remaining in the model altered substantially when removed (Kleinbaum et al., 1988).

15. Logical Memory II Story B

Table 15: Multiple Linear Regression Model Predicting Logical Memory II Story B Performance While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-2.85	1.03	-2.77	.008
Age	-0.19	0.08	-2.44	.018
IQ	0.11	0.06	1.87	.067
F=7.90, p=.000				
Adjusted R Square=.260				

Note: B = unstandardised regression coefficient
[a]Two-tailed

16. Logical Memory Recognition

Table 16: Multiple Linear Regression Model Predicting Logical Memory Recognition Performance While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-1.37	0.53	-2.56	.013
Age	-0.12	0.04	-2.83	.007
IQ[b]	0.01	0.03	0.33	.746
F=4.75, p=.005				
Adjusted R Square=.158				

Note: B = unstandardised regression coefficient

[a]Two-tailed

[b]IQ retained in final model despite probability greater than 0.1 because estimates of variables remaining in the model altered substantially when removed (Kleinbaum et al., 1988).

17. Logical Memory Recognition Story B

Table 17: Multiple Linear Regression Model Predicting Logical Memory Recognition Story B Performance While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-0.39	0.12	-3.23	.002
Age	-0.04	0.02	-1.92	.060
F=7.83, p=.001				
Adjusted R Square=.188				

Note: B = unstandardised regression coefficient

[a]Two-tailed

18. Verbal Paired Associates Total (over four trials)

Table 18: Multiple Linear Regression Model Predicting VPA Total Performance While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-2.87	1.79	-1.60	.114
Sex	-5.46	1.70	-3.22	.002
IQ	0.13	0.09	1.50	.140
F=8.36, p=.000				
Adjusted R Square=.272				

Note: B = unstandardised regression coefficient

[a]Two-tailed

19. Verbal Paired Associates I List 'a' (first presentation)

Table 19: Multiple Linear Regression Model Predicting VPA I List 'a' Performance While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-1.32	0.69	-1.91	.061
Sex	-1.84	0.66	-2.81	.007
IQ[b]	0.02	0.03	0.62	.539
F=7.06, p=.000				
Adjusted R Square =.236				

Note: B = unstandardised regression coefficient
[a]Two-tailed
[b]IQ retained in final model despite probability greater than 0.1 because estimates of variables remaining in the model altered substantially when removed (Kleinbaum et al., 1988).

20. Verbal Paired Associates I List 'b' (second presentation)

Table 20: Multiple Linear Regression Model Predicting VPA I List 'b' Performance While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-0.84	0.55	-1.54	.129
Sex	-1.69	0.52	-3.27	.002
IQ[b]	0.04	0.03	1.56	.124
F=8.42, p=.000				
Adjusted R Square =.274				

Note: B = unstandardised regression coefficient
[a]Two-tailed
[b]IQ retained in final model despite probability greater than 0.1 because estimates of variables remaining in the model altered substantially when removed (Kleinbaum et al., 1988).

21. Verbal Paired Associates I List 'c' (third presentation)

Table 21: Multiple Linear Regression Model Predicting VPA I List 'c' Performance While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-0.44	0.43	-1.03	.309
Sex	-0.99	0.41	-2.42	.019
IQ	0.06	0.02	2.60	.012
Age	-0.08	0.03	-2.52	.015
F=7.18, p=.000				
Adjusted R Square =.295				

Note: B = unstandardised regression coefficient
[a]Two-tailed

22. Faces I

Table 22: Multiple Linear Regression Model Predicting Faces I Performance While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-3.11	0.99	-3.15	.003
Anxiety	0.09	0.05	1.91	.061
F=5.88, p=.005 Adjusted R Square=.142				

Note: B = unstandardised regression coefficient
[a]Two-tailed

23. Faces II

Table 23: Multiple Linear Regression Model Predicting Faces II Performance While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-3.03	1.06	-2.85	.006
F=8.13, p=.006 Adjusted R Square=.108				

Note: B = unstandardised regression coefficient
[a]Two-tailed

24. Family Pictures I

Table 24: Multiple Linear Regression Model Predicting Family Pictures I Performance While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-12.31	2.45	-5.02	.000
IQ[b]	-0.20	0.13	-1.53	.131
Anxiety	0.24	0.11	2.14	.037
F=9.33, p=.000 Adjusted R Square=.298				

Note: B = unstandardised regression coefficient
[a]Two-tailed
[b]IQ retained in final model despite probability greater than 0.1 because estimates of variables remaining in the model altered substantially when removed (Kleinbaum et al., 1988).

25. Family Pictures II

Table 25: Multiple Linear Regression Model Predicting Family Pictures II Performance While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-10.59	2.62	-4.04	.000
Age	-0.37	0.20	-1.85	.069
IQ[b]	-0.11	0.15	-0.73	.467
F=8.54, p=.000				
Adjusted R Square=.277				

Note: B = unstandardised regression coefficient
[a]Two-tailed
[b]IQ retained in final model despite probability greater than 0.1 because estimates of variables remaining in the model altered substantially when removed (Kleinbaum et al., 1988).

26. Letter Number Sequencing

Table 26: Multiple Linear Regression Model Predicting Letter Number Sequencing Performance While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-1.78	0.72	-2.48	.016
IQ	0.07	0.04	1.83	.073
F=7.13, p=.002				
Adjusted R Square=.172				

Note: B = unstandardised regression coefficient
[a]Two-tailed

27. Digit Span Total

Table 27: Multiple Linear Regression Model Predicting Digit Span Total Performance While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-2.61	0.94	-2.77	.008
IQ	0.14	0.05	2.75	.008
F=11.56, p=.000				
Adjusted R Square=.264				

Note: B = unstandardised regression coefficient
[a]Two-tailed

28. Digit Span Backwards

Table 28: Multiple Linear Regression Model Predicting Digit Span Backwards Performance While Adjusting For Potential Confounders (N=60).

Variable	B	SE	t	p[a]
Group	-2.12	0.54	-3.92	.000
IQ	0.05	0.03	1.69	.096
F=12.89, p=.000				
Adjusted R Square=.287				

Note: B = unstandardised regression coefficient

[a]Two-tailed

APPENDIX V:

SIGNIFICANT FINAL MULTIPLE REGRESSION MODELS FOR COMPARATIVE ANALYSES BETWEEN CURRENT AND ABSTINENT MDMA-USERS

The final regression models presented in this appendix were reduced using the backward elimination method where variables are removed from the model if they are not statistically significant (Kleinbaum et al., 1988). This method was employed to maximise the power and precision of the models. The process began with a full model, which included intelligence, sex, age, anxiety, depression, and other drug use. If none of the potential confounding variables were significant, the unadjusted model is presented. The final regression models are also presented for cases where differences between the two groups were no longer apparent after controlling for potential confounders.

1. Immediate Memory Index

Table 1: Multiple Linear Regression Model Predicting Immediate Memory Index While Adjusting For Potential Confounders (N=61)

Variable	B	SE	t	p[a]
Group	-3.85	3.23	-1.19	.239
IQ[b]	0.16	0.12	1.38	.173
Sex[b]	-5.27	3.18	-1.66	.103
F=2.89, p=.043				
Adjusted R Square=.086				

Note: B = unstandardised regression coefficient

[a]Two-tailed

[b]IQ and sex retained in final model despite probability greater than 0.1 because estimates of variables remaining in the model altered substantially when removed (Kleinbaum et al., 1988).

2. General Memory Index

Table 2: Multiple Linear Regression Model Predicting General Memory Index While Adjusting For Potential Confounders (N=61)

Variable	B	SE	t	p[a]
Group	-4.66	2.62	-1.78	.081
IQ	0.20	0.09	2.09	.041
Sex[b]	-2.75	2.58	-1.06	.292
F=4.11, p=.010				
Adjusted R Square=.135				

Note: B = unstandardised regression coefficient

[a]Two-tailed

[b]Sex retained in final model despite probability greater than 0.1 because estimates of variables remaining in the model altered substantially when removed (Kleinbaum et al., 1988).

3. Auditory Delayed Index

Table 3: Multiple Linear Regression Model Predicting Auditory Delayed Index While Adjusting For Potential Confounders (N=61)

Variable	B	SE	t	p[a]
Group	-4.12	2.84	-1.45	.153
IQ[b]	0.17	0.10	1.63	.108
Sex	-5.18	2.80	-1.85	069
F=3.93, p=.013				
Adjusted R Square=.128				

Note: B = unstandardised regression coefficient

[a]Two-tailed

[b]IQ retained in final model despite probability greater than 0.1 because estimates of variables remaining in the model altered substantially when removed (Kleinbaum et al., 1988).

4. Logical Memory II Total

Table 4: Multiple Linear Regression Model Predicting Logical Memory II Total Performance While Adjusting For Potential Confounders (N=61)

Variable	B	SE	t	p[a]
Group	-2.50	1.70	-1.48	.145
Sex	-3.16	1.70	-1.86	.068
F=4.08, p=.022				
Adjusted R Square=.093				

Note: B = unstandardised regression coefficient

[a]Two-tailed

5. Logical Memory II Story B

Table 5: Multiple Linear Regression Model Predicting Logical Memory II Story B Performance While Adjusting For Potential Confounders (N=61)

Variable	B	SE	t	p[a]
Group	-1.29	0.83	-1.56	.124
Age	-0.19	0.08	-2.48	.016
IQ	0.11	0.05	2.23	.030
F=4.19, p=.009 Adjusted R Square=.138				

Note: B = unstandardised regression coefficient
[a]Two-tailed

6. Family Pictures I

Table 6: Multiple Linear Regression Model Predicting Family Pictures I Performance While Adjusting For Potential Confounders (N=61)

Variable	B	SE	t	p[a]
Group	-5.50	2.30	-2.39	.020
Age	-0.46	0.20	-2.28	.027
F=5.86, p=.005 Adjusted R Square=.139				

Note: B = unstandardised regression coefficient
[a]Two-tailed

7. Family Pictures II

Table 7: Multiple Linear Regression Model Predicting Family Pictures II Performance While Adjusting For Potential Confounders (N=61)

Variable	B	SE	t	p[a]
Group	-5.55	2.44	-2.27	.027
IQ[b]	0.08	0.10	0.82	.416
Age	-0.49	0.22	-2.25	.028
F=4.10, p=.011 Adjusted R Square=.134				

Note: B = unstandardised regression coefficient
[a]Two-tailed
[b]IQ retained in final model despite probability greater than 0.1 because estimates of variables remaining in the model altered substantially when removed (Kleinbaum et al., 1988).

8. Letter Number Sequencing

Table 8: Multiple Linear Regression Model Predicting Letter Number Sequencing Performance While Adjusting For Potential Confounders (N=61)

Variable	B	SE	t	p[a]
Group	-0.74	0.51	-1.45	.152
Age[b]	-0.06	0.05	-1.34	.186
IQ	0.08	0.02	3.82	.000
F=6.80, p=.001 Adjusted R Square=.225				

Note: B = unstandardised regression coefficient

[a]Two-tailed

[b]Age retained in final model despite probability greater than 0.1 because estimates of variables remaining in the model altered substantially when removed (Kleinbaum et al., 1988).

9. Digit Span Total

Table 9: Multiple Linear Regression Model Predicting Digit Span Total Performance While Adjusting For Potential Confounders (N=61)

Variable	B	SE	t	p[a]
Group	-1.76	1.05	-1.67	.100
IQ[b]	0.07	0.04	1.65	.105
F=3.44, p=.039 Adjusted R Square=.075				

Note: B = unstandardised regression coefficient

[a]Two-tailed

[b]IQ retained in final model despite probability greater than 0.1 because estimates of variables remaining in the model altered substantially when removed (Kleinbaum et al., 1988).

10. Digit Span Backwards

Table 10: Multiple Linear Regression Model Predicting Digit Span Backwards Performance While Adjusting For Potential Confounders (N=61)

Variable	B	SE	t	p[a]
Group	-1.23	0.70	-1.76	.084
Lifetime Heroin[b]	-0.37	0.80	-0.46	.647
IQ[b]	0.04	0.02	1.59	.118
F=3.05, p=.036 Adjusted R Square=.093				

Note: B = unstandardised regression coefficient

[a]Two-tailed

[b]IQ and lifetime heroin use retained in final model despite probability greater than 0.1 because estimates of variables remaining in the model altered substantially when removed (Kleinbaum et al., 1988).