The pattern of memory and perceptual dysfunctions in recreational ecstasy users

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Declaration

I declare that this thesis reports my original work, that no part has been previously accepted and presented for the award of any degree or diploma from any university, and that, to the best of my knowledge, no material previously published or written by any other person is included, except where due acknowledgement is given.

John Anthony Brown
“If MDMA neurotoxicity in humans is a myth, then it is a myth with a very heavy serotonergic component.”

(Turner & Parrott, 2000)
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Abstract

There is a growing body of evidence that the main psychoactive ingredient of the recreational drug “ecstasy” (methylenedioxymethamphetamine; MDMA) causes lasting changes to the serotonin system in both animals and humans, including the hippocampus (involved in memory) and the occipital lobe (involved in visual perception). Previous studies have often found memory deficits in ecstasy users. However, the results have been far from consistent across studies. None of the methods used to date have adequately isolated the hippocampal component of memory from the contribution of other brain regions. Three memory studies were conducted in this thesis to clarify which components and processes of memory are in deficit in ecstasy users.

In the first memory study, ecstasy users (n=32) did not differ from non-drug using controls (n=29) on implicit memory (automatic non-conscious retrieval, as revealed by a stem-completion task), or explicit memory (conscious recollection, as revealed by stem-cued recall). In the second memory study, no significant differences were found between ecstasy users (n=30) and non-drug using controls (n=34) on tests designed to clarify the findings on explicit memory, or on two standard neuropsychological tests of long-term memory (prose recall and Auditory Verbal Learning Test) that allowed greater use of elaborative processing at study. In the third memory study, a number of tests were applied that differed in their elaborative processing demands, including the California Verbal Learning Test, Visual Paired Associates, and Verbal Paired Associates. Ecstasy users (n=32) had poorer recall, and made less strategic use of elaborative processing compared to both cannabis-using controls (n=33) and non-drug using controls (n=33). Also, on a novel test of elaborative processing (“Verbal Triplet Associates”), both cannabis users and ecstasy users had memory deficits on the first trial, but only ecstasy users had a significant learning deficit over successive trials. On the basis of the localisation of the components and processes of memory in literature, it was concluded that long-term memory deficits in ecstasy users may reflect changes in elaborative processes localised in the frontal lobes, or global deficits, rather than just changes to the memory functions of the hippocampus.

With regard to visual perception, no studies have been published to date that have examined MDMA-related changes to the behavioural functioning of the occipital lobe in humans. In the current thesis, this was investigated using the tilt aftereffect illusion. In accordance with expectations, ecstasy users had a larger tilt aftereffect compared to
non-drug using controls (n=34). Unexpectedly, this result was only obtained for a subset of 12 ecstasy users (out of n=30) who had not used amphetamines in the recent past. It was concluded that the results for ecstasy users who had not recently used amphetamines were consistent with the proposal that ecstasy-related serotonergic changes in the occipital lobe broaden the tuning bandwidth of orientation sensitive neurons, and that the recent use of amphetamines appears to counteract that effect.
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Chapter 1. The pharmacology, use patterns and neurotoxicity of MDMA

1.1 Introduction

“Ecstasy” is a popular recreational drug in many parts of the world. However there is a growing body of evidence which suggest that the main psychoactive ingredient of ecstasy, namely methylendioxymethamphetamine (MDMA), not only causes pleasurable effects for users, but also appears to cause irreparable harm to the chemistry of the brain and cognitive functioning. In this thesis, a series of empirical studies are reported which investigate the performance of ecstasy users on tests of long-term memory and low level visual perception compared to other drug users and non-drug using controls.

1.2 The chemical classification of MDMA

MDMA is the most commonly accepted abbreviation of 3,4-methylendioxymethamphetamine, which has been described as a synthetic ring-substituted phenethylamine that is structurally related to both amphetamine-like stimulants and mescaline-like hallucinogens (Fantegrossi, Ullrich, Rice, Woods, & Winger, 2002). Many synthetic phenethylamines have been found to act as stimulants (e.g., amphetamines) or hallucinogens (e.g., 2C-B). In contrast, MDMA and other related 3,4-methylendioxy-substituted amphetamines, such as MDA and MDEA, produce feelings of euphoria and social closeness (as described in Nichols & Oberlender, 1990; Shulgin, 1990; Steele, McCann, & Ricaurte, 1994).

1.3 The use of MDMA as a recreational drug

1.3.1 A brief history of the use of MDMA as a recreational drug

The earliest record of MDMA is a German patent filed in 1912 on the basis that MDMA could aid the synthesis of other therapeutically active compounds (Green, Mechan, Elliott, O'Shea, & Colado, 2003; Shulgin, 1990). In the late-1970’s, psychotherapists in the United States started using MDMA to facilitate better communication in therapy and to boost self-esteem. At this time, the recreational use of MDMA also began to emerge. However, within a decade research begun to emerge that MDMA and related compounds produced lasting changes to the serotonin system in the rat brain (Ricaurte,
Bryan, Strauss, Seiden, & Schuster, 1985; Slikker et al., 1988). In response to that research and concerns about the potential for abuse of the drug, the human use of MDMA was rapidly banned in the USA and around the world. Despite this, in the 1990s the popularity of MDMA in the form of “ecstasy” tablets bloomed within rapidly expanding subcultures which normalised recreational drug use (Agar & Reisinger, 2004). It is now the third most commonly used illicit recreational drug amongst young people (Degenhardt, Barker, & Topp, 2004).

### 1.3.2 Current ecstasy use in Australia and Australian Capital Territory

Ecstasy users are typically single, young, students or employed people of average education, who use the drug on weekends, but not every weekend. In 2001, the Australian National Household Survey revealed that ecstasy is the third most commonly used illicit drug behind cannabis and amphetamines. In total, 6.1% of people aged 14 years and older reported having used ecstasy at least once, with 2.9% reporting that they had used it within the last year (Degenhardt et al., 2004). In comparison, 83.5% had used alcohol, 12.8% had used cannabis, and 3.4% had used amphetamines within the last year. Ecstasy use was highest in the younger age groups, with 19.7% of 20-29 year olds and 7% of 14-19 year olds reporting ever having used the drug, and 10.5% of 20-29 year olds and 5.0% of 14-19 year olds reporting they had used it in the last year. Ecstasy users did not differ from non-ecstasy users on the level of education attained, or income, but were more likely to be single and male. Two-thirds of the people who used ecstasy within the last year had only used it relatively rarely (once every three months or less often), with only 20% reporting that they used the drug at least once per month. Users generally consumed only one tablet on each typical occasion, with 20% using 2 tablets and 10% using 3 or more tablets on each typical occasion. Since the Australian National Household Survey was first conducted in 1995, the proportion of people reporting they have recently used ecstasy has more than trebled (Degenhardt et al., 2004). However, increased use has slowed for males, with only females reporting an increased prevalence of use between 1998 and 2001.

The composition of ecstasy tablets and usage patterns have been shown to vary over time, as well as between countries, regions and even cities. Therefore it is important to understand the patterns of ecstasy use in the region in which research is conducted. All of the new empirical studies presented later in this thesis were conducted in Canberra,
Australian Capital Territory (ACT), Australia. An annual survey of ecstasy users in the ACT in 2003 recruited a sample in which 59% of participants had used ecstasy on a monthly to fortnightly basis, and a 33% on a fortnightly to weekly basis (Proudfoot & Ward, 2004). All users reported that the preferred route of administration was by ingesting ecstasy tablets, although nearly half (49%) reported that they had snorted ecstasy within the last six months and 6% reported having smoked it. Analysis of Australian Federal Police seizures in the ACT between 1999 and mid-2003 has revealed that purity had fluctuated from 61mg to 132mg of MDMA per tablet (Proudfoot & Ward, 2004). Most users typically took 2 tablets each time they used the drug, increasing to 4 on heavier nights. For a 70kg person this equates to a dose of between 1.74mg/kg and 7.54mg/kg of MDMA depending on the number and strength of the pills they self-administer. The ecstasy usage statistics in the ACT are largely consistent with Australian national averages, except that ecstasy users in the ACT sample tended to use the drug slightly less often but take slightly more tablets on each occasion (Breen et al., 2004). All current ecstasy users in the ACT reported the use of other drugs as well, including alcohol (100%), cannabis (97%), nicotine (92%), methamphetamine (powder: 88%, crystal 71%), LSD (59%), nitrous oxide (56%), amyl nitrate (50%), ketamine (49%), and cocaine (47%), as well as less common usage of other drugs (Proudfoot & Ward, 2004).

1.4 The effects of MDMA administration

The time course of the effects of MDMA administration can be divided into three distinct phases, namely the acute, residual and long-term effects. The acute effects encompass the immediate effects of the drug from the time it is administered until the time that most of the drug has been metabolised and passed out of the system. Residual effects are generally taken to refer to effects experienced in the days immediately following administration. In particular these effects are thought to result from prolonged consequences of drug action prior to completion of the restoration of neurotransmitter functioning. In contrast, long-term effects are thought to arise from lasting dysfunctions in neural and bodily systems that are apparent in the months and years following administration.
1.4.1 Acute effects

The acute effects of MDMA are caused by the effect of MDMA on neurotransmitter systems. MDMA is an indirect monoaminergic agonist which in animals has been shown to cause a massive release and reuptake inhibition of serotonin, and to a lesser extent of dopamine, norepinephrine (noradrenaline), and acetylcholine, as well as interruptions to serotonin and dopamine synthesis (Nash, Meltzer, & Gudelsky, 1990; Sprague & Nichols, 1995; Stone, Stahl, Hanson, & Gibb, 1986; Vollenweider, Liechti, Gamma, Greer, & Geyer, 2002; White, Obradovic, Imel, & Wheaton, 1996). The acute depletion of serotonin in rats has been shown to recover to pre-treatment levels within 24 hours of administration of a single moderate dose (Schmidt, 1987).

While it has been widely assumed that the acute effects of MDMA on neural systems in animals also occurs in humans, there is some evidence of limitations in the extent to which such generalisations are valid. For example, the prepulse inhibition (PPI) of the acoustic startle reflex is known to be mediated by serotonin reuptake in both humans and rats (Liechti, Geyer, Hell, & Vollenweider, 2001; Vollenweider, Remensberger, Hell, & Geyer, 1999). However, the acute effect of MDMA has been found to significantly increase PPI in humans but decrease PPI in rats (Quednow, Kuhn, Hoenig, Maier, & Wagner, 2004; Vollenweider et al., 1999). This suggests that despite MDMA causing an acute release of serotonin and other neurotransmitters in both species, that these changes cause an opposite effect in rats compared to humans in at least one serotonin-mediated system. Therefore, the remainder of this review of acute effects will focus on results obtained from human research where possible.

In humans, it has been shown that placebo-controlled double-blind administration of MDMA causes acute changes in a wide range of physiological measures, including regional cerebral blood flow (rCBF), electrical activity, and neuroendocrine levels, as well as immunocompetence and cardiovascular measures. These results have been consistently found following MDMA administration to both current ecstasy users (Cami et al., 2000; Chang et al., 2000; de la Torre et al., 2000; Downing, 1986; Grob, 1998; Harris, Baggott, Mendelson, Mendelson, & Jones, 2002; Mas et al., 1999) and previously MDMA-naïve participants (Frei et al., 2001; Gamma, Buck, Berthold, Hell, & Vollenweider, 2000; Greer & Tolbert, 1986). Participants typically received a controlled administration of 1.5 to 1.7mg/kg of MDMA, with few significant effects.
detected or reported for doses less than 1mg/kg. Typical experimental doses cause rCBF to significantly increase in the ventromedial frontal and occipital cortex, inferior temporal lobe and cerebellum, and decreased in the motor and somatosensory cortex, and temporal lobe, including the left amygdala (Gamma, Buck et al., 2000). A similar distribution of changes to brain activity has also been found using an electroencephalogram (EEG) to measure brain electrical activity (Frei et al., 2001).

Neuroendocrine studies have shown significant acute effects on the levels of corticotropin (ACTH), dehydroepiandrosterone (DHEA), cortisol and prolactin, all peaking between 1.5 and 2.5 hours after administration, with levels returning to normal by about 6 hours after administration (de la Torre et al., 2000; Farre et al., 2004; Grob, 2000; Harris et al., 2002; Mas et al., 1999).

Immunocompetence is a term used to describe readiness of an organism to react defensively against antigens. Immunocompetence has been shown to be compromised by MDMA in a non-linear fashion, such that a subsequent controlled-dose of MDMA yields an unexpectedly large decrease in immunocompetence compared to the initial dose (Connor, 2004; Connor, Connelly, & Kelly, 2001; Farre et al., 2004; Pacifici et al., 2001). This is particularly relevant to regular ecstasy users who typically administer multiple doses of MDMA in one evening at dosage levels much greater than in controlled studies.

Cardiovascular changes include increased heart rate commencing one hour after administration and declining two hours after administration, plus increased blood pressure with little or no change in body temperature (de la Torre et al., 2000; Downing, 1986; Farre et al., 2004; Gamma, Buck et al., 2000; Grob, 1998; Harris et al., 2002; Liechti et al., 2001; Mas et al., 1999; Vollenweider, Gamma, Liechti, & Huber, 1998).

On subjective measures, participants who received controlled administration of MDMA report significantly enhanced positive mood, extroversion, emotional excitability, state anxiety (as distinct from apprehension anxiety), and openness to other people (intimacy), relaxation and contemplativeness, with moderate derealisation, depersonalisation, distortions in the perceptions of time and space, and the absence of hallucinogenic effects (Cami et al., 2000; Davidson & Parrott, 1997; Downing, 1986; Frei et al., 2001; Gamma, Buck et al., 2000; Greer & Tolbert, 1986; Liechti et al., 2001; Solowij, Hall, & Lee, 1992; Vollenweider et al., 1998). The most common acute
adverse effects reported are bruxism (jaw clenching), headaches, loss of appetite, difficulty concentrating, sweating, increased sensitivity to cold, and impaired balance and motor restlessness, which may persist for 24 hours or more (Downing, 1986; Gamma, Buck et al., 2000; Greer & Tolbert, 1986; Liechti et al., 2001; Vollenweider et al., 1998). Recreational ecstasy users report a similar pattern of subjective positive and adverse effects to those who received MDMA in controlled laboratory conditions. However, some studies found relatively higher proportions of ecstasy users reported hallucinogenic effects and hyperthermia, which may be due to factors such as having taken the drug in higher doses and in hot crowded conditions at dance parties (Davidson & Parrott, 1997; Liester, Grob, Bravo, & Walsh, 1992; Peroutka, Newman, & Harris, 1988).

Recreational ecstasy use can lead to severe reactions requiring hospitalisation, and, in some cases, the death of the user (Ben-Abraham, Szold, Rudick, & Weinbroum, 2003; Schifano, 2004). However, deaths are comparatively rare compared to other drugs (Cole, Sumnall, & Grob, 2002; Green, 2004). A review of ecstasy-related deaths in Australia concluded that most deaths were due to contaminants such as paramethoxyamphetamine (PMA) or salt imbalance rather than directly caused by MDMA (Gowing, Henry-Edwards, Irvine, & Ali, 2002).

1.4.2 Residual effects

The residual effects of MDMA are thought to be largely mediated by a transient depletion of serotonin. However, there has been relatively little research on these effects. In rats it has been shown that that serotonin levels are restored to pre-MDMA-treatment levels within 24 hours of administration of a single 10mg/kg, but then declined again over the following week, and that decreased tryptophan hydroxylase activity may be still apparent two weeks after administration (Schmidt, 1987; Schmidt & Taylor, 1987; Stone, Merchant, Hanson, & Gibb, 1987).

In humans, one placebo-controlled double-blind study showed that the acute decrease in rCBF following controlled MDMA administration in eight subjects persisted for at least three weeks in many brain regions (Chang et al., 2000). In contrast, recreational ecstasy users who had abstained from ecstasy for four months (average 6.6 months, range .5 to 26 months) had rCBF levels that were not significantly different from controls. This
suggests that the residual MDMA effect on rCBF persists for some time longer than 3 weeks but less than 4 months.

Residual effects have also been studied in humans by recruiting people in nightclubs or parties who report having used the drug that evening, or people who are just about to go to a nightclub or party with the intention of taking ecstasy. Changes to relevant variables are then investigated over the following days (e.g., comparison of measurements taken on days 0, 4 and 7). In addition, the drug users may also be compared to a non-drug using control group on each day of the study. Studies have found that ecstasy users have higher aggression, irritability, depression and, in some cases, anxiety scores, as well as lower sociability compared to controls two to five days after self-administration with MDMA, however, these restore to levels not significantly different from controls within seven days (Curran, Rees, Hoare, Hoshi, & Bond, 2004; Curran & Travill, 1997; Parrott & Lasky, 1998; Verheyden, Hadfield, Calin, & Curran, 2002). Furthermore, the size of the effects appears to depend on both the frequency of reported ecstasy use and possibly the participant’s sex. In one study, more frequent users had more severe residual effects (Curran et al., 2004), while in another study females were more subject to depression, while the number of ecstasy tablets taken just prior to recruitment was correlated with the level of aggressiveness after four days for males but not for females (Verheyden et al., 2002).

Surveys of ecstasy users suggest that residual effects vary considerably between users (Peroutka et al., 1988; Travers & Lyvers, 2005; Verheyden, Henry, & Curran, 2003). For example, in one study, the most common effects of ecstasy 24 hours after self-administration were “drowsiness”, reported by 36% of participants, and “muscle aches and fatigue”, reported by 32% of participants (Peroutka et al., 1988). Other effects included “depression” (21%) and “a sense of closeness to other people” (22%) and “irritability” (12%). However, no individual symptom was reported by a majority of users.

1.4.3 Long-term effects

The present thesis is concerned with the long-term effects of ecstasy use. There is now a large body of evidence from animal studies that MDMA administration can cause lasting changes to the serotonin system in animals, and an increasing body of convergent evidence that recreational ecstasy use is sufficient to cause equivalent
changes in humans (see reviews in the following sections). Of particular relevance to this thesis is the finding that ecstasy use can cause lasting deficits in long-term memory in humans (reviewed in Chapter 3). In addition, many studies have also shown lasting changes in mood, aggression, somatic complaints, psychopathology and executive functioning in ecstasy users (e.g., Bond, Verheyden, Wingrove, & Curran, 2004; Daumann, Fimm, Willmes, Thron, & Gouzoulis-Mayfrank, 2003; Gerra et al., 2001; Gerra et al., 1998; Hanson & Luciana, 2004; McCardle, Luebbers, Carter, Croft, & Stough, 2004; McGuire, 2000; McGuire, Cope, & Fahy, 1994; Parrott, Milani, Parmar, & Turner, 2001; Parrott, Sisk, & Turner, 2000; Schifano, Di Furia, Forza, Minicuci, & Bricolo, 1998). However, these findings have been also controversial and not universally reported (Cole et al., 2002; Croft, Mackay, Mills, & Gruzelier, 2001; Dafters, Duffy, O'Donnell, & Bouquet, 1999; Klugman, Hardy, Baldeweg, & Gruzelier, 1999). All of these functional changes are thought to result from long-term MDMA-related changes to the serotonin system. In order to better understand the impact of MDMA on serotonergic functions in the brain, the following section provides a basic overview of the organisation of the serotonin system.

1.5 The organisation of serotonergic axons

In rats, primates and humans, all the cell bodies of serotonergic neurons are primarily located in the raphe nucleus. Ascending axons then innervate many parts of the brain, and descending axons innervate the spinal column (Jacobs & Azmitia, 1992).

Focussing on humans, Figure 1.1 illustrates that serotonergic neurons which have ascending axons are primarily located within the rostral raphe nuclei (Heimer, 1994; Rubenstein, 1998). The axons all ascend through the diencephalon before diverging in separate fibre bundles. Axons which innervate the cerebral cortex mainly project through the septal area into the forebrain, then caudally throughout the remainder of the cortex with some very long axons eventually reaching the occipital lobe. Axons innervating the hippocampus mainly project dorsomedially through the cingulate cortex.
1.6 Long-term changes to the serotonin system in animals

1.6.1 The nature of the neurochemical and neuroanatomical changes

MDMA administration has been shown to result in long-term neurochemical and neuroanatomical changes to the serotonin systems in a variety of animal species, including mice, rats, guinea pigs, and higher primates. With regard to the neurochemical changes, a recent review (Green et al., 2003) highlighted that over sixty papers had now been published which show that either a single large dose (e.g., 20mg/kg) or frequent smaller doses (e.g., 4mg/kg) of MDMA administered to rats results in long-term dose dependent depletion of serotonin and its metabolite 5-hydroxyindoleacetic acid (5-HIAA). In primates, lasting serotonergic depletions have been found for even lower doses (e.g. 2.5mg/kg, Ricaurte, Forno et al., 1988). In contrast, there is no evidence of any lasting changes to dopamine, epinephrine and norepinephrine neurotransmitter levels or associated neurons (Battaglia, Brooks, Kulsakdinun, & De Souza, 1988; Green...
et al., 2003; O'Hearn, Battaglia, De Souza, Kuhar, & Molliver, 1988; Ricaurte, Forno et al., 1988).

With regard to lasting neuroanatomical changes to the serotonin system, the primary evidence has come from histological examinations of MDMA-related damage to serotonergic axons using various staining techniques in rats and higher primates. While it has been noted that the techniques used vary in their specificity to serotonergic axons, the overall findings of the studies suggest that frequent large doses of MDMA (in rats, typically 20 mg/kg every 12 hours for 4 days, then sacrificed 2 to 4 weeks after the first dose) results in a marked reduction in the density of stained serotonergic axon fibres throughout much of the brain (Commins et al., 1987; Green et al., 2003; O'Hearn et al., 1988; Slikker et al., 1988). Similarly treated rats also have a marked decrease in the transport of radioactive material injected into serotonergic cell bodies (Callahan, Cord, & Ricaurte, 2001). In rats which have not been treated with MDMA the radioactive material would normally be transported along the axon fibres to axon terminals in other parts of the brain. The reduction in transportation of the radioactive material in the MDMA treated rats could indicate either that there are fewer axon fibres to transport the material, or that the axons remain intact but are functionally impaired (Callahan et al., 2001).

Several studies have shown reduced uptake of radioactive material which has a high affinity for serotonin uptakes sites with doses in rats as low as 5mg/kg on two consecutive days (e.g. Battaglia et al., 1987; McGregor et al., 2003; O'Shea, Granados, Esteban, Colado, & Green, 1998). Since the serotonin uptake sites are predominantly found on serotonergic axon terminals, the reduction in the uptake of the radioactive material also suggests that MDMA either causes a reduction in the number of functioning uptake sites on serotonergic axon terminals, or the axons are structurally damaged to the extent that there is an overall reduction in the number of functioning axon terminals (Callahan et al., 2001; Green et al., 2003; Kuhar & Aghajanian, 1973).

Recent evidence suggests that all of these results should be interpreted as showing a dysfunction rather than the destruction of the axon or the axon terminals. It was found that three 7.5mg/kg treatments in three hours in rats failed to produce any changes in the levels of a protein (GFAP) thought to be critical to axonal structure, but was sufficient to cause lasting serotonin and 5-HIAA depletion (Wang, Baumann, Xu, & Rothman,
This suggests that while it has commonly been assumed in literature that MDMA leads to the destruction of serotonergic axon terminals, it remains possible that these axons remain structurally intact but are partially or completely disabled.

The long-term effects of MDMA on serotonergic axons are not evenly distributed throughout the rat and primate brain. In the first few months after MDMA-administration, the regional density of axonal dysfunctions tends to be proportional to the extent of serotonergic innervation in each part of the brain. An exception to this are thick axons in the hippocampus, hypothalamus, and basal forebrain which appear to be less affected by MDMA administration than thick axons in the forebrain and fine axons throughout the brain (O'Hearn et al., 1988). Longer studies of between one and seven years duration have shown complete recovery on various neurotoxic markers in some parts of the brain, especially for moderate doses (e.g. 10mg/kg in rats) and especially in areas proximal to the serotonin cell bodies in the raphe nucleus. However, most of these studies have also shown that significant axon dysfunction persists in more distal regions of the brain for at least one year in rats in the hippocampus, the frontoparietal cortex, and the occipital cortex, and for at least seven years in higher primates in the same brain regions (Green et al., 2003; Hatzidimitriou, McCann, & Ricaurte, 1999; Ricaurte, Martello, Katz, & Martello, 1992; Sabol, Lew, Richards, Vosmer, & Seiden, 1996; Scanzello, Hatzidimitriou, Martello, Katz, & Ricaurte, 1993).

While MDMA appears to cause lasting dysfunctions in the axons of serotonin neurons, the cell bodies of the neurons appear to remain unaffected (Commins et al., 1987; Green et al., 2003). However, the loss or disabling of the serotonin axons means that the otherwise functional cell bodies in the raphe nucleus have either reduced or completely lost their ability to communicate with cells in other parts of the brain. They therefore have a reduced contribution to brain functioning, or no longer contribute at all.

1.6.2 The dosage at which the detectable effects occur

The dose required for the long-term effects of MDMA to emerge is species dependent. Some specifics of rats, including Sprague-Dawley, Hooded Lister, and Wister rats, typically require several 20mg/kg doses to produce significant levels of serotonin depletion measured in the first few weeks after administration, whereas a single dose of 10 mg/kg is sufficient in Dark Agouti rats (Green et al., 2003). In general effects have not been found using lower doses (O'Shea et al., 1998; Scanzello et al., 1993). In
primates, doses of 40mg/kg of MDMA produced larger long-term neurochemical changes compared to the same dosage given to Sprague-Dawley rats (Slikker et al., 1988). Furthermore, lasting serotonin depletion has been detected in squirrel monkeys (weighing 0.6 to 0.7kg) with as little as 2.5mg/kg (Ricaurte, Forno et al., 1988).

The finding outlined above that the neurotoxic dose of MDMA is lower for monkeys than for rats is consistent with the principle of inter-species scaling (Mordenti & Chappell, 1989). This principle is based on findings that basic physiological parameters across animal species, such as heart rate and drug metabolism, change logarithmically rather than linearly with increased species size. In general, this principle predicts that because larger species eliminate drugs relatively slowly, they require a smaller dose to maintain a particular plasma concentration for a given period of time. Thus, in accordance with the findings regarding neurotoxic MDMA doses outlined above, relatively large animals like primates require a lower dose of MDMA to achieve a sustained plasma level sufficient for neurotoxicity to occur compared to smaller animals.

Further extrapolation of the principle of interspecies scaling suggests that the neurotoxic dose for humans should be even lower than that for primates. As outlined earlier, for a 70kg human who consumes a dose of 2 to 4 ecstasy tablets per occasion (i.e. a typical dose for regular ecstasy users in the ACT) may ingest between 1.7 to 7.5mg/kg of MDMA depending on the number and strength of the pills they self-administer (based on data provided in Proudfoot & Ward, 2004). Furthermore, the typical pattern in recreational ecstasy users of ingesting multiple doses over several hours has been shown to cause non-linear changes in MDMA plasma concentrations, such that several smaller doses of MDMA results in unexpectedly high MDMA plasma levels (de la Torre & Farre, 2004). High ambient temperatures common in dance club environments have also been shown to further exacerbate the negative effects of repeated MDMA administration in rats and possibly exacerbates the negative outcomes of ecstasy use in humans (Parrott, 2004b; Sanchez et al., 2004). Overall these findings strongly suggest that regular recreational ecstasy users typically self-administer neurotoxic doses of MDMA whenever they obtain and use MDMA-based ecstasy tablets.
1.7 Convergent evidence of long-term MDMA-related neural changes in humans

The evidence outlined above – of significant long-term changes caused by administration of MDMA to animals – gives sufficient reason to be concerned about the possible consequences on the serotonin systems of recreational ecstasy users. This statement in part is based on the premise that there are sufficient similarities between the human, rat and primate brains for the effects observed in animals to also occur in humans. However, despite some similarities in the serotonergic axon innervation patterns across the species, there are also significant differences in the types and distributions of serotonin receptors, as well as obvious physiological differences (Berger, Trottier, Verney, Gaspar, & Alvarez, 1988; Duncan et al., 1992; Morrison, Foote, Molliver, Bloom, & Lidov, 1982; Pazos, Probst, & Palacios, 1987a, 1987b). For instance, the 5-HT$_{3B}$ serotonin receptor is common to both rats and humans. However, evolutionary changes appear to have rendered the receptor non-functional in humans (Grailhe, Grabtree, & Hen, 2001). It is also possible that interspecies differences in the metabolic pathways of MDMA could provide humans with some protection from MDMA neurotoxicity (de la Torre & Farre, 2004). It has therefore been necessary to conduct research to confirm if the serotonergic changes observed in animals also occur in humans at normal recreational doses, and that these changes cause functional consequences. Since it would be unethical to administer to humans doses of MDMA that would be expected to result in enduring neurological damage, the investigation of the long-term effects of MDMA in humans has relied on the comparison of convenience samples of existing ecstasy users to groups of people who do not use ecstasy.

1.7.1 Human neuroimaging studies

Neuroimaging provides a means of studying regional brain chemistry and the integrity of neuronal structures in living organisms. These techniques include Positron Emission Tomography (PET), Single Proton Emission Computed Tomography (SPECT), Magnetic Resonance Imaging (MRI), and Proton Magnetic Resonance Spectroscopy ($^1$H MRS). Other neuroimaging techniques which detect changes in brain functioning, such as Functional MRI (fMRI) and Electroencephalography (EEG), will be reviewed in later chapters where relevant.
PET and SPECT scans involve the administration of a ligand (also referred to as a radioligand), which is a compound that has been tagged with a radioactive isotope. The isotope does not disrupt the normal functioning of the compound but is detectable by the scanning technique, thereby allowing the movement of the ligand in the brain to be traced (Toga & Mazziotta, 1996). The PET radioligands (+)-[\(^{11}\)C]McN-5652 and [\(^{11}\)C]DASB have been found to selectively label serotonin transporters in the baboon and human brain (Frankle et al., 2004; Houle, Ginovart, Hussey, Meyer, & Wilson, 2000; Scheffel et al., 1998; Szabo et al., 1995; Szabo et al., 2002). Since serotonin transporters are a structural element of serotonin axon terminals, the density of serotonin transporters has been taken as an indicator of the density of functional serotonergic axon terminals (Reneman, Booij, Majoie, Van Den Brink, & Den Heeten, 2001). A 1.5mg/kg dose of MDMA has been shown to cause an acute reduction in (+)-[\(^{11}\)C]McN-5652 binding in many areas of the brain 90 minutes after administration to human volunteers, which is consistent with MDMA causing a acute reduction of serotonin reuptake (Ametamey et al., 2000). However, rather than providing any indication of long-term changes, the binding ratios in that study returned to pre-administration levels within 4 weeks. Other studies have shown that current ecstasy users have lower (+)-[\(^{11}\)C]McN-5652 and [\(^{11}\)C]DASB binding than non-drug using controls in most brain areas, including the hippocampus and occipital lobe, but also that binding ratios recover during abstinence from ecstasy use (Buchert et al., 2003; Buchert et al., 2004; McCann, Szabo, Scheffel, Dannals, & Ricaurte, 1998; McCann et al., 2005). A similar pattern of the recovery of ligand binding in former ecstasy users has also been found for SPECT imaging with ligand [\(^{123}\)I]β-CIT (de Win, Reneman et al., 2004; Reneman, Lavallaye et al., 2001; Semple, Ebmeier, Glabus, O'Carroll, & Johnstone, 1999). [\(^{123}\)I]β-CIT has been shown to selectively bind to serotonin transporters throughout most of the brain with the exception of the striatum where it binds to dopamine transporters (de Win, de Jeu et al., 2004; Farde et al., 1994; Heinz et al., 2004; Laruelle et al., 1993; Pirker et al., 1995; Reneman, Booij, Habraken et al., 2002). However, given that there is no evidence of dopaminergic neurotoxicity for even extreme human recreational doses of MDMA in animals, it is likely that differences in [\(^{123}\)I]β-CIT binding ratios observed in ecstasy studies largely reflect dysfunctions within the serotonergic system.

The PET and SPECT studies outlined above seem to suggest that the changes in the density of functioning serotonin transporters caused by MDMA administration in
humans are temporary, and that they return to normal functioning within a few months. However, this is inconsistent with evidence from the animal literature and other types of human imaging studies (outlined below) which suggest that axonal dysfunction persists for several years at least. An alternative explanation is that the restoration of (+)-[^11]C]McN-5652 binding is due to the up-regulation of post-synaptic receptors which has been shown to occur in ecstasy users who have been abstinent from MDMA for two months, and rats which have been abstinent from MDMA for one month (Buchert et al., 2003; Reneman, Booij, Schmand, van den Brink, & Gunning, 2000; Reneman, Endert et al., 2002; Reneman, Habraken, Majoie, Booij, & den Heeten, 2000; Terriere et al., 1995). However, it has not been specified in literature how the up-regulation of the post-synaptic receptors facilitates greater binding of ligands in PET and SPECT studies. A plausible explanation is that the up-regulation of the post-synaptic receptors reduces the amount of extracellular serotonin that is free to bind to those pre-synaptic serotonin transporters which are still functional. Consequently, there are a greater number of functioning presynaptic serotonin transporters available for the ligands to bind to. If this is the case, then the decrease in serotonin transporter density observed in most parts of the brain may persist well beyond the few months suggested by the PET and SPECT studies.

The changes to the serotonin system observed using (+)-[^11]C]McN-5652 PET binding appear to be specific to ecstasy use, as distinct from being an acute, residual, or long-term effect of any other drug.[^11]C]McN-5652 binding in users of other drugs were found to be not significantly different from non-drug using controls in most brain regions, despite being lower in ecstasy users who also used other drugs (Buchert et al., 2003; Buchert et al., 2004). One exception to this was that users of other drugs in one study had significantly lower ligand binding in the caudate compared to controls, which was thought to be an effect of acute cocaine withdrawal in some participants (Buchert et al., 2003).

Several neuroimaging techniques used in human ecstasy research have produced results that are consistent with lasting changes to neural structures such as axons, although they are non-specific regarding which neurotransmitter system the damaged structures are part of. One such technique is Proton MR Spectroscopy (^1H-MRS). This technique is used to detect a range of compounds in the brain including NAA, which is found almost exclusively in functional neuronal cell bodies and axons. A reduction in the ratio
of NAA to Creatine (Cr) and/or Choline (Cho) is taken as a sign of the loss or dysfunction of cell bodies or axons. Some studies have found lower NAA/Cr and NAA/Cro ratios in ecstasy users compared to users of other drugs in the grey matter of the frontal lobes, although not in the grey matter of the occipital lobe or parietal white matter (Reneman, Majoie, Flick, & den Heeten, 2002; Reneman, Majoie, Schmand, van den Brink, & den Heeten, 2001). However, other $^1$H-MRS studies have failed to detect significant decreases in regional NAA content, but detected other changes including an increase in a different compound (MI) in the parietal lobes which is taken as a indicator of the enlargement or proliferation of glial cells caused by brain injury or repair processes, and a non-significant trend ($p=.07, n=13$ ecstasy users compared to 6 cannabis users) towards a lower NAA/Cr ratio in the left hippocampus (Chang, Ernst, Grob, & Poland, 1999; Daumann, Fischermann, Pilatus et al., 2004). One very small study, which only investigated NAA in the hippocampus of five ecstasy users compared to five non-drug using controls failed to detected a significant difference between the groups (Obergriesser, Ende, Braus, & Henn, 2001). The inconsistent results between these studies may be due to limited power of the studies to detect effects due to the small number of participants, as well as different demographic and drug use characteristics of the ecstasy users and comparison groups in each study. Despite these limitations, the statistically significant results are consistent with MDMA causing the loss or dysfunction of neuronal tissue.

In contrast to $^1$H-MRS, evidenced gathered using Diffusion-weighted Magnetic Resonance (MR) imaging is thought to specifically indicate structural damage to cell bodies and axons, rather than leaving open the possibility they remain intact but have been rendered dysfunctional. Diffusion-weighted MR provides a measure called the **Apparent Diffusion Coefficient (ADC)** which indicates the diffusion motion of water molecules in living tissue (Reneman, Majoie, Habraken, & den Heeten, 2001). An increase in ADC is taken as an indicator of degenerating tissue, since the removal of structural tissue allows greater movement of water molecules. Elevated levels of ADC have been found in the globus pallidus of ecstasy users who had been abstinent for an average of 14 weeks (range 3-52) compared to non-drug using controls (Reneman, Majoie, Habraken et al., 2001), which suggests that the MDMA-related damage to axons has caused a breakdown in their physical structure. Similarly, another MR scanning technique called Voxel-Based Morphometry (VBM) has been used to produce evidence of a breakdown in neural grey matter in ecstasy users compared to users of
other drugs in the frontal, temporal, and occipital lobes, as well as the cerebellum and brain stem (Cowan et al., 2003).

Overall, human imaging studies have produced evidence of lasting neural changes in many different brain regions of recreational ecstasy users. Research using $^1$H-MRS studies suggest the lasting loss or dysfunction of neuronal structures in ecstasy users, while Diffusion-weighted MR and VBM support the loss of neural matter. While these techniques cannot determine which neurotransmitter system/s are impacted, or whether the damage is to axons or to cell bodies, the results are consistent with the findings of animal studies that MDMA causes lasting damage to the serotonergic axons.

**1.7.2 Other evidence of lasting MDMA-related changes in human brain chemistry and structures.**

Neuroendocrine challenge studies have been used in ecstasy research to infer the state of the serotonin system by measuring the response of relevant serotonin-mediated hormone levels to manipulation of serotonin levels. Administration of the serotonin precursor $\text{L-}$Tryptophan in humans is known to increase the concentration of prolactin (PRL) in the blood (Green et al., 2003). This is thought to be due to a $\text{L-}$Tryptophan-mediated increase in the synthesis and release of serotonin, which in turn increases PRL concentrations in the blood. In one study, the peak in PRL concentration following $\text{L-}$Tryptophan administration to ecstasy users (abstinent for at least 20 days, mean= 8.6 weeks) was not significantly different from their pre-administration baseline (Price, Ricaurte, Krystal, & Heninger, 1989). In contrast, the peak PRL concentration for controls was significantly different from baseline. This seems to be consistent with a deficit in the functioning of the serotonin system in ecstasy users. However, the peak concentration for ecstasy users was not significantly lower than controls. Furthermore, another study in which ecstasy users had been abstinent for an average of 18 weeks also failed detect any significant differences in peak PRL concentrations (McCann, Ridenour, Shaham, & Ricaurte, 1994). This seems to indicate that the PRL response to $\text{L-}$Tryptophan challenge returns to normal given a sufficient period of abstinence from ecstasy. It has been argued that this may be due to the PRL response being mediated by serotonin axons innervating the hypothalamus, which have been shown to undergo significant recovery in the months following cessation of MDMA administration (McCann et al., 1994; Ricaurte et al., 1992). In contrast to the results of the above $\text{L-}$
Tryptophan challenge studies, long lasting effects have been found using the serotonin agonist \( \text{D}-\)fenfluramine (Gerra et al., 2000; Gerra et al., 1998). Ecstasy users who had been abstinent from all illicit drugs for three weeks, had a lower PRL response following \( \text{D}-\)fenfluramine administration compared to controls. This difference remained highly significant after the ecstasy users had been abstinent from all illicit drugs for one year. This is consistent with the long lasting changes to the serotonin system observed in animal studies.

Cerebrospinal Fluid (CSF) studies of ecstasy users suggest that the MDMA-related long-term depletion of the serotonin metabolite 5-Hydroxyindole Acetic Acid (5-HIAA) observed in animals also occurs in humans. In non-human primates it has been shown that CSF depletion of 5-HIAA provides an estimate of 5-HIAA depletion in the brain two weeks after administration of a neurotoxic dose of MDMA, as confirmed by direct chemical analysis after the animal was sacrificed (Ricaurte, DeLanney, Wiener, Irwin, & Langston, 1988). In humans, most studies have found decreased levels of 5-HIAA in current ecstasy users who had not taken ecstasy for at least two or three weeks compared to other drug users (Bolla, McCann, & Ricaurte, 1998; McCann, Mertl, Eligulashvili, & Ricaurte, 1999; McCann et al., 1994), with one study finding a statistically significant negative correlation between CSF 5-HIAA concentration and average monthly ecstasy dose (Bolla et al., 1998). One study failed to detect CSF 5-HIAA depletions in ecstasy users, possibly due to the small sample size and insufficient ecstasy use by participants \((\text{n}=5, \text{number of doses} = 1, 17, 18, 22, \text{and} 33)\) (Peroutka, Pascoe, & Faull, 1987). Overall these studies suggest that recreational ecstasy users do have lasting 5-HIAA depletions compared to other drug users.

Effects lasting substantially longer than two months in ecstasy users have been found using the glucose ligand \( \text{FDG} \) to indicate changes in glucose utilisation, especially in the hippocampus, amygdala, putamen, caudate (Buchert et al., 2001; Obrocki et al., 1999; Obrocki et al., 2002). However, it is not clear from the studies if the changes in glucose utilisation were specifically due to ecstasy use, as distinct from the use of other drugs, or if the changes were mediated by dysfunctions in the serotonin system (Gamma, 2003; Obrocki et al., 2003).
1.7.3 Summary of the long-term effects of MDMA on the neurochemistry and neuroanatomy of the brain

The review above demonstrates that animal and human findings converge to show long-term effects of MDMA and recreational ecstasy use on the neurochemistry and anatomy of the brain. In animals, MDMA has been shown to cause long-term dose-dependent depletions of serotonin and its metabolite 5-HIAA in the brain, with an absence of long-term effects on other neurotransmitter systems. There is also a lasting reduction in the density of functioning serotonin axons throughout much of the brain, but particularly in areas distal to the serotonin cells bodies and which are richly innervated with serotonergic axons. Empirical evidence also supports the principle of interspecies scaling, namely that the dose of MDMA required for the lasting changes to occur is lower for larger animals than for smaller animals. Extrapolation of this principle suggests that regular recreational ecstasy users self-administer a neurotoxic dose of MDMA whenever they ingest a typical number of MDMA-based ecstasy tablets.

In humans, neuroendocrine challenge studies, especially those using the serotonin agonist D-fenfluramine, as well as CSF studies indicate that the long term depletion of serotonin and its metabolite 5-HIAA observed in animals also occurs in human recreational ecstasy users. PET and SPECT-based neuroimaging studies on humans also suggest that recreational ecstasy use causes a residual decrease in the density of functional serotonin axons in the brain (indicated by the density of serotonin transporters available for ligand binding), but evidence regarding the duration of the decrease is unclear. The measure used to indicate the density of the functional axons has been shown to return to baseline values within a matter of months; however, other evidence suggest that this may be due to the up-regulation of post-synaptic receptors rather than a recovery in the density of functional presynaptic axons. Other neuroimaging studies using Proton MR Spectroscopy, Diffusion-weighted MR and VBM also support the long term dysfunction of neural matter in ecstasy users, although the evidence gathered using these particular techniques is non-specific regarding which neurotransmitter system the degraded neural structures are associated. However, given the serotonin-specific evidence from PET, SPECT and CSF studies, as well as the lack of evidence supporting the breakdown of any other neurotransmitter system in animals or humans, it is reasonable to assume that the damage is being done to the serotonin system.
Overall, the results of human research regarding the effects of ecstasy on brain functioning are largely consistent with the findings of animal studies. This strongly suggests that typical ecstasy doses ingested by regular ecstasy users are sufficient to cause lasting changes to the human serotonin system.

1.8 Rationale for the current series of studies

The previous section outlined evidence of long-term physiological changes to the serotonin system in animals and humans caused by MDMA and recreational ecstasy use. Given this evidence, there is sufficient reason to be concerned about the possible functional impacts of recreational ecstasy use. The broad aim of the current research project is to examine the behavioural consequences of the ecstasy-related neural changes on cognitive and perceptual functioning humans.

Brain regions which have been shown to be particularly vulnerable to MDMA-related damage to the serotonin system are those which are heavily innervated by serotonergic axons and which are distal to the serotonergic cell bodies in the raphe nucleus. For this thesis, I chose two brain regions to be the focus of my research, namely the hippocampus and occipital lobe. The hippocampus and occipital lobe are both heavily innervated by serotonergic axons and in the studies reviewed above have been consistently shown to be vulnerable to neurotoxic doses of MDMA (e.g., Buchert et al., 2004; Cowan et al., 2003; Hatzidimitriou et al., 1999; Semple et al., 1999).

The memory functions known to be associated with the hippocampus have attracted a lot of attention in the ecstasy research literature (reviewed in Chapters 3 - 6). However, I will argue that none of the research studies to date has adequately isolated the hippocampal component of memory processes from the contribution of other brain regions. Therefore, in order to examine the hippocampal component of memory more specifically, I conducted a series of memory studies (reported in Chapters 4-6) that commenced with an experiment based on established cognitive research methods that are known to be particularly sensitive to hippocampal functioning (Chapter 4).

In contrast to the hippocampus, the occipital lobe is innervated by the longest serotonin axons in the brain (Heimer, 1994; Rubenstein, 1998), and therefore may be particularly vulnerable to MDMA-related damage. However, to date there have been no published studies which have examined MDMA-related changes to the behavioural functioning of
the occipital lobe in humans. On this basis, I conducted an initial study of the occipital lobe functioning of ecstasy compared to non-drug controls (Chapter 7).

All of the original studies reported in this thesis are quasi-experimental retrospective cohort studies. The following chapter deals with design and methodological issues that are common to all of the studies, and which affect the type of conclusions that can be drawn from the results. Particular emphasis is given to Hill’s (1965) criteria regarding the attribution of causal inferences on the basis of cohort studies, and the implications of those criteria for the design and methodologies used in this thesis. This includes the formulation of the inclusion and exclusion criteria, and the collection of drug histories, as well as the measurement and various means of controlling for the influence of potential covariates.

In Chapter 3, the theoretical basis is developed for the three empirical studies of long-term memory in the subsequent chapters. The rationale for the selection and design of the memory tests is described, as well as the literature basis for inferring the localisation of ecstasy deficits from the results of those tests. This includes particular consideration of the function of the hippocampus in tests of long-term memory.

In Chapter 4, I report an empirical study in which I compare ecstasy users and non-drug using controls on implicit and explicit memory performance. This was the first known test of implicit memory in ecstasy users. There were no statistically significant deficits on either implicit or explicit memory for lists of single unrelated words in ecstasy users, but the results regarding explicit memory were not compelling enough to conclude that there was no effect of ecstasy on explicit memory for such stimuli.

The empirical study in Chapter 5 includes a number of tests designed to clarify the explicit memory results of the study reported in Chapter 4 in a sample of ecstasy users who had, on average, administered a much higher lifetime dose of ecstasy. The results again show no indication of explicit memory deficits for lists of single unrelated words in ecstasy users. It is therefore concluded that, in the current samples of ecstasy users at least, ecstasy use does not cause significant deficits in long-term explicit memory for lists of single unrelated words. The possible role of elaborative processing on the performance of ecstasy users on tests of long-term memory was also investigated in this study. This was achieved by applying two standard neuropsychological tests which have been used in published studies to show memory deficits in ecstasy users, namely prose
recall and the Auditory Verbal Learning Test (AVLT). As distinct from the tests of implicit and explicit memory used above, the AVLT allows much greater opportunity for the strategic use of elaborative processing at study. In contrast, the prose recall task specifically requires elaborative processing at study, but unlike the AVLT, the semantic structure of the information is provided at study (i.e., the ‘story’). On both of these tests, no significant deficits were detected in ecstasy users, which is interpreted as indicating that elaborative processing under these conditions does not cause significant deficits in long-term memory in ecstasy users.

The third and final memory study reported in Chapter 6 focuses exclusively on the role of elaborative processing on long-term memory performance in ecstasy users compared to controls. This is achieved mainly through the use of tests of memory for lists of multi-component items (e.g., word pairs, and a novel word-triplet test), as well as a standard neuropsychological test for a list of single words drawn from four semantic categories, which includes a measure of the degree to which participants engaged in elaborative processing (the California Verbal Learning Test (CVLT), Delis, Kramer, Kaplan, & Ober, 1987). The results showed that after statistically controlling for the effect of covariates, ecstasy users made less strategic use of elaborative processing than controls in the CVLT, and had significantly poorer recall for multi-component items, especially word-triplets. Furthermore, ecstasy users learnt word triplets at a significantly lower rate than both non-drug using controls and other drug users who had never regularly used ecstasy (cannabis-controls). Overall, the results of the memory studies are interpreted as indicating that long-term memory deficits in ecstasy users appear to emerge from deficits in elaborative processing, which are known to be localised in the frontal lobes, or from the aggregation of smaller deficits in many brain systems when loaded concurrently, rather than just from central memory structures such as the hippocampus.

In Chapter 7, the focus of the thesis is shifted to low-level visual perception. A theoretical basis for effects of ecstasy on low-level visual processes is developed, based in part on evidence of serotonergic involvement in simple orientation processing. The results show the first empirical evidence of changes in low-level visual processes associated with occipital lobe behavioural functioning in ecstasy users, as revealed by an increase in the magnitude of the tilt aftereffect illusion. Interestingly, this evidence was only found in ecstasy users who had not recently used amphetamines. This suggests
that ecstasy and the recent use of amphetamines may have opposite effects on occipital lobe functioning.

This thesis concludes in Chapter 8 with an evaluation of the specificity of the results to drug use, ecstasy, and MDMA, and a discussion of issues regarding the testing of cognitive and perceptual deficits in ecstasy users in the current thesis and in future research.
Chapter 2. Retrospective cohort studies: Methodological issues

2.1 Introduction

When interpreting the results of retrospective cohort studies regarding the effects of MDMA, a key question that needs to be addressed is, “To what degree can we be confident that any differences observed between ecstasy users and control subjects are due to MDMA?” Many of the factors that influence the confidence with which results can be attributed to MDMA are aspects of the experimental design and methodology, and therefore need to be considered before testing is commenced. This chapter explores a number of issues that I considered when developing the current series of retrospective cohort studies.

2.2 Inferring causal relationships in retrospective cohort studies

2.2.1 Hill’s (1965) criteria

Logically, it is not possible to establish a definitive cause of effects in retrospective cohort studies, because the possibility that the proposed cause and observed effects were both caused by some other unmeasured factor or factors cannot be completely eliminated. However, a set of criteria specified by Hill (1965) enables the evaluation of the degree of confidence which can be placed in causal inferences generated by cohort studies. These criteria were used to establish the link between smoking and lung cancer (Hennekens & Buring, 1987). The criteria against which Hill recommends that causal inferences should be evaluated are the strength, consistency, specificity, temporality, biological gradient, plausibility, and coherence of the results, plus the experimental design and whether the results are supported by analogy with comparable effects. Of these, the analogy criterion is not relevant to the current research, because it is used to assess causal relationships for which no direct evidence has been gathered, but for which there are known causal relationships that are similar enough to argue for a causal inference by analogy. This is not required in the current series of studies because of the volume of evidence that exists regarding the effects of MDMA and ecstasy outlined in the literature reviews. Each of the remaining criteria proposed by Hill will now be defined and applied to the current research.
Hill’s (1965) *experimental design* criterion requires that consideration be given to the strength of evidence that an experimental design can provide. Ethical considerations prohibit the use of randomised controlled trials in research regarding the long-term consequences of ecstasy use, because such a design would involve the administration of potentially neurotoxic doses of MDMA to MDMA-naive participants. The retrospective cohort designs used in the current series of studies are consistent with those used in published literature, and are considered to provide the strongest form of evidence when looking for associations between a potentially harmful agent and negative outcomes in participants (McAlister, Laupacis, Wells, & Sackett, 1999; NHMRC, 2005).

A number of Hill’s (1965) criteria affect the interpretation of results and consideration of relevant literature, rather than issues regarding the design and implementation of the experiment. For this reason issues regarding the following criteria will be addressed where applicable in literature reviews and results sections contained in later chapters: *strength* refers to the strength of the association in the proposed causal-relationship; *consistency* refers to the degree of convergence between results obtained by different researchers, methodologies, and cohorts of participants; *plausibility* refers to whether the proposed causal relationship is consistent with other relevant knowledge about the cause (e.g., the biochemistry of MDMA neurotoxicity and the role of the serotonin system in cognition); and *coherence* refers to whether the proposed causal-relationship conflicts with established knowledge about the condition (e.g., the known effects of controlled MDMA administration in animals).

In contrast, the application of the *biological gradient, specificity, and temporality* criteria affect the details of the experimental design. Therefore, their relevance to the current series of studies will now be examined.

### 2.3 Factors which effect the ability to detect a biological gradient in the results of the current series of studies

Hill’s (1965) *biological gradient* criterion refers to evaluation of dose dependent (also called ‘dose response’) relationships. An example of a dose dependant relationship in the current series of studies would be if memory deficits in ecstasy users were more severe in those participants with greater lifetime ecstasy use. In order to examine dose-dependent relationships for ecstasy (as well as control for other drug use using statistical means), it is necessary to establish the drug use history of the participants. In the current
series of studies, methods such as urine and blood testing are of limited use because they only give an indication of drug use over the previous few days. This is inadequate for studies of the effects of long-term drug use where a drug history going back many years is required. Hair analysis is able to provide information going back many years if the participant has sufficiently long hair. However, many people have hair that is too short to provide information regarding their entire drug using history. Furthermore, they may have dyed their hair so a valid analysis cannot be conducted, or be unwilling to provide a sufficient sample for analysis. In contrast, self reported drug histories can be used with all participants and have been shown to be largely consistent with urine and hair analyses in research environments (Morgan, 2000). In particular, time-line interviews have been shown to be moderately reliable and valid for drug use histories over at least the previous 14 years (Anglin, Hser, & Chou, 1993).

Time-line interviews involve establishing a time line of notable events in the participant’s life (e.g., progression through education, travel, employment, residences and relationships) and then recording their recollected drug use within each period. From the data gathered it is possible to calculate a range of measures for each drug, including the total lifetime dose and maximum monthly dose, as well as determine when they first and last took each drug. In one study, time-line interviews were administered to 323 narcotics users at the start of the study, then again 10 years later (Anglin et al., 1993). On both occasions the interviews referred to the four- to five-year period prior to their first timeline interview. A comparison of the two interviews for that overlapping period showed strong correlations of .63 and .71 for daily narcotics use and abstinence, respectively. This suggests that recollections in time-line interviews are reasonably reliable even after a 10-year test-retest delay. Recollections for “infrequent events” was less reliable, including daily non-narcotics use ($r=.20$) and heavy alcohol use ($r=.48$). However, the reliability of such data was enhanced by disaggregating the data into 3-month portions. Reliability may also be severely compromised if outcomes for the participant are dependant on the drug history given (e.g., whether or not the person gets parole). Since there are no drug history dependent outcomes for participants in the original studies reported in this thesis, the time-line method can be used with reasonable confidence. On the basis of the above findings, the current series of studies used timeline interviews to gather information about all relevant illicit drugs, plus alcohol.
2.4 Factors which effect the specificity and temporality of results in the current series of studies

2.4.1 Possible levels of specificity

Hill’s (1965) specificity criterion refers to the confidence with which the observed effect is related to exposure to the proposed cause and not related to other possible causes. For the current series of studies this criterion was broken down into an inverted hierarchy of questions about the confidence with which it can be said that the results are due to:

- drug use - as distinct from socio-demographic factors such as age, sex, and education, as well as pre-existing genetic and/or biochemical differences and other factors relevant to the experimental tasks (e.g., the effect of intelligence on memory tasks)

- ecstasy - as distinct from the use of other drugs such as alcohol, cannabis, amphetamines, LSD, cocaine, and heroin

- MDMA - as distinct from other psychoactive chemicals which have been found in ecstasy tablets or which may be sold on the pretence that they are MDMA-base tablets

As the level of specificity being considered is increased from ‘drug use’ to ‘ecstasy’ to ‘MDMA’, the number of variables (possible ‘covariates’) that need to be controlled also increases. The level of specificity possible in any particular experiment will be limited by the degree of control exercised over possible covariates exercised in the experimental design and measurement procedures. Potential covariates can be controlled by the use of exclusion criteria, sample matching and statistical control. These terms are defined and explained in the following sections.

2.4.2 Methods used to control possible covariates: exclusion criteria, sample matching and statistical control

The potential influence of some covariates can be eliminated or drastically reduced by excluding people to which that covariate is known to apply. For example, heroin abuse is known to cause brain abnormalities (for review see Buttner, Mall, Penning, & Weis, 2000). Since heroin use is relative rare amongst party drug users it was possible to eliminate the potential influence of heroin abuse in the current series of studies by
excluding people who had ever injected heroin. Similarly, by excluding people outside a restricted age range it was possible to reduce the potential influence of age on the results of the current series of studies. However, other covariates such as sex and intelligence cannot be practically controlled in this way. Similarly, excluding people on the basis of alcohol use would make it practically impossible to locate an adequate number of participants. Therefore, such variables must be controlled for by using either sample matching or statistical control.

The most rigorous form of sample matching is achieved by the selection of cohorts such that they have exactly the same distribution of scores on the variables being matched. For example, if ecstasy user and comparison cohorts were being matched on age and sex, then the two groups would contain the same number of 21 year-old males, 21 year-old females, 22 year-old males, etc. The more criteria the cohorts are matched on, the more difficult it becomes to obtain cohorts of eligible participants. This often necessitates the use of a less rigorous form of sample matching in which the distributions on the matching variables are allowed to differ to a small degree, while still trying to keep the cohorts as closely matched as possible. Such cohorts maybe considered to be matched as long as the cohort means on the matching variables are not statistically different.

Sample matching can only be used to control variables for which the data can be easily collected when screening potential participants. If it is not possible to match cohorts on a relevant covariate, then statistical control of the covariate can be conducted after data collection. Statistical control refers to the use of covariate analysis in Analysis of Variance (ANCOVA) or regression analysis to determine if the possible covariate has a statistically significant influence on the result. A limitation of these forms of analysis is that the sample sizes used in MDMA cohort studies are often not large enough to provide strong statistical control of the covariates for which there is a large natural range of individual scores. Also, it may not be possible to conduct covariate analysis on particular variables due to violation of the assumptions of the tests, such as there being an insufficiently even distribution of scores on the covariate in one or both of the cohorts (e.g., if all members of an ecstasy cohort failed to complete high school, but all members of the control group had graduated from university). For these reasons, it is preferable to control for covariates by sample matching where possible. Otherwise, it is
important to attempt to obtain an even distribution of scores on the covariates in order to maximise the effectiveness of statistical control.

In the following sections, I outline how I used these methods to control for possible covariates within the inverted hierarchy of specificity outlined earlier, i.e., drug use, ecstasy use and MDMA. In addition, I also outline other design considerations used to further enhance the specificity with which conclusions could be made within that inverted hierarchy.

2.4.3 Factors which influence the specificity of the findings to drug use

2.4.3.1 Control of possible covariates

As outlined above, the ability to attribute differences between ecstasy users and non-drug using controls to drug use depends on the confidence with which possible covariates can be eliminated as plausible alternate explanations. The relevant covariates will depend on what factors other than drug use are known or likely to have an effect on the variable of interest.

The general focus of the present research was memory and visual perception functioning in ecstasy users. Several factors are known to be associated with broad scale cognitive and perceptual decline, including increasing age, heroin abuse, and depression, as well as some medications, medical conditions and head injuries. These factors were all controlled by exclusion of relevant people from the studies. In particular, people were excluded if they were not within a restricted age range, or if they reported having ever injected heroin, or having ever had an injury or illness that could have affected their brain in any way (e.g., bacterial meningitis, Anderson, Anderson, Grimwood, & Nolan, 2004), or having ever been diagnosed or medically treated for a chronic psychiatric or emotional condition known to be associated with cognitive deficits (e.g., chronic Posttraumatic Stress Disorder, Sachinvala et al., 2000).

Memory test performance is also known to vary according to sex, age, highest level of education attained, intelligence, and mental health status (e.g., non-clinical stress, consider Halpern & LaMay, 2000; Lezak, Howieson, & Loring, 2004; Park et al., 1996; Quraishi & Frangou, 2002). These factors were controlled for in the current series of studies using sample matching and statistical control. Sex and the highest level of education attained are variables which could be easily determined at the time that
participants were recruited. Since there are many non-drug using controls in the community who match drug users on these variables, it was possible to largely match samples on age and sex between cohorts of ecstasy users and controls, and to a lesser extent the highest level of education attained. Significant differences detected between the cohorts are therefore unlikely to be due to these variables. The inclusion of age amongst the sample matching variables further reduced the potential influence of the variable beyond what had already been achieved by limiting the age range of participants. In contrast, intelligence and mental health status could not easily be determined at recruitment. These variables were therefore measured during the study and controlled for statistically where necessary.

In contrast, the test used to assess the functioning of the occipital lobe is thought to be relatively robust against socio-demographic factors. Consequently the cohorts used in the memory studies could be used in the visual experiment without needing to control for any additional potential covariates.

2.4.3.2 Recruited verses random samples

Another potential methodological confound in cohort studies is the practice of purposively recruiting participants, rather than randomly selecting them from the population. Recruitment of drug users to cohort studies is a common practice because of the small proportion of the population who are regular drug users, which renders random sampling impractical and expensive. It is possible that drug users recruited through advertising may be distinctly different from ‘typical’ drug users on variables other than their drug use, and therefore that differences observed between the recruited drug users and controls reflect these differences rather than the effects of drug use. In the current series of studies the same recruitment methods were used for all of the cohorts in order to minimise the possibility that any recruitment effects could affect one cohort more than the others. However, some recruitment factors only apply to drug users, such as the necessity that they identify themselves as having engaged in illegal activities (i.e., that they have obtained and used illegal drugs). It could be argued that the willingness to make such a statement is a major difference between drug users who participated in the studies and those who did not, and therefore that those groups of drug users may differ on other variables as well. However, while the extent of neurotoxicity experienced by the different groups of ecstasy users may vary, it is difficult to imagine
how specific effects caused by a chemical assault on the brain (i.e., MDMA administration) could be the same as those caused by whether or not drug users are recruited or randomly selected from the population. Furthermore, an Australian study examined the demographics and drug use patterns of users identified in a random sampled household survey and found them to be “strikingly similar” to recruited sample (Topp, Barker, & Degenhardt, 2004). Therefore, as long as other relevant covariates are controlled for, such as level of education and intelligence in memory studies, it is unlikely that the practice of recruiting and paying participants in the current series of studies had a significant effect on the outcomes of the research, as compared to if the participants had been randomly selected from the population.

2.4.3.3 The temporal order of the proposed cause and the observed effects

For drug use to have caused an observed effect, the drug use must have occurred prior to the emergence of the observed difference between drug users and controls (Hall, 1987; Hill, 1965). It has been argued that some differences observed between ecstasy users and controls could reflect pre-existing differences, rather than the effects of drug use (Jansen & Forrest, 1999; Morgan, 1999a; Reed, Winstock, Cleare, & McGuire, 1999). This is likely to be the case with regard to some aspects of personality. It has been shown that drug users in general, and ecstasy users in particular, differ from controls on personality variables, such as ‘sensation seeking’, which have been shown to have a strong heritable component in twin studies (Daumann, Hensen et al., 2004; Hur & Bouchard, 1997; Zuckerman, 1994). However, with regard to the effect of MDMA on the serotonin system, the animal studies outlined in Chapter 1 unequivocally substantiate the temporal order of the controlled administration of MDMA causing the effect of lasting changes to the serotonin system. Other studies also clearly show a temporal order of MDMA administration causing behavioural changes in rats (e.g., McGregor et al., 2003). Given the strength of the temporality evidence from MDMA animal literature, as well as the sampling methods and the high degree of control over possible covariates used in the current series of studies, there is little reason to suspect that the temporal order in the current studies is reversed, or that the drug users had poorer cognitive or perceptual abilities prior to taking illicit drugs.
2.4.4  **Factors which influence the specificity of the findings to ecstasy use**

Having addressed issues regarding the likelihood that any significant differences in the results are due to drug use, the next level of specificity to address is the likelihood that results are due to the use of ecstasy, as distinct from other recreational drugs. In the current thesis, significant differences were only found between ecstasy users and non-drug using controls in the final memory study (Chapter 6) and the visual perception study (Chapter 7). In the final memory study, one of the main memory variables was correlated with a measure of cannabis use. Therefore, to examine the specificity of the results to ecstasy in that study, a comparison was conducted between ecstasy users and people who had never regularly used ecstasy but had used cannabis on a regular basis (cannabis-controls). In addition to enabling the comparison of ecstasy users to cannabis users, the inclusion of the cannabis-control group also increased the statistical power with which the dose dependence of alcohol and cannabis could be determined using regression analysis, and to a lesser extent other drugs such as amphetamines, cocaine, nitrous oxide, and amyl nitrate. In contrast, it was not necessary to test a cannabis-control group in the visual perception study because the results were uncorrelated with cannabis use.

The cannabis-control group was not tested until it was clear that significant differences existed between the ecstasy users and non-drug using controls that could be due to cannabis use. This was done to avoid expending the considerable effort required to recruit and test the cannabis-controls in experiments in which no effects of drug use were found. In comparison, non-drug using controls were relatively easy to recruit, and provided an initial indication of whether there were drug related effects to investigate before the effort to test the cannabis-controls was expended. In this way, the current series of studies sought to answer two questions in turn: the first being, “Can a drug related effect be detected?” Then, “If so, then did ecstasy make a significant contribution to the observed effects?”

2.4.5  **Factors which influence the specificity of the findings to MDMA**

The major factors in addressing the specificity of results to MDMA are the composition of the ecstasy pills which people ingest, and the extent to which drugs other than MDMA contained in the pills may contribute to the results. Since ecstasy is an illegal drug made in private facilities, there is no formal control or regulation over what the
pills contain. The composition of ecstasy pills has been investigated in analytical laboratories using pills sourced from drug seizures, “amnesty bins” in nightclubs, or direct from users. A recent review of studies conducted in Europe and the USA found that the vast majority of ecstasy pills did contain MDMA and that the purity of ecstasy tablets had generally improved in the late 1990s to early 2000s compared to previous decades (Parrott, 2004a). Hair analysis of users in Toronto who always asked for ecstasy when buying pills revealed that most users had administered MDMA, but a significant minority tested positive for MDA as well, or negative for MDMA and MDA but positive for methamphetamine (Kalasinsky, Hugel, & Kish, 2004).

In Australia, analysis of seized drugs reveal that the purity of ecstasy pills can vary significantly (Australian Bureau of Criminal Intelligence, 2002; Proudfoot & Ward, 2004). In extreme cases, pills contained little or no MDMA but significant quantities of other drugs such as methamphetamine, ketamine, MDA, or PMA. Recent evidence in gathered in the Australian Capital Territory has not revealed any sustained trend towards improved purity, and that it is common for pills to contain other active drugs (Australian Bureau of Criminal Intelligence, 2002). However, local ecstasy pills that contain some MDMA usually contain a significant dose of the drug (being around 87mg per pill in 2001 to 2002, followed by a slight decrease to 61mg per pill in early-2003) regardless of the presence of other substances (Proudfoot & Ward, 2004). The testing of pill scrapings collected at a rave in South Australia in 2002 revealed that 69% contained MDMA (Camilleri & Caldicott, 2005). Ketamine was the next most common drug, detected in 26% of pills. In nearly all cases ketamine was combined with some combination of methamphetamine, caffeine or MDA.

The presence of other drugs in ecstasy pills has implications for the degree of confidence with which results of retrospective cohort studies can be attributed to MDMA. The evidence outlined above indicates that even though the local supply of ecstasy may not be as pure as that in Europe and the USA, that most ecstasy pills do contain MDMA, and therefore that regular ecstasy users will predominantly be administering regular doses of MDMA. However, the presence of other drugs in ecstasy pills means that in addition to the known quantities of other drugs they intentionally consume (e.g., when they knowingly and intentionally take methamphetamine, ketamine or MDA), they will also be administering unmeasurable quantities of drugs other than MDMA contained in ecstasy pills, albeit it in typically much smaller and/or
less regular doses than MDMA. Therefore the specificity of the results is limited to the results being caused by regular administration of the combination of relatively significant doses of MDMA combined with less significant doses of the other drugs contained in the ecstasy pills. However, the extent to which the results are consistent with the known effects of MDMA, and distinct from the effects of the other drugs, can increase the confidence with which results can be attributed to MDMA.

It is important to note that the presence of other drugs in ecstasy pills does not necessarily mean that the dose of those drugs is sufficient to cause or alter the long-term effects that would otherwise be attributed to MDMA. For example, one study conducted in the USA found that current ecstasy users who also used amphetamines had lower \[^{123}\text{I}]\beta\text{-CIT}\) binding in the striatum compared to ecstasy users who did not use amphetamines (Reneman, Booij, Lavalaye et al., 2002). Since \[^{123}\text{I}]\beta\text{-CIT}\) has been shown to principally bind to dopamine transporters in the striatum, these results are consistent with animal studies which show that methamphetamine, but not MDMA, can cause lasting changes to the dopamine system (de Win, de Jeu et al., 2004; Volkow et al., 2001). However, the results also showed that the \[^{123}\text{I}]\beta\text{-CIT}\) binding in the striatum of ecstasy users who did not use amphetamines was actually slightly higher than non-drug using controls, which suggests that the accumulated lifetime dose of ecstasy pills administered by those users had not contain sufficient methamphetamine to cause dopaminergic neurotoxicity. This suggests that while there are sufficient reasons to be cautious about attribution of the results of retrospective cohort studies to MDMA, it is also important to avoid overstating the potential impact of impurities in the local ecstasy supply.

2.5 Summary of design considerations

The aim in selecting my research designs was to maximise the degree of confidence with which the results could be attributed to drug use, and more specifically to ecstasy and MDMA, within the limitations of the resources available to conduct the studies. To achieve this, the following features were incorporated into the current series of studies. Firstly, each study was a retrospective cohort quasi-experimental design. Secondly, potential participants were excluded if they reported: having ever injected heroin; having ever had an injury or illness that could have affected their brain in any way; ever having been diagnosed or medically treated for a chronic psychiatric or emotional condition known to be associated with cognitive or perceptual deficits; or were outside a
restricted age range. Thirdly, cohorts were matched as closely as practical on age, sex and highest level of education. Fourthly, other possible covariates relevant to the variables of interest were controlled for statistically by ANCOVA or regression analysis where they made a significant contribution to the results. Covariates treated this way included estimated intelligence, mental health status, personality variables, and other drugs (specifically, alcohol, cannabis, and amphetamines). Fifthly, dose dependent relationships were examined using data gathered from a drug use history obtained from all participants using a time-line interview.

In addition to design and analysis issues, the degree of confidence with which any differences could be attributed to ecstasy and MDMA was evaluated in light of previous literature. This included studies on the effects of MDMA on animals, the functioning of the serotonin system, the effects of other drugs on animals and humans, and the likelihood of contaminates in the local ecstasy supply significantly altering the results.

2.6 The recruitment and collection of drug use histories in the present thesis

The methods used to recruit participants and collect drug use histories were identical in all of the empirical studies conducted in the current thesis. These methods are explained in the following sections.

2.6.1 Recruitment

Ecstasy-users and controls were recruited using the respondent-driven sampling technique, in which participants were encouraged to actively recruit other people into the study. This form of “snowball” sampling has been shown to result in a groups of participants that are more representative of the source population compared to if the experimenters do the recruiting from contact details supplied by participants (Wang et al., 2005).

The initial set of ecstasy-users were recruited via advertisements displayed around the Australian National University campus, and via chain emails sent to associates of the author which were cross-posted by some recipients to local dance-scene forums on the web. On arrival, all participants were required to read an information sheet about the experiment and to sign the consent form, both shown in Appendix B.
Textbox 2.1. An outline of the drug use history interview used in the current study

Participants were assured regarding that the security and level of confidentiality of the data, including that no identifying information would be stored with their data, and only group aggregates would be published.

A list of drugs was then read out and the participant was asked to indicate for each drug whether or not they had ever taken it, even if they had only taken it on one occasion. For those drugs that they had used, they were then asked to name the year in which they first used the drug and the day when they last used it. To aid this process a time line of major life events was drawn up from the first time that had use any drug until the present day (eg. years at school and University, as well as changes in jobs, dwellings, and personal relationships).

Finally, taking each they had used drug in turn, they were asked how often (or on how many occasions) they used the drug during the first year that they used it, and what was their average and maximum doses during that year. This was repeated for each year they had used that drug, before progressing to the next drug. If necessary periods shorter than a year were used if they had been marked changes in their drug use part way through a year. Often several years would be linked together to form longer periods (eg if alcohol consumption was the same for years 1988 to 1991). For some people it was necessary to record several average doses of alcohol reflecting different concurrent patterns of drinking. For example, “I’d have two stubbies of beer 3 nights a week, and 5 schooners on Saturday and Sunday nights every week, plus 15 schooners at a party once a month”.

2.6.2 Drug use history

The drug use history was collected by a semi-structure interview based on the time-line method used by Anglin, Hser, and Chou (1993) (see Textbox 2.1). The units used for recording each drug were ‘standard drinks’ for alcohol, ‘grams’ for amphetamines (“speed” power) and cocaine, and ‘tablets’ for ecstasy and Benzodiazepines. In order to have a uniform measure of amphetamines across participants who had used very different forms of the drug, the use of crystal (“Ice”) and base (“paste”) forms were initially recorded in “points” (0.1 grams), then multiplied by five to give an approximation of the equivalent of grams of “speed” (power) required to give the same effect. In light of the difficulties in qualifying amount of cannabis, hallucinogens and inhalants used on any particular occasion, these drugs were recorded in the number of ‘units’ administered per occasion. A unit was defined as a discrete administration of the drug which may be repeated several times on any given occasion. For example, if on one occasion a person shared a joint early in the evening with someone else, and another one later in the evening, this was recorded as being two units of cannabis.
The drug use history data consisted of the estimates of the first year and the last occasion on which each participant administered each drug, as well as their estimation of the frequency or number of occasions, the usual dose, and the maximum dose with which they used each drug within idiosyncratically defined periods. From this data an estimation was calculated of the total lifetime dose, highest average monthly dose, and number of days since they last used each drug.
Chapter 3. Introduction to memory deficits in ecstasy users

As will be reviewed below, previous studies have found memory deficits in ecstasy users. However, the results have not been consistent across studies. One possible explanation for this inconsistency is that the standard neuropsychological tests used in these studies confound the contributions of different components of memory. The principal aim of the series of original memory studies in the following chapters (Chapters 4 – 6) was to explore whether specific components of the memory system were impaired in ecstasy users.

This chapter provides background material to the original memory studies in the following chapters, commencing with an introduction to the basic processes and components of memory, and their localization to specific regions of the brain. This is followed by an introduction to the general findings regarding the effect of ecstasy on memory. Finally, there is a brief overview of the empirical memory studies in the current thesis.

3.1 Basic processes and components of the human memory system

Memory is neither a single indivisible cognitive system, nor implemented in a single brain area. It has various components and processes that can be measured and damaged independently. Memory processes can be conceptualised as involving three basic stages, namely encoding, storage and retrieval (Eysenck & Keane, 1995). Underlying these basic cognitive processes is an array of interactive biological systems. For example, in cognitive neuropsychology a distinction is made between verbal and visual memory – that is memory for visual and verbal materials – on the basis that those types of materials involve distinct perceptual processing centres in different parts of the brain, i.e. the temporal lobe and parietal lobe, respectively (e.g., Lezak et al., 2004). However, the encoding and retrieval of both verbal and visual memories also involves some shared cortical and central brain structures, such as the hippocampus and frontal lobes (e.g., Thiel, 2003). Differences in the involvement of these shared brain structures results in other components of memory such as long-term memory and working memory, as well as specific memory processes such as elaborative and associative processing. These functional memory components and processes are defined in the following sections.
3.1.1 Long-term memory and working memory

Investigations of memory deficits in ecstasy users to date have invariably used standard neuropsychological tests designed for clinical research and/or clinical practice. Some of these tests are designed to principally assess working memory, which is conceptualised as a time- and capacity-limited multi-component processor, which includes the capacity to retain small amounts of information (e.g., 6 integers) for a few seconds (if not refreshed) for use in other cognitive operations (e.g., to sum the 6 integers) (Baddeley & Hitch, 1974; Baddeley & Logie, 1999). There are a number of different theoretical models of working memory, but they generally agree that functions performed by working memory include the capacity to: mentally rehearse verbal information; manipulate visual patterns; and perform “executive functions” such as calculations and the solving of logical problems (Baddeley & Hitch, 1974; Miyake & Shah, 1999). Standard neuropsychological tests used to assess working memory include tests of working memory span such as Digits Forward (the immediate recall of a sequence of digits read aloud, for progressively longer digit sequences until the participant can no longer successfully recall an entire sequence) and Digits Backwards (same as Digits Forwards except digits have to be recalled in reverse order), as well as problem solving tasks such as the Tower of London (requires participants to rearrange three different coloured balls on three vertical pegs, from a starting arrangement to a goal arrangement, in the minimum number of moves, where each move consists of moving the highest ball form one of the pegs and place it on the top of a different peg) and n-back tasks (e.g., each time an ‘a’ occurs in a randomised sequence of letters, recall of the n$^{th}$, say 3$^{rd}$, most previous letter).

In contrast, long-term memory involves the retention of information far in excess of the time and capacity limitations of working memory (e.g., the recall or recognition of the contents of a story or list of words heard 30-minutes ago). In practical terms, this means that long-term memory tests generally involve the retention of more items than can he held in working memory, and include some form of filled delay to inhibit the opportunity to maintain the information in working memory – even if this is just to attend to the remainder of a sufficiently long list of items or story (e.g., word list recall and prose recall tasks).
Standard neuropsychological tests that are often used to reveal long-term memory are verbal learning tasks, such as the Auditory Verbal Learning Task (AVLT described in Lezak et al., 2004; Mitrushina, Boone, & D'Elia, 1999), prose recall (e.g., Logical Memory as described in Wechsler, 1997a), or memory for non-verbal stimuli such as geometric figures (Osterrieth, 1944; Rey, 1941) and visual associations (e.g., the LGT-3 logos recognition task, Bäumler, 1974 described in Gouzoulis-Mayfrank, Thimm, Rezk, Hensen, & Daumann, 2003). Tests that use verbal stimuli generally involve the auditory or visual presentation of a list of words or story, followed by a test of immediate recall. To assess the improvement in performance over successive trials, the study and immediate recall test may be repeated up to five times in succession with the same stimuli. Finally, after a filled interval of, say, 20 to 30 minutes, a delayed recall and/or recognition test is applied, without any further exposure to the study materials. Long-term memory functioning is reflected in the immediate recall test/s, insofar as the number of items to be remembered exceeds working memory capacity, and therefore at least some items need to be recalled from long-term memory in order to recall all of the items. However, since there is no inhibition of the use of working memory to retain at least some study information between study and test, the overall immediate recall performance reflects some idiosyncratic combination of long-term and working memory, depending on the memory strategies used by each individual. In contrast, delayed recall represents a relatively pure test of long-term memory, because the filled delay effectively prevents the retention of study materials in working memory between study and test.

3.1.2 The use of elaborative and associative processing to aid the encoding of material in long-term memory

Elaborative processing refers to any process that involves the active use of word meanings (e.g., understanding or generating prose), as distinct from mere exposure to verbal material, or purely perceptual processes. Elaborative processing can be used in a variety of ways during both study and test, depending on task demands. In prose recall, elaborative processing is used to understand the story as it progresses, as well as extract themes and details to encode into long-term memory. Another form of elaborative processing is associative processing, which involves the generation of meaningful associations between stimuli at study. For example, if a person is asked to remember two words “bird” and “shoulder”, they may use associative processing to generate and
encode in memory an image of a bird sitting on a shoulder. An important distinction between the use of elaborative processing in studying prose and associative processing, is that in prose recall a coherent semantic structure for the study material is provided within prose, whereas in associative tasks the participant must generate the semantic structure themselves. As will be seen in Chapters 5 and 6, this emerges as a potentially important distinction in understanding the impact of ecstasy on elaborative processing in long-term memory tasks.

Memory tasks vary in the degree to which associative processing is required, or strategically useful, at study. Verbal-paired associates tests (e.g., Wechsler, 1997a) specifically require the use of associative processing at study. Such tasks investigate participants’ memory for pairs of words such as bird-shoulder, cat-table, etc., which cannot be completed successfully without generating some sort of semantic association for each pair of words. In contrast, tests for memory of lists of single words and prose do not require associative processing at study, but it can be used strategically to effectively reduce the number of items to be stored. For example, when exposed to a list of twelve single unrelated words, a participant may associate the words into, say, four different composite images or sentences, each representing a few of the words. Then, instead of trying to remember the 12 original words, they only need to remember the four images or sentences. Similarly, in prose recall, rather than trying to remember every individual detail of the story, associative processing can be used to associate themes, scenes or plot lines with previously learned examples in memory, thus reducing the overall amount of new material that needs to be memorised.

The California Verbal Learning Task (CVLT, Delis et al., 1987) is a word-list learning task specifically designed to test the strategic use of associative processing. In that task, the lists are comprised of words selected from four semantic categories (e.g., ‘tools’ and ‘clothing’). The words are read in a randomised order, and the presence of the semantic categories is not explained to the participants. If the participants notice the categories, they can use them to assist in the encoding and retrieval of the words. An index of the semantic clustering of words at recall is used as a global indicator of the extent to which a participant has used elaborative processing to identify and use the categories.
Explicit memory and implicit memory

Long-term memory contains two dissociable components, namely explicit long-term memory and implicit long-term memory. Explicit memory is defined as a form of memory which involves the conscious and deliberate recollection of previously learned material (Schacter, 1987). As such, most standard neuropsychological tests of long-term memory primarily reflect explicit memory performance. This includes any delayed test of free recall or recognition, such as the word list learning and prose recall tasks discussed above, as well as cued-recall tasks in which retrieval is assisted by provision of a cue, such as the first few letters of a word (i.e., the word ‘stem’, e.g., cal____).

In contrast, implicit memory involves enhanced performance on a task facilitated by prior exposure to material but without any conscious or intentional reference to that material (Schacter, 1987). Implicit memory can be revealed in a stem completion task in which participants study a list of words, and later (in an ostensibly unrelated task) are instructed to complete a list of word stems (e.g., cal____) with the first word that comes into their mind (e.g., calorie, calendar, or calcium, etc.). Implicit memory is revealed by the extent to which they complete the stems with words from the earlier study list (‘studied words’) in excess of what they achieve for stems from a list of words that they had not previously been exposed to (‘unstudied words’, which provide the ‘baseline’ response rate). As long as the use of conscious explicit memory strategies at retrieval is avoided (see Chapter 4), this involves the accessing of the memory of the studied words without conscious intention. Implicit memory is also revealed in reaction time tasks such as a lexical decision task, in which participants are quicker to decide if a verbal stimulus (e.g., WAVE, or MAVE) is a word or a non-word on a second or subsequent presentation than they are on the first presentation.

Thus, at test, implicit memory is conceptualised as relying on unconscious automatic memory retrieval processes, as distinct from explicit memory which relies on conscious deliberate retrieval processes. A major source of evidence for the distinction between implicit and explicit memory came from studies which showed that people with anterograde amnesia have severe explicit memory deficits, but intact implicit memory (e.g., Warrington & Weiskrantz, 1970).

Processes that dissociate implicit memory from explicit memory in non-brain damaged participants include dividing attention at study, and/or short study time (e.g., 1 second
per item), both of which are associated with a marked decrease in explicit memory performance, but intact implicit memory performance (Schmitter-Edgecombe, 1996; Wolters & Prinsen, 1997). Similarly, a change of modality between study and test (e.g., auditory presentation at study and visual presentation at test) is associated with a decrease in implicit cued recall, but intact explicit cued recall (Hayman & Rickards, 1995; Schacter & Graf, 1989).

3.1.4 The localisation of long-term memory components in the brain

A secondary focus of the series of memory studies in this thesis was to evaluate if long-term memory deficits in ecstasy users reflected hippocampal dysfunctions in particular, or patterns of deficits associated with other brain regions. This was achieved through consideration of the localisation of brain activation – as reported in literature – for the memory tests used. This section contains an outline of the localisation in the brain of the memory components and processes that were tested.

The functioning of implicit memory is thought to rely on largely sensory information which is stored in the sensory areas of the cortex (Schacter & Buckner, 1998; Schott et al., 2005). In particular, implicit memory is thought to not rely on the hippocampus or the frontal lobes.

The consolidation of new and existing information involved in the use of explicit long-term memory, especially during conscious retrieval, has been shown to critically rely on the hippocampus. This is supported by a review of 147 case studies of amnesia involving hippocampal damage which found that all cases showed severe deficits in conscious retrieval (i.e. explicit memory), but intact non-conscious retrieval (i.e., implicit memory, Spiers, Maguire, & Burgess, 2001). Also, in fMRI studies, explicit memory has been found to be associated with neural activation of the hippocampus, in addition to the sensory areas also activated by implicit memory (Thiel, 2003).

Depending on the explicit memory task, some activation of the prefrontal cortex is also common, possibly reflecting intentional conscious processing (Schott et al., 2005; Thiel, 2003). In particular, familiarity processes which are used in explicit retrieval by recognition are localized in the prefrontal cortex and parietal regions (Henson, Rugg, Shallice, Josephs, & Dolan, 1999; Manns, Hopkins, Reed, Kitchener, & Squire, 2003; Wixted & Squire, 2004). So while the hippocampus is known to be critically involved
in explicit memory, there is also task-dependant activation of other areas of the brain. Therefore in order to evaluate the contribution of changes in the hippocampus to long-term memory performance, it is important to minimise and control for possible deficits in these other brain regions.

The elaborative and/or associative processing of words has been shown in functional neuroimaging studies to activate specific parts of the frontal lobes, in particular, the prefrontal cortex\(^1\) (Posner, Petersen, Fox, & Raichle, 1988; Roskies, Fiez, Balota, Raichle, & Petersen, 2001; Schreckenberger et al., 1998; Shaywitz et al., 1995). Consequently, performance on verbal memory tasks that have a high compulsory requirement for elaborative and/or associative processing at study and/or retrieval may reflect relatively large frontal lobe involvement in addition to hippocampal functioning, (e.g., in verbal paired associates tests), compared to performance on verbal memory tasks which have relatively moderate elaborative and/or associative processing requirements at study and/or retrieval will more closely reflect hippocampal functioning (e.g., recall of a list of unrelated words). This distinction has been used in the selection and design of memory tasks in the current thesis with the aim of evaluating the relative contributions of the hippocampus and frontal lobe processing to test performance.

In combination, the above outline of the localisation of processes involved in implicit memory, explicit memory, and elaborative processing, suggests that each process relies on a particular region in addition to those brain regions required for the previous component or processes outlined. In review, implicit memory relies principally on sensory areas, whereas explicit memory critically relies on the hippocampus in addition to the sensory areas shared with implicit memory. Finally, tests of elaborative processing rely more on frontal lobe processing, in addition to the hippocampal and sensory areas involved in explicit memory. This information is used in the present thesis to infer from behavioural tests of memory what brain areas are likely to be implicated in any apparent memory deficits. For instance, a deficit in explicit memory (i.e., a deficit in some aspect of sensory memory areas plus the hippocampus) in the presence of intact implicit memory (i.e., intact sensory memory areas) would support a hypothesis of

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\(^1\) These studies also show the activation of relevant perceptual and language centres in the brain, localised in the temporal and occipital lobes, which are activated by all memory tests for verbal material regardless of which component of memory is being tested.
hippocampal damage. Whereas, a deficit on a memory test which required significant elaborative processing (some aspect of sensory + hippocampal + frontal performance), in the presence of intact implicit and explicit memory (i.e., sensory + hippocampal), would support a hypothesis of either specific frontal lobe damage, or global damage which is only apparent when several brain regions are loaded concurrently.

3.2 Why study memory deficits in ecstasy users?

3.2.1 Brief overview of research to date

To date, a wide range of memory tests has been applied to ecstasy users in a large number of studies. In general, significant deficits have been found in ecstasy users in tests of long-term memory for verbal stimuli, such as word-list learning and prose recall (reviewed in the following chapters), as well as visual stimuli, such as pattern recognition and visual association tasks (Bolla et al., 1998; Daumann, Fischermann, Pilatus et al., 2004; Fox et al., 2002; Gouzoulis-Mayfrank et al., 2000; Gouzoulis-Mayfrank, Thimm, Rezk, Hensen, & Daumann, 2003; Verkes et al., 2001; Yip & Lee, 2005). The finding of deficits for both visual and verbal stimuli suggest that the deficits may be due to the dysfunction of some central structure, such as the hippocampus and/or the frontal lobes, rather than only to distinct visual and verbal centres. Significant deficits have also been found on working memory tasks, including digit span forwards (e.g., Croft et al., 2001; McCardle et al., 2004), digit span backwards (e.g., Croft et al., 2001; Gouzoulis-Mayfrank et al., 2000), verbal fluency (e.g., Bhattachary & Powell, 2001; Fox et al., 2002), Tower of London (e.g., Fox, Parrott, & Turner, 2001; von Geusau, Stalenhoef, Huizinga, Snel, & Ridderinkhof, 2004), and the Wisconsin Card Sorting Task (e.g., Dafters et al., 1999; von Geusau et al., 2004).

Most studies have found at least one significant cognitive deficit in ecstasy users. However, on any given test, the pattern of results between studies has been far from consistent. For instance, Gouzoulis-Mayfrank et al. (2000) found that ecstasy users performed worse than controls on the digit span backwards but not digit span forwards, while McCardle et al. (2004) found the opposite, that is, a deficit in ecstasy users on

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2 Results of particular types of tests will be review in more detail in Chapters 4 to 6 as they become relevant
digit span backwards but not on digit span forwards. Similarly, for every test listed in the previous paragraph, a number of other studies have reported finding no significant difference between ecstasy users and controls on the same or a similar test, e.g., word-list learning and prose recall (reviewed in the following chapters); pattern recognition and visual association tasks (e.g., Back-Madruga et al., 2003; Bhattachary & Powell, 2001); verbal fluency (e.g., Curran & Verheyden, 2003; Klugman et al., 1999), Tower of London (e.g., Fox et al., 2002; Morgan, 1998), the Wisconsin Card Sorting Task or equivalent (e.g., Dafters, Hoshi, & Talbot, 2004; Fox, Parrott et al., 2001) and memory for non-verbal stimuli (Back-Madruga et al., 2003; Bhattachary & Powell, 2001; Croft et al., 2001; Gouzoulis-Mayfrank et al., 2003; Thomasius et al., 2003).

Each finding of a significant ecstasy effect adds to the growing body of evidence that ecstasy use is associated with cognitive deficits. However, the lack of consistency across studies means that any conclusions remain equivocal regarding whether those effects are real, or whether they occur on some tasks but not others. Factors that could conceivably contribute to the variability of findings include different patterns of drug use, and possibly ethnic/genetic differences in vulnerabilities to drug related neural damage, between different groups of ecstasy users.

Another factor that may contribute, at least in part, to the unreliability of findings regarding memory deficits in ecstasy users is that the standard neuropsychological and clinical research tests used to date confound the performance of different components of memory. For instance, as outlined earlier, tests of immediate recall in standard neuropsychological tests, such as word-list learning tasks, confound the recall of some words from long-term memory with the recall of words from working memory (i.e., retaining words by uninterrupted mental repetition in working memory). In addition, there is no restriction on the use of implicit memory in such tasks. Each component of memory may be affected differently by different recreational drugs, and/or different patterns of drug use. Since no two samples of drug users have identical patterns of drug use, this could produce different patterns of memory deficits in different samples of drug users. A more consistent pattern of results may emerge if each component of memory was measured separately, in studies designed to enable results to be as specific as possible to ecstasy.
3.2.2 Memory studies in the current thesis

The overall approach taken in the current thesis was to commence with tests that were as specific as possible to a particular component of memory. This involved dissociating long-term implicit- and explicit-memory performance to assess the contribution of hippocampal functioning. Then, progressing from the findings of those initial tests, variations and alternative tests were conducted in subsequent studies to evaluate contributions of other memory components and processes.

Three memory studies were conducted, each of which included a number of different memory tests. The samples of ecstasy users in the second and third studies included some ecstasy users from the previous studies, as well new ecstasy users. In addition, each sample of ecstasy users had, on average, used more ecstasy over a longer period, and at a greater frequency than the previous sample. In the final study, an additional control group of cannabis users was added to assist in the evaluation of the specificity of the results to ecstasy.
Chapter 4. The consequence of ecstasy use on implicit and explicit memory for lists of unrelated words

4.1 Introduction to the present study

4.1.1 Overview

As outlined in Chapter 3, research to date regarding long-term memory in ecstasy users has generally used tests that confound the contributions of different components of memory, including implicit, explicit and working memory. The broad aim of the original study reported in this chapter is to compare the implicit and explicit memory performance of ecstasy users to that of controls, using tests that are as specific as possible to those components. The study includes the first known test of implicit memory performance in ecstasy users.

As described in the previous chapter, an important difference between implicit and explicit memory is that implicit retrieval is thought to rely largely on sensory information stored in the sensory areas of the cortex, whereas the hippocampus has been shown to be critically involved in explicit retrieval (but not implicit retrieval). On this basis, hippocampal deficits in ecstasy users would be revealed by the combination of intact implicit memory and a deficit in explicit memory. In the present study, implicit and explicit memory were tested in tasks that were as similar as possible to allow direct comparison of performance of those components of memory.

The standard neuropsychology test of explicit memory that is most specific to hippocampal functioning is the delayed recall of lists of unrelated words. This is because the filled delay prohibits the retention of words in working memory between study and test, and memory for unrelated words involves less elaborative (frontal lobe) processing than other memory tasks, e.g., associative tasks. Implicit memory can also be revealed following the study of lists of unrelated words, in retrieval tasks in which the use of explicit memory strategies is severely interrupted.

As a basis for investigating implicit and explicit memory deficits in ecstasy users, this chapter commences with a review of the general literature regarding involvement of serotonin in those components of memory. This is followed by a review of the performance of ecstasy users on the delayed recall for lists of unrelated words. Consideration is then given to the possibility of implicit memory deficits in ecstasy
users. These reviews lead to an expectation that implicit memory deficits may occur in ecstasy users, but that if such deficits are detected then they are likely to be relatively small compared to any explicit memory deficits.

### 4.1.2 Evidence from tryptophan depletion studies of serotonergic involvement in implicit and explicit memory

The association between long-term memory performance and serotonin has been investigated using tryptophan depletion. This section commences by outlining the tryptophan depletion technique, followed by a review of long-term memory studies that have used the technique. In particular, some findings regarding the effects of tryptophan depletion on explicit memory suggest that serotonin is specifically involved in the consolidation of explicit memories after stimulus exposure, as distinct from immediate or delayed retrieval processes.

#### 4.1.2.1 The tryptophan depletion technique

Tryptophan hydroxylase (or “tryptophan”) is an enzyme that is critically involved in the regulation of serotonin synthesis in the brain. Very little tryptophan is stored in the brain, and consequently the availability of the enzyme is largely dependant on dietary intake. The tryptophan depletion technique (described in Bell, Abrams, & Nutt, 2001; Reilly, McTavish, & Young, 1997) involves replacing normal food intake with a drink which does not contain tryptophan, and instead contains several amino acids which compete with tryptophan for transportation over the blood-brain barrier. This typically lowers plasma tryptophan level by 80% within 5-7 hours of ingestion in humans. Furthermore, one neuroimaging study suggests that it lowers serotonin synthesis in the human brain by approximately 90-95% (Nishizawa et al., 1997). Administration of one of the competing amino acids (L-valine) in rats has been shown to result in a 52% reduction in the amount of serotonin released following electrical stimulation of the hippocampus (Gartside, Cowen, & Sharp, 1992).

The effect of tryptophan depletion on cognitive processes provides a means of investigating the kinds of deficits that ecstasy-related serotonergic dysfunctions may also cause. However, it is important to remember that tryptophan depletion and ecstasy use are understood to disrupt the serotonin system in quite different ways. Ecstasy use is thought to result in the chronic depletion of serotonin in the brain, and to render a dose...
dependent proportion of serotonergic axons dysfunctional, or even destroyed. The chronic nature of this disruption leaves open the possibility of equally long-term compensatory changes occurring in the brain, such as the up-regulation of post-synaptic receptors, which may reduce the impact of the serotonergic damage. In contrast, tryptophan depletion is thought to cause a severe but acute change in serotonin synthesis, in the absence of lasting damage to the serotonergic axons. Therefore, it is not possible from a tryptophan-depletion study to predict that a particular deficit will be found in ecstasy users, but it does provide a useful tool for indicating behavioural functions that could potentially be affected by ecstasy-related serotonergic changes.

4.1.2.2 Review of tryptophan depletion studies: Serotonergic involvement in long-term implicit memory

Only one published study to date has investigated the impact of tryptophan depletion on long-term implicit memory. In that study, Burgund, Marsolek, and Luciana (2003) tested implicit retrieval using a stem completion task in which there was a perceptual match between the study and test presentation of visually presented words (e.g., study: MARBLE; test: MAR____). They found tryptophan depletion reduced the average number of stems (above baseline) completed with previously studied words. This suggests that serotonin does have a role in implicit retrieval, at least when there is a high perceptual match between study and test.

4.1.2.3 Review of tryptophan depletion studies: Serotonergic involvement in long-term explicit memory

In contrast to implicit memory, there have been quite a number of studies published regarding the affects of tryptophan depletion on explicit memory. The delayed recall of words learnt prior to treatment has been found to be unaffected by tryptophan depletion (Schmitt et al., 2000; Sobczak et al., 2002). For words learnt after treatment, some studies have found that tryptophan depletion is associated with significantly poorer

\[ \text{Burgund et al. (2003) also attempted to investigate the effects of tryptophan depletion on implicit memory when there was a perceptual mismatch between visual study and test phases (e.g., Study: marble; test: MAR____). However, they didn’t detect any significant use of implicit memory (i.e., any increase in the completion of stems with studied words above baseline) in either the control or tryptophan depletion conditions. Therefore no determination of the effect of tryptophan depletion on implicit memory on that task could be made.} \]
recall of word lists and visual patterns learnt following medium (e.g., 25 to 30 minute) and long (e.g., 7 to 24 hours) delays between learning and test (Harrison et al., 2004; Klaassen, Riedel, Deutz, & Van Praag, 2002; Riedel, Klaassen, Deutz, van Someren, & van Praag, 1999; Rubinsztein et al., 2001; Schmitt et al., 2000; Sobczak et al., 2002). Interestingly, tryptophan depletion does not appear to cause immediate recall deficits for words learnt after treatment (Harrison et al., 2004; Riedel et al., 1999; Schmitt et al., 2000). Rather, tryptophan depletion-related deficits appear to emerge during the first 30-minutes after exposure to the word list, and do not significantly change in magnitude over at least the following 4 hours (Schmitt et al., 2000). Also, an EEG study found that while tryptophan depletion was associated with significant recall deficits, these deficits occurred in the absence of changes to electrophysiological measures thought to correspond to retrieval processes (McAllister-Williams, Massey, & Rugg, 2002). In combination, these studies strongly suggest that serotonin is selectively involved in the consolidation of new explicit memories within the first 30 minutes after stimulus exposure, as distinct from being involved in the immediate recall of new information, or the retrieval of previously consolidated explicit memories.

Other studies have failed to find an effect of tryptophan depletion on delayed recall, or have not found the effect under all conditions (Curran & Verheyden, 2003; Evers et al., 2005; Hughes et al., 2003; Klaassen, Riedel, Deutz, van Someren, & van Praag, 1999; Shansis et al., 2000). These studies generally showed non-significant trends in the expected direction (where reported) which may have failed to reach significance for any of a number of commonly cited reasons, such as sample size, sample characteristics, or methodological differences (e.g., the use of novel tryptophan depletion drinks in Evers et al., 2005; Hughes et al., 2003). Other studies suggest these non-significant results may, at least in part, be due to the influence of other more interesting factors. In one repeated-measures study, the long-term memory of elderly participants (mean age=75 years, SEM=1.2) was tested four hours after administration of a tryptophan depletion and placebo drinks (in separate testing sessions, conducted one-week apart in counterbalanced order, Porter, Lunn, & O'Brien, 2003). In the tryptophan depletion condition, a free plasma depletion of tryptophan of 73% was obtained after 4 hours, which is comparable to that generally obtained with younger participants (e.g., Klaassen et al., 2002; Riedel et al., 1999). However, despite achieving this level of tryptophan depletion, there was no significant reduction in long-term explicit memory performance. The authors suggested that their non-significant findings on the memory tests may be
due to age-related changes to serotonin functioning. Another study found that tryptophan depletion did cause significant explicit memory deficits, but not if noradrenaline and dopamine were also depleted at the same time (Matrenza et al., 2004). The contrast between these results and the significant findings reported earlier, suggests that the outcomes from tryptophan depletion studies may be affected by potentially complex interactions between a number of factors. However, insofar as significant results have been obtained, they are consistent with serotonin having an involvement in the consolidation of explicit memories.

All of the tryptophan depletion findings reviewed so far have involved the free recall of information from explicit memory. Other findings of the impact of tryptophan depletion on explicit memory have been obtained using recognition tests. Two studies found no effect of tryptophan depletion on short (5-minute), medium (30-minute) or long-delayed (24-hour) accuracy for the recognition of previously studied words (Klaassen et al., 1999; McAllister-Williams et al., 2002). One study found no deficit on picture recognition, but a marginally significant deficit on word recognition which was no-longer significant after Bonferroni correction (Sobczak et al., 2002). Finally, one study reported a significant deficit for recognition of a list of 30 unrelated words after delays of 30-minutes and 9 hours, using a measure that combined hits and false alarms (all of the other studies outlined just analysed hits) (Schmitt et al., 2000). This final result in particular suggests that serotonin depletion may result in recognition deficits, but that more research is required to understand the conditions in which this reliably occurs.

As outlined in Chapter 3, explicit retrieval by recognition involves familiarity processes localized in the prefrontal cortex and parietal regions, in addition to the critical involvement of the hippocampus. However, the (possible) impairment of both recall and recognition by tryptophan depletion reported in the previous paragraphs is at least consistent with the involvement of shared structures such as the hippocampus in underlying the deficits.

4.1.2.4 Summary of the evidence from tryptophan depletion studies regarding implicit and explicit memory

Overall the evidence from tryptophan depletion studies indicates that serotonin appears to have a role in both implicit memory – at least when there is a good perceptual match between study at test – and in the consolidation of new information into explicit
memory within the first 30 minutes of exposure to the stimulus. There are some contradictory findings in explicit recall, but there is also some evidence that this may be due, at least in part, to the influence of potentially complex interactions between factors such as age and the levels of other neurotransmitters, rather than excluding a role of serotonin in explicit memory. Finally, some findings also support an effect of tryptophan depletion on the conscious recognition of stimuli, which is consistent with the recall and recognition deficits being due, at least in part, to brain structures involved in both of those tasks, such as the hippocampus.

4.1.3 A review of evidence regarding on memory for lists of unrelated words (explicit memory) in ecstasy users

It is possible that the above findings associated with the acute disruption of the serotonin system due to tryptophan depletion may also occur following chronic disruption to the serotonin system caused by recreational ecstasy use. There have been no published reports to date that have investigated the impact of ecstasy on long-term implicit memory functioning. In contrast, explicit memory in ecstasy users has attracted a lot of research interest. This section reviews evidence from studies that have measured memory for lists of unrelated words, which – as outlined earlier – is the standard neuropsychological test that is most specific to the functioning of the hippocampus in explicit memory.

4.1.3.1 Evidence from standard neuropsychological tests of delayed memory retrieval

Table 4-1 and Table 4-2 summarise previous findings regarding ecstasy-related performance on the recall of lists of unrelated words. I have split those studies into two tables because the studies vary in the degree of specificity with which any cohort differences can be attributed to ecstasy. The majority of ecstasy users in most studies also use a variety of other drugs, and participants in “non-drug using” control groups are not excluded for having drunk alcohol or smoked nicotine. This is tolerated in this field of research because it is generally considered impractical to obtain samples that don’t smoke or use alcohol, and/or ecstasy users who don’t use other drugs. As a consequence, evidence with the greatest degree of specificity to ecstasy comes from studies that statistically control for the use of other drugs, and/or compare ecstasy users to a control group of people who use other drugs, but have never used ecstasy. In
Table 4-1 Memory for lists of single unrelated words for studies with relatively strong control over the influence of drugs apart from ecstasy

<table>
<thead>
<tr>
<th>Study</th>
<th>Immediate recall</th>
<th>Delayed recall</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Croft et al., 2001)</td>
<td>.ns</td>
<td>.ns</td>
<td>using the pre-treatment results</td>
</tr>
<tr>
<td>(Curran &amp; Verheyden, 2003)</td>
<td>.ns</td>
<td>sig.</td>
<td></td>
</tr>
<tr>
<td>(Fox, Toplis, Turner, &amp; Parrott, 2001)</td>
<td>sig.+DD</td>
<td>sig.+DD</td>
<td></td>
</tr>
<tr>
<td>(Gouzoulis-Mayfrank et al., 2000)</td>
<td>sig.+DD</td>
<td>(.ns delayed recognition)</td>
<td></td>
</tr>
<tr>
<td>(McCardle et al., 2004)</td>
<td>sig. (trials 4 &amp; 5)</td>
<td>sig.</td>
<td></td>
</tr>
<tr>
<td>(Reneman, Lavalaye et al., 2001)</td>
<td>sig.</td>
<td>sig.</td>
<td></td>
</tr>
<tr>
<td>(Semple et al., 1999)</td>
<td></td>
<td>sig.</td>
<td></td>
</tr>
<tr>
<td>(Simon &amp; Mattick, 2002)</td>
<td></td>
<td>sig.</td>
<td></td>
</tr>
<tr>
<td>(Thomaisius et al., 2003)</td>
<td>sig.+DD</td>
<td>sig.+DD</td>
<td></td>
</tr>
<tr>
<td>(Yip &amp; Lee, 2005)</td>
<td>sig.</td>
<td>sig.+DD</td>
<td>non-drug controls but ecstasy users and controls had no sig. other drug use (including alcohol or nicotine)</td>
</tr>
</tbody>
</table>

Note. sig. = significant deficit in ecstasy users compared to controls. Unless otherwise stated, the findings shown are in comparison to a control group of drug users who don’t use ecstasy. .ns = no significant difference between ecstasy users and controls, p>.05. .ns$^d$ = no difference between ecstasy users and other drug users, but significantly different from non-drug using controls. DD = Dose Dependence to some measure of ecstasy use

In addition, studies with a high degree of specificity to the long-term effects of ecstasy also require sufficient abstinence from recreational drugs to ensure that participants are free of acute and residual effects, and control for other potential covariates by: excluding people with a history of relevant psychiatric conditions; matching cohorts on sex and age; and statistically control for any differences between cohorts on estimated IQ, mental health and level of education (as outlined in Chapter 2).

The studies in Table 4-1 exercised a relatively higher degree of control over possible confounding variables compared to those in Table 4-2. Of the ten of these studies in Table 4-1 that tested delayed memory, six reported a significant deficit in ecstasy users compared to other drug users (except were noted in the table). Despite being statistically significant, the size of the deficit detected was quite small, typically 6% to 14%, such that ecstasy users only recall one or two words less than controls on a list of 15 words (Curran & Verheyden, 2003; Fox, Toplis et al., 2001; McCardle et al., 2004). Larger deficits in ecstasy were found by Reneman, Lavalaye et al (2001, 22% = 10.1 v. 13.1
words on a 15 word list), as well as Yip and Lee (2005, 55% = 5.28 v. 13.52 words on a 15 word list, discussed in more detail later in this section). Particularly strong evidence was provided by three studies which also found a significant dose dependant effect between some measure of ecstasy use and delayed recall (Fox, Toplis et al., 2001; Thomasius et al., 2003; Yip & Lee, 2005). These were supported by two studies in Table 4-2 that also found significant delayed recall deficits in ecstasy users, but in the absence of statistical evaluation of the potential influence of other drugs (Gouzoulis-Mayfrank et al., 2000; Reneman, Booij et al., 2000; Reneman, Majoie, Schmand et al., 2001).

In contrast, four of the relatively well controlled studies in Table 4-1 failed to detect a difference between ecstasy users and controls on delayed memory, or detected a difference which failed to remain significant after controlling for other drug use and/or other potential covariates (Croft et al., 2001; Semple et al., 1999; Simon & Mattick,
A further three studies in Table 4-2 also failed to detect any significant effect (Back-Madruge et al., 2003; Bolla et al., 1998), although one study only just failed to reach significance (Bolla et al., 1998). Despite the lack of significant effects in these studies, ecstasy users tended to perform worse than controls, except for Back-Madruge et al. (2003), in which ecstasy users scored almost the same as controls (10.6 words in ecstasy users and 10.4 words in controls, $p=.83$), and Croft et al. (2001) in which ecstasy users tended to perform worse than non-drug using controls but better than cannabis users who had not used ecstasy.

All of the word list-learning studies in Table 4-1 and Table 4-2 also tested immediate recall. As noted in Chapter 3, immediate recall performance reflects some combination of long-term memory and working memory performance, because there is no inhibition of the use of working memory to retain items between study and test. There was a mix of significant and non-significant results across the studies similar to the delayed memory results. However, one relatively well-controlled study (Curran & Verheyden, 2003), and two of the less strictly controlled studies found deficits on delayed recall, but not on immediate recall (Reneman, Booij et al., 2000; Reneman, Majoie, Schmand et al., 2001). This may indicate that the use of continuous rehearsal in working memory to retain some words in the immediate recall test is less affected by ecstasy than the retention of words in long-term memory.

One study in Table 4-1 deserves particular consideration, because it produced very striking results on both immediate and delayed tests for lists of unrelated words. Yip and Lee (2005) reportedly tested 200 participants who had never consumed alcohol or nicotine on a regular basis, and had not consumed alcohol as often as one drink per week in any six month period within the two years prior to testing. One hundred of the participants had used ecstasy (average 35.8 tablets, range 16–60 tablets), but not other illicit drugs, were compared to the remaining 100 participants who had not used ecstasy. The results show exceptionally large deficits on an immediate and delayed list-learning task, in which the ecstasy users performed at less than half the level of controls. For the delayed condition, controls average recall was 13.52 (SD=1.26) words from a list of 15 words, whereas ecstasy users recalled an average of only 5.28 (SD=1.57) words, which is a deficit of 55%. The only other study to report significant deficits in ecstasy users
with such a low average use of ecstasy was McCardle et al. (2004)\(^4\), but the deficit detected was only 6.3% (12.13 vs 11.18 words recalled from a list of 15 words). In comparison, deficits of 14% were obtained by Curran and Verheyden (2003, 8.06 v. 5.81 words recalled from a list of 15 words) in users with an average lifetime dose of 707\(^5\) tablets, and Fox, Toplis et al. (2001, 12.7 vs. 10.6 words recalled from a list of 15 words)\(^6\) in users with an average lifetime dose of 811.5 tablets. Others did not find a statistically significant deficit in users who had also used several hundred ecstasy tablets in their lifetime (e.g, Semple et al., 1999). In addition, Yip and Lee (2005) state that step-wise canonical discriminant analysis based on measures of verbal and non-verbal memory, as well as verbal fluency, was able to accurately classify 99% of ecstasy users and 100% of controls. The large sample size and exclusion of alcohol and nicotine as possible confounds do not seem adequate to account for why this study found such a large deficits and such high discriminability in users who had used only 35 tablets of ecstasy on average. It remains to be seen if the findings can be replicated, and if so, why the deficits obtained are so large.

4.1.3.2 Evidence for an association between long-term memory deficits and changes in neural functioning in ecstasy users

Of the studies in Table 4-1 and Table 4-2 that examined differences in performance on standard neuropsychological tests of delayed memory retrieval, some also examined the association between memory performance and indicators of neural functioning in ecstasy users. Using Proton Magnetic Resonance Spectroscopy, Reneman, Majoie et al. (2001) measured NAA/CR ratios in the prefrontal cortex, occipital grey matter and temporo-parietal white matter (no other NAA/CR ratios were measured). They found a significant association between delayed recall but not immediate recall, as well as lower NAA/CR ratios in the prefrontal cortex. As outlined in Chapter 1, a reduction in the NAA/Cr ratio is taken as a non-specific indicator of the loss or dysfunction of cell bodies or axons. However, since little control was exercised over the influence of other drugs in that study, it is not possible to determine if the finding is specific to ecstasy, or

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\(^4\) Actual lifetime use of ecstasy was not reported, but the median number of occasions on which participants had used ecstasy was 4-9 times, and the average number of tablets per occasion was 1.65 (McCardle et al., 2004).

\(^5\) Calculated from the usage data reported

\(^6\) Recalled words read from graphs
to some other drug or combination of drugs. The fact that delayed recall was associated with the prefrontal cortex is consistent with the earlier argument that while explicit memory is known to critically rely on the hippocampus, tests of explicit memory also cause a task-dependent activation of frontal lobe processes.

Associations between memory performance and indicators of neural functioning in ecstasy users have also been found using neuroimaging techniques. PET (+)-[11C]McN-5652 binding and SPECT [123I]-5-R91150 binding are taken as indicators of serotonin transporter availability. Some studies have found that binding on those ligands was correlated with performance on delayed word recall and visual list-learning tasks (Reneman, Booij et al., 2000; Thomasius et al., 2003).

In contrast, other studies have failed to find a significant correlation between SPECT [123I]β-CIT binding and long-term memory performance, despite finding significantly lower binding in current ecstasy users compared to users of other drugs (Reneman, Lavalaye et al., 2001; Semple et al., 1999). Thus, evidence for an association between neural functioning and memory performance exhibits a similar lack of consistency to that obtained for memory deficits in standard neuropsychological tests.

4.1.3.3 Summary of and interpretation of evidence regarding the performance of ecstasy users on explicit memory

In the published ecstasy literature, the delayed recall of lists of unrelated words is the measure that is most specific to explicit memory. Based on the results of such tests, some studies have clearly found deficits on explicit memory in ecstasy users, but the results are far from consistent across studies. Where significant deficits have been found they are generally small. Some studies also produced strong dose-dependant evidence of ecstasy-related deficits on word list learning tasks, while also controlling for the influence of other potential confounding variables through group matching and statistical means. Other studies have shown that such memory deficits are related to neural serotonergic changes in ecstasy users. In contrast, some well-controlled studies

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7 See section 1.7.2 regarding the possibility that the apparent “recovery” ligand binding in ex-users in Reneman, Lavalaye et al. (2001) may be due to the up-regulation of post-synaptic receptors rather than restoration of damaged pre-synaptic axon terminals.
have either failed to detect a significant difference between ecstasy users and non-drug using controls, or between ecstasy users and other drug users. Despite this, the results of such studies often show a non-significant trend toward ecstasy users performing worse than controls.

The reasons for the variability in results are unclear. Plausible factors include: regional differences in the potency and contaminants contained in ecstasy pills; differences between samples on the pattern of drug use (e.g., number and frequency of single-drug and polydrug binges, versus the regularity of small dose-usage of each drug that participants take, etc.); and heritable differences in susceptibility to neurotoxic effects of MDMA between regions. The variability may also result from the apparent small size of the effects (when they are detected), which renders them difficult to detect in the population.

The inconsistent findings, and the small size of the memory deficits when they are found, is surprising in light of the large amount of animal research which shows that MDMA administration can cause considerable damage to the serotonin system (outlined in Chapter 1). The variability of results in humans does not necessarily mean that MDMA-related neurotoxicity does not occur, or that brain functions are not lost or altered. It has been argued that there has been a sufficient number of positive findings of ecstasy-related cognitive deficits to warrant considerable cause for concern (Green, 2004). It has also been argued that research which has failed to reveal significant deficits in humans in the face of evidence for the neurotoxicity of MDMA may simply demonstrate the extent of the “robustness and redundancy of the neuronal systems in subserving brain functions” (Kosten & Price, 1992).

### 4.1.4 The possibility of implicit memory deficits in ecstasy users

To date there have been no published studies which have measured implicit memory performance in ecstasy users. In contrast, a small number of studies have investigated the relationship between implicit memory and other recreational drugs. These studies have found that implicit memory (when there is a good perceptual match between study and test) is unaffected by the acute or residual effects of either ketamine or cannabis administration or the long-term effects of alcohol or cocaine abuse (Brunfaut & d'Ydewalle, 1996; Curran, Brignell, Fletcher, Middleton, & Henry, 2002; Curran & Morgan, 2000; Jasiukaitis & Fein, 1999). There have been no reported investigations of
the effects of amphetamines on implicit memory in published literature. Despite the consistency of the negative findings for other drugs, it is possible that MDMA may affect implicit memory functioning. Earlier in this chapter, a study was outlined which found that the acute disruption to the serotonin caused by tryptophan depletion decreased implicit memory performance. This suggests that implicit memory may also be affected by the long-term serotonergic dysfunctions caused by MDMA/ecstasy use. This was investigated for the first time in the present study by comparing the performance on ecstasy users to non-drug using controls on an implicit memory task.

4.1.5 The present study

The approach taken to the design of the current study was to investigate, as far as possible in a cognitive study, the veracity of attributing long-term (explicit) memory deficits in ecstasy users to hippocampal dysfunctions (e.g., Gouzoulis-Mayfrank et al., 2003; Parrott, 2000). As outlined above, both the implicit and explicit components of memory rely on the sensory areas of the cortex, but only explicit memory critically relies on the hippocampus and frontal lobes. Therefore, a significant deficit in hippocampal functioning would be revealed by a deficit in explicit, but not implicit, memory. Alternatively, no difference between ecstasy users and controls on both implicit and explicit memory tests would suggest that the impact of ecstasy on the serotonin system in the hippocampus does not result in significant implicit or explicit memory deficits.

In the present study, implicit retrieval was tested using a stem completion task that was ostensibly unrelated to the prior visual study of a list of unrelated words. Explicit retrieval was tested using a separate stem-cued recall task on a different list of unrelated words. The stem completion and stem-cued recall tasks had identical study, filled delay, and test phases, except for the instructions given at test. The stem completion task instructions were to complete the stems as quickly as possible with the first word that came to mind, whereas the stem-cued recall instructions were to only respond with words that they remembered from the study lists.

In stem completion tasks, there is no guarantee that the test will provide a pure measure of implicit memory unless measures are implemented to limit the opportunity for participants to use explicit memory strategies ("explicit contamination", for discussion see Jacoby, 1991; McKone, 1997; Schacter, 1985; Schacter, Bowers, & Booker, 1989;
Toth, Reingold, & Jacoby, 1994). The measures used in the present study included implementing the test phase as a timed task, which minimised the opportunity for participants to deliberately engage explicit memory processes, and by conducting the testing phase as ostensibly unrelated to the earlier word learning task (i.e., the study phase), which minimised the likelihood that participants would be tempted to deliberately complete a portion of the stems with previously studied words. Also, since participants were required to know about the relationship between the study and test phases in order to do the stem-cued recall (explicit memory) task, it was necessary to always order the tasks so that participants did the implicit memory first, and then the explicit memory test. Finally, after the stem completion test, participants were asked if they had deliberately tried to complete stems with words from the earlier word-learning task, and were excluded from the analysis if they reported that they had.

The effectiveness of the strategies used to minimise explicit contamination of the implicit memory results was evaluated by comparing stem completion and stem-cued recall performance under both full- and divided attention conditions. It has been shown that dividing attention at study reduces explicit retrieval but not implicit retrieval (Mulligan, 1998) – presumably because dividing attention effectively interrupts the consolidation of new and existing information required to form explicit memories, and thus there is no explicit memory formed to access at retrieval. Consequently, in the present study it was expected that dividing attention would not significantly affect stem completion task performance (implicit memory) if explicit contamination had not occurred, but would have a marked effect on stem-cued recall performance (explicit memory).

Groups of ecstasy users and non-drug using controls were recruited, using similar exclusion criteria to many of the well-controlled studies listed in Table 4-1. To enhance the specificity of any statistically significant findings to ecstasy, I also planned to test an additional control group comprised of people who had never used ecstasy, but who had used other drugs on a regular basis (‘cannabis-controls’). However, it was not necessary to test a cannabis-control group because there were no statistically significant differences between ecstasy users and non-drug using controls in the present study.
4.2 Method

4.2.1 Participants

Participants were recruited using the respondent-driven “snowball” sampling technique described in detail in Chapter 2 (section 2.6). Sixty-one people were allocated to one of two groups on the basis of their drug use history. Participants in the ecstasy-users group (n=32) had used ecstasy on at least ten separate occasions and at least once in the past six months, and had never used heroin. Participants in the non-drug using control group (n=29) had never used ecstasy, and had never binged on, or regularly used, any other illicit drug. Some use of cannabis was tolerated in the control group due to the difficulty in finding people who had never tried the drug (details below). People were excluded from the study if they reported any of the following: (a) having ever had an injury or illness that could have affected their brain in any way; (b) having ever been diagnosed or medically treated for a psychiatric or emotional condition known to be associated with cognitive deficits; (c) having consumed alcohol on the day of the experiment, cannabis within the past 48 hours, ecstasy or amphetamines within the past 2 weeks, or any other psychoactive drug in the past week (with the exception of nicotine and caffeine). For the purpose of the verbal memory tests, it was also necessary to require all participants to be Australian-educated English speakers.

Potentially important characteristics of each group are summarised in Table 4-3 (for more details see Appendix A: Table A-1). With regard to demographic variables, the cohorts were not significantly different in terms of age or highest level of education attained. There was a higher proportion of males amongst the ecstasy users than the controls, although a 2-tailed Chi-squared test revealed that the difference was not statistically significant, $\chi^2(1,n=61)=.77$, $p=.45^8$.

Other possible covariates that were measured included: estimated IQ, mental health status, and sensation seeking. IQ was estimated using the Contextual AusNART (Hennessy & Mackenzie, 1995; Lucas, Carstairs, & Shores, 2003), which is an Australian version of the National Adult Reading Test (NART, Nelson, 1982) in which the words to be read aloud have been put into meaningful sentences. Estimated IQ was estimated using the Contextual AusNART (Hennessy & Mackenzie, 1995; Lucas, Carstairs, & Shores, 2003), which is an Australian version of the National Adult Reading Test (NART, Nelson, 1982) in which the words to be read aloud have been put into meaningful sentences. Estimated IQ was

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8 Throughout this thesis, the assumptions of all statistical tests were met unless otherwise stated.
Table 4-3 Selected characteristics of ecstasy users and controls in the first memory study

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=29)</th>
<th>Ecstasy (n=32)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>sex (male %)</td>
<td></td>
<td></td>
<td>.ns</td>
</tr>
<tr>
<td>age (years)</td>
<td>24.0 (7.9)</td>
<td>22.5 (5.3)</td>
<td>.ns</td>
</tr>
<tr>
<td>highest level of education</td>
<td>3.31 (0.60)</td>
<td>3.19 (0.47)</td>
<td>.ns</td>
</tr>
<tr>
<td>estimated IQ</td>
<td>108.3 (4.4)</td>
<td>104.8 (5.4)</td>
<td>0.009</td>
</tr>
<tr>
<td>Ecstasy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lifetime dose (tablets)</td>
<td>-</td>
<td>115.5 (23.1)</td>
<td></td>
</tr>
<tr>
<td>abstinence (days)</td>
<td>-</td>
<td>81.3 (34.2)</td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lifetime dose (standard drinks)</td>
<td>1486.4 (582.4)</td>
<td>4171.6 (879.1)</td>
<td>&lt;.014</td>
</tr>
<tr>
<td>maximum monthly dose</td>
<td>29.1 (8.1)</td>
<td>92.5 (16.4)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>maximum ever dose</td>
<td>11.0 (1.4)</td>
<td>18.7 (1.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>duration of use (years)</td>
<td>9.12 (1.34)</td>
<td>9.97 (1.24)</td>
<td>.ns</td>
</tr>
<tr>
<td>Sensation Seeking Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>experience seeking</td>
<td>6.21 (1.55)</td>
<td>7.78 (1.52)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>disinhibition</td>
<td>4.29 (2.11)</td>
<td>6.69 (2.05)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Note. Further characteristics are shown in Appendix A: Table A-1. SEM = Standard Error of the Mean. .ns indicates p>.05.

*1=Year 10 (lower secondary education); 2=Year 12 (upper secondary education); 3=Bachelor undergraduate degree; 4=post-graduate degree

calculated from the number of reading errors using a formula developed on a sample of 18 to 34 year old Australians, where estimated (full scale) IQ=117.33-(0.69*E), where E = the number of errors on the Contextual AusNART (Lucas et al., 2003). The estimated IQ of ecstasy users was less than that of controls by a small, but statistically significant, amount.

Mental health status was determined using the Brief Symptom Inventory (BSI, Derogatis, 1993). This inventory consists of three global indexes, and nine symptom scales. The indexes are the Global Severity Index (GSI), which provides an overall indication of mental health status, the Positive Symptom Distress Index (PSDI), which indicates the intensity of symptoms, and the Positive Symptom Total (PST) index, which indicates the number of self-reported symptoms. The nine symptom scales are:
Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism. In the present study, there were no significant differences between ecstasy users and controls on any of the indexes or symptom scales (Appendix A: Table A-1).

Sensation seeking has been shown to be a consistent predictor of drug use which has a strong heritable component (see section 2.4.3.3, Dughiero, Schifano, & Forza, 2001; Zuckerman, 1994). It was measured in this study using the Sensation Seeking Scale (Zuckerman) to show that any differences in memory performance between ecstasy users and controls were unrelated to this aspect of personality. The scale consists of four sub-scales, namely Thrill and Adventure, Experience Seeking, Disinhibition, and Boredom Susceptibility. As expected, ecstasy users scored significantly higher on the Experience Seeking and Disinhibition subscales compared to controls. This is consistent with the established pattern of results in literature that drug users are motivated to seek out novel experiences (“Experience Seeking”) and are less perturbed by possible negative consequences (“Disinhibition”) than their control group counterparts (Zuckerman, 1994).

A drug use history was collected from all participants using the semi-structured “time line” interview described in detail in Chapter 2 (section 2.6). The ecstasy users had an average lifetime dose of 115.5 tablets (SD=130.4) of ecstasy, which is well within the range where ecstasy-related full attention explicit memory deficits have been detected in other published studies (eg., 50 tablets (SD unreported) (Morgan, 1999b); 93.4 tablets (SD=119.9) (Gouzoulis-Mayfrank et al., 2000); and 166 tablets (SD=171) (median=104 tablets, Hall, 2001; Ward, Hall, & Haslam, in press)). Ecstasy users had generally used cannabis and amphetamines in addition to ecstasy (see Appendix A: Table A-1 for details), and some users reported occasional use of amyl nitrate, nitrous oxide, and un-prescribed benzodiazepines.

With regard to other drugs, the only drug used by most control group participants was alcohol. Three control group participants reported that they had never consumed a standard drink of alcohol on any given occasion. Of the remaining control group participants, ecstasy users exceeded controls on several alcohol measures, including: lifetime dose, maximum dose in a one-month period, and maximum ever dose on any given occasion. The duration of alcohol use was not significantly different between
ecstasy users and controls. This indicates that the ecstasy users had on average consumed nearly three times as much alcohol as controls over a similar period.

As mentioned earlier, some cannabis use was tolerated in the control group due to the difficulty in finding people who had never tried the drug (n=9, lifetime dose: mean= 6.8 times (SD=7.0) [range 1-24 times]. Last use: mean= 1625.7 days prior to testing (SD=2589.4) [range 3-8096]). In comparison, all of the ecstasy users had used cannabis (n=32, lifetime dose: mean= 1406.6 times (SD=2717.7) [range 1-12847 times]. Last use: mean= 148.4 days prior to testing (SD=324.5) [range 2-1144], further details in Appendix A: Table A-1).

In summary, these cohort characteristics indicate that any differences between the cohorts on memory performance would not be due to age, highest level of education attained or mental health status, but could reflect differences between the cohorts on estimate IQ, alcohol use, or sensation seeking personality variables. The potential influence of these later variables on the outcomes of the study, were controlled for by statistical means. Any statistically significant differences remaining after the statistical control of covariates is likely to be due to the use of ecstasy or other drugs. As mentioned earlier, the planned testing of a cannabis-control group to help control for the use of other drugs was not conducted, due to lack of any statistically significant differences between the ecstasy users and non-drug using controls.

**4.2.2 Structure of participant contact and test session**

The initial contact with each participant was by phone or email in order to inform them of what the study entailed, and to check their eligibility to participate in the study. The full sequence of events that took place while testing each participant is shown in Table 4-4. The drug use history interview took between 10 minutes and one hour, depending on the drug use of the participant. The remainder of the testing took an additional hour.

**4.2.3 Experimental design**

In a 2x2x2 mixed factorial retrospective cohort design, the within-subjects independent variables were type of memory test instructions (stem completion, stem-cued recall) and level of attention at study (full, divided). The between-subjects independent variable was drug cohort (ecstasy users, non-drug using controls). As shown in Table 4-4, the experiment commenced with the study phase, distractor task and stem completion task
Table 4-4 The sequence of events that took place with each participant

1. Informed consent (see Appendix B)
2. Drug use history interview
3. Memory tests:
   i) Practice trials for the divided attention procedure
   ii) Implicit memory test:
       a) Study phase
           learn one list of words under full or divided attention
           learn a second list of words under the opposite attention condition
           repeat learning the first list of words
           repeat learning the second list of words
       b) Distractor phase
       c) Test phase
   iii) Explicit memory test:
       a) Study phase
       b) Distractor phase
       c) Test phase
4. Contextual AusNART
5. Explanation, debrief, and answer participant questions about the study

designed to assess implicit memory, followed by the study phase, distractor task and stem-cued recall task designed to assess explicit memory. In order to enhance overall implicit memory performance, there was a very high perceptual match between the presentation of the words at study, and the word stems at test. Each study phase consisted of reading aloud and learning two lists of words, with one list learned under full attention conditions, and the other list learned when attention was divided by a digit-monitoring task (secondary task) conducted simultaneously with the word reading task (primary task).

The order of presentation of the full- and divided-attention study conditions was counterbalanced across subjects. In the divided attention conditions, evidence that the participant was attending to both tasks was obtained by recording: (a) the number of correctly read words in the word-learning task, and (b) the reaction time and accuracy of responses in the digit-monitoring task. The study phase was then repeated (i.e. each word list was learned twice). Pilot testing had revealed that this was necessary to avoid floor effects on the subsequent memory tests.

The test phase consisted of either a stem completion (for implicit memory) or a stem-cued recall (for explicit memory) task. These tasks were identical except for the instructions given. The test stimuli were three-letter word stems (e.g., “cal” from the
word “calendar”). For each participant, half of the stems corresponded to words presented during the corresponding study phase (studied target words), and half corresponded to words that had not been presented (unstudied target words). For the stem completion task, the instructions were to complete the stems as quickly as possible with the first word that came to mind. For the stem-cued recall task, the instructions were to only respond with words that they remembered from the study lists. Since the stem-cued recall instructions would negate the possibility of participants being naïve about the purpose a subsequent stem completion task, it was necessary to conduct the stem completion task first for all participants. The dependent variables for both memory tests were the number of target word responses to the stems of unstudied words (baseline), and the number of target word responses to the stems of studied words minus the corresponding baseline (memory score).

### 4.2.4 Experimental stimuli

There were 96 target words, of which 48 were obtained from McKone and French (2001). The remainder were extracted from lists contained in Kucera and Francis (1967). The target words were selected so that the corresponding three-letter word stem was unique in the set, did not constitute a word in its own right, and could be completed to form at least five possible words. Target words were five to eight letters in length. It was important that the baselines for target words were low to ensure that memory effects could be detected without encountering ceiling effects. Baselines were minimised by using low and medium frequency target words with a word frequency range of between 1 and 120 occurrences per million (Kucera & Francis, 1967). Potential target words were pilot-tested by asking an independent group of participants (n=18) to complete the stems with the first word that came to mind. Stems were replaced if five or more participants completed it with the target word.

The final 96 target words were allocated to eight lists of 12 words, so that a different list could be used in each of the eight experimental conditions (studied and unstudied words, in the stem completion and stem-cued recall tasks, under both full and divided attention conditions). The lists had similar average word lengths, word frequencies, number of syllables, and baseline response rates (all F5 <1). The lists were allocated to experimental conditions in counterbalanced order across participants and cohorts, such that each list was used approximately an equal number of times in each condition by
each cohort. An additional set of words was compiled, without strict adherence to the above criteria, for use as practice items.

### 4.2.5 Experimental procedure

#### 4.2.5.1 Study phase

In each study phase, participants read aloud a list of 12 words presented at a rate of one word every 3.5 seconds. They were instructed to learn the words for a later memory test. The words were presented in lower case letters on an iMac computer using PsyScope software (Cohen, MacWhinney, Flatt, & Provost, 1993). The number of reading errors and omissions were recorded. In the divided attention condition, the secondary task used was an odd-or-even digit-monitoring task (Schmitter-Edgecombe & Nissley, 2000). Pre-recorded audible digits between ‘1’ and ‘9’ were played at random intervals of between 2 and 3 seconds by Inquisit software (Draine, 2003) on a second (PC) computer. Participants pressed one computer key for odd numbers, and a different key for even numbers. They were instructed to respond as fast and as accurately as they could. Accuracy and reaction times were recorded. To ensure that attention was divided for the entire length of the study task, there were two digit-monitoring task trials before the first study word was displayed, and two or three trials after the last study word had disappeared, making a total of 20 digit-monitoring trials.

Practice with each task was given at the beginning of the experiment. First, the word-learning task was demonstrated alone using three words from the practice list. Participants were then given two sets of 20 practice trials on the digit-monitoring task by itself. Finally, participants repeatedly practiced doing the word-learning and digit-monitoring tasks simultaneously until they achieved an accuracy level of 80% or more on the digit-monitoring task in two consecutive sets of trials. Reading errors on the word-learning task were rare, such that most participants read all of the words correctly.

#### 4.2.5.2 Distractor phase

Each distractor phase lasted approximately 3 to 6 minutes. It was produced by administering either the Sensation Seeking Scale (Zuckerman, 1994) or the Brief Symptom Inventory (Derogatis, 1993) in counterbalanced order across participants within each cohort.
In each test phase, participants were given a sheet of paper containing a randomly ordered list of 48 word stems, which corresponded to the 24 studied (12 full attention and 12 divided attention) and 24 unstudied (12 full attention and 12 divided attention) target words. To ensure that there was a good perceptual match between study and test for each memory task, the same font and physical font-size was used in all of the study and test phases.

For the stem completion task (implicit memory), participants were instructed to complete each stem, in the order that they were presented on the sheet, with the very first word that came to mind. To minimise the possibility of participants using deliberate recall of the study lists to complete the stems (“explicit contamination”, see section 4.1.5), participants were told that the purpose of the exercise was to see how quickly they could generate one word for each word stem, and that it didn’t matter what the words were, as long as they completed the word stems as quickly as possible. Emphasis on speed was added by visibly timing participants with a stop-watch, and by repeating the instruction (while preparing to start the stop watch) that they should respond as fast as possible to each stem with the very first word that came to mind, regardless of what the words are.

No mention was made of the connection between this task and the study phase. Once completed, the participants were asked the following questions to assess if any explicit memory contamination had occurred: (1) What do you think the purpose of the word stem completion task was? (2) What was your general strategy when completing the word stems? and (3) Did you deliberately try to complete the word stems with words you remembered from the study list? Two participants were excluded from the study and replaced because they indicated that they deliberately completed word stems with words from the study lists rather than with the first word that came to mind.

For the stem-cued recall task (explicit memory), participants were instructed to complete the stems with words from the study phase, in the order they were listed, and to leave a stem blank if no matching study phase word could be recalled. They were instructed that they could take as long as they needed to complete the task. During pilot testing, some participants simply stated that they could not remember any words without even looking at the list of stems. To prevent this from occurring in the study,
participants where shown how to use a blank sheet of paper to reveal and focus their attention on one stem at a time.

4.2.6 Statistical analysis of cohort effects and covariates: General approach

Throughout this thesis, the statistical tests used for the primary analysis of within- and between cohort effects varied according to the number and characteristics of the variables being tested, as well as the whether the data met the assumptions of particular tests. All data analyses were performed using SPSS version 13.0 for Windows (SPSS, 2004).

In general, analysis commenced with group comparisons on the main variables of interest using ANOVA, Repeated-Measures ANOVA, or the multivariate approach for dealing with the violation of the sphericity assumption of Repeated-Measures ANOVA, depending on the characteristics of the variables and data. Where relevant, follow-up contrasts were [generally] conducted using either t-tests or the contrasts reported by SPSS. In all cases, a priori tests were also conducted comparing cohorts on each measure in turn, even where the conditions formed part of a more complex design.

Covariates were then identified using bivariate correlations between the variable/s of interest and estimated IQ, age, sex, level of education attained, the four subscales of the Sensation Seeking Scale (as an indicator of personality), and all of the indexes and subscales of the Brief Symptom Inventory (as an indicator of mental health). The influence of the those variables which correlated with the variables of interest at \( p < .10 \), if any, was then evaluated using a backward elimination ANOVA, in which the least significant covariate was removed from the model in successive tests, until only those covariates with significant main and/or interaction effects remain in the model (Kleinbaum, Kupper, & Muller, 1988). The significance of the covariates that remain in the model are reported, along with the remaining cohort effect.

Dose dependence was then evaluated using bivariate correlations between the variables of interest and drug use measures. If dose dependence was found for drugs other than ecstasy, then ANCOVA or regression analysis was conducted to determine the significance of cohort differences once the influence of other drug use was taken into account.
Table 4-5 Performance on the word-learning task (words correctly read aloud) and digit-monitoring task (accuracy of odd-even decisions) as a function of level of attention (full, divided) and cohort (controls, ecstasy users)

<table>
<thead>
<tr>
<th>Study phase</th>
<th>Controls (n=29)</th>
<th>Ecstasy users (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>percent correct (SD) and [range]</td>
<td>percent correct (SD) and [range]</td>
</tr>
<tr>
<td>Full attention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word reading</td>
<td>99.9 (0.8) [95.8-100.0]</td>
<td>99.7 (0.9) [95.8-100.0]</td>
</tr>
<tr>
<td>Divided attention</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word reading</td>
<td>100.0 (0.0) [100.0-100.0]</td>
<td>99.3 (1.6) [93.8-100.0]</td>
</tr>
<tr>
<td>Digit-monitoring</td>
<td>97.1 (3.7) [85.0-100.0]</td>
<td>98.1 (2.6) [90.0-100.0]</td>
</tr>
</tbody>
</table>

4.3 Results

4.3.1 Study phase: Performance on the word-learning and digit-monitoring tasks

The performance at study of participants on the word-learning task and digit monitoring tasks was nearly perfect for both controls and ecstasy users (see Table 4-5). This confirms that both cohorts effectively attended to the study words under full attention conditions, and effectively attended to both the word learning and digit-monitoring tasks under divided attention conditions. Importantly, there were only trivial differences between the performances of the cohorts on each task.

4.3.2 Test phase: Baseline response rates

As desired, the baseline rate of completion of unstudied stems with target words in the implicit memory condition was low (see Table 4-6). With regard to the explicit memory condition, the completion of unstudied stems with target words (i.e., false memories) condition was very low. There was no statistically significant difference between the cohorts on their baseline response rates on either task, indicating that memory for studied items can be validly compared across cohorts.

4.3.3 Test phase: Replication of standard test-type by attention interaction

For both the implicit and explicit tasks, memory scores were then calculated as the number of target word completions of studied items minus the number of target word completions of unstudied items (i.e., studied - baseline). Before examining cohort effects, an initial analysis of the memory scores was conducted within each cohort to
confirm that the memory tests provided distinct measures of implicit and explicit memory, and to assess the effectiveness of the divided attention task. Specifically, I expected to replicate the standard finding in the literature that explicit memory performance is considerably reduced by dividing attention, while implicit memory is not (Mulligan, 1998).

Figure 4.1a and Figure 4.1b show the mean memory scores within each cohort for the stem completion and stem-cued recall tasks. For controls, the interaction apparent in Figure 4.1a between type of memory test instructions and level of attention was statistically significant, $F(1,31)=4.80$, MSE = .02, $p<.04$. In accordance with the established pattern in literature for explicit memory, dividing attention considerably lowered stem-cued recall task performance, $t(28)=4.84$, $p<.001$. However, dividing attention also reduced stem completion task performance by a small but statistically significant amount, $t(28)=2.08$, $p=.05$. This suggests that there was some explicit memory contamination of the stem completion task result for controls. Despite this, under full attention the stem completion task performance was still considerably less than stem-cued recall, $t(28)=4.87$, $p<.001$, which suggests that the explicit contamination was small and that the stem completion task does provide a moderately pure gauge of implicit memory performance, especially under divided attention conditions.

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Ecstasy users</th>
<th>$t$ (59)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Implicit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full attention</td>
<td>3.7% (5.2)</td>
<td>5.6% (5.8)</td>
<td>1.39</td>
<td>0.17</td>
</tr>
<tr>
<td>Divided attention</td>
<td>4.5% (5.7)</td>
<td>5.7% (6.9)</td>
<td>0.70</td>
<td>0.49</td>
</tr>
<tr>
<td>Explicit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Full attention</td>
<td>1.1% (2.8)</td>
<td>1.3% (3.0)</td>
<td>0.20</td>
<td>0.84</td>
</tr>
<tr>
<td>Divided attention</td>
<td>0.6% (2.1)</td>
<td>0.8% (3.3)</td>
<td>0.32</td>
<td>0.75</td>
</tr>
</tbody>
</table>
For ecstasy users, the interaction in Figure 4.1b between type of memory test instructions and level of attention was also statistically significant, $F(1, 31)=4.83$, $MSE=.08$, $p<.04$. In this case, dividing attention significantly lowered performance on the stem-cued recall task, $t(31)=3.13$, $p=.004$, but had no significant impact on the stem completion task performance, $t(31)=0.31$, $p=.76$. This suggests that, for the ecstasy users at least, the stem completion task performance does provide a pure measure of implicit memory.

### 4.3.4 Test phase: Cohort effects: Was ecstasy use associated with implicit and/or explicit memory deficits?

The primary aim of the present study concerned possible ecstasy effects on various components of memory. Figure 4.2 shows a comparison between the cohorts on their scores for each memory task. There was no evidence of an ecstasy-related deficit in the divided attention conditions, but there were some trends towards deficits in the full attention conditions.

![Figure 4.1 Memory scores (target word completions of studied stems – baseline) on stem completion (implicit) and stem-cued recall (explicit) memory tasks as a function of level of attention (full, divided) and cohort (controls, ecstasy users). Error bars = standard errors](image)
A three-way ANOVA (type of memory test, by level of attention at study, by cohort) showed that there was no main effect of cohort, no interaction between cohort and type of memory test, and no three-way interaction, all $F_s<1$. The only significant cohort interaction was with level of attention, $F(1,59)=4.71$, $MSE=.02$, $p<.05$. However, post-hoc t-tests of attention type collapsed across memory test revealed no significant effect of cohort under either full attention, $t(59)=1.7$, $p=.10$, or divided attention, $t(59)=.86$, $p=.40$, conditions. The effect of cohort was also not significant when each condition was considered alone (see Figure 4.2). From the effects of dividing attention reported earlier, it appeared that there had been some explicit contamination of the stem completion performance under full attention in the control group (Figure 4.1a and Figure 4.2 stem completion full attention). If this had not been the case, then the tendency toward a difference between the cohorts under full attention would have been restricted to the stem-cued recall task.
The test of explicit memory used in the present study that was most comparable with list-learning tests using in previous literature was the stem-cued recall task under full attention. Calculations revealed that the power of the current study to detect an effect of the size observed was 0.22, which corresponds to probability of a Type II error of 0.78. Thus, while there was no statistically clear evidence that there was an explicit memory deficit in ecstasy users, it is also difficult to conclude that there was no deficit.

The above analysis examined ecstasy-related effects by comparing the mean performance of ecstasy users and controls. An alternate way of detecting drug effects is to analyse dose dependence effects within the drug users group alone, that is, correlations between memory scores and drug use measures within the users of the respective drug. For ecstasy users, there were no significant correlations between the memory scores on any memory task and any of the ecstasy use measures.

In summary, no evidence was found for any association between ecstasy use and implicit or explicit memory deficits under full- or divided-attention conditions. While there was some suggestion of cohort differences under full attention, this effect was not statistically significant, and was uncorrelated with ecstasy dosage, frequency and recency measures.

### 4.3.5 Subsidiary results: An ecstasy advantage in dual task performance?

In the course of running the digit-monitoring task, reaction times were measured throughout the practice phase and the experimental divided attention study phases (see Figure 4.3). The reaction times of controls and ecstasy users were not significantly different when practicing the digit-monitoring task alone, \( t(59) = 0.68, p > 0.05 \) and \( t(59) = 1.56, p > 0.05 \), respectively. This extends findings in the literature that ecstasy use

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9 Further calculations revealed that a difference of the magnitude obtained may have been statistically significant had 79 participants been tested in each group.

10 For ecstasy users, there were some small but significant correlations between stem completion performance under full attention conditions and several cannabis use measures, specifically, lifetime dose, \( r(32) = -0.35, p < 0.03 \), maximum monthly frequency \( r(32) = -0.30, p < 0.04 \), and maximum ever dose \( r(32) = -0.36, p < 0.03 \). However, overall, ecstasy users did not perform significantly worse than controls on the stem completion task (implicit memory) under either full- or divided attention conditions. Also, the only other study which has examined such an association found that implicit memory was unaffected by cannabis use (Curran et al., 2002). No significant correlations were found for the users of any other drug.
A potentially interesting result emerged when the digit-monitoring task was conducted under dual task conditions. There was a non-significant trend towards ecstasy users having faster reaction times than controls on the first set of dual task practice trials, $t(50.3)=1.95$, $p=.057$, and ecstasy users were significantly faster on the second set of dual task practice trials, $t(59)=2.93$, $p<.01$. There was also a trend toward ecstasy users having faster reaction times for the digit-monitoring tasks during the study phase of the stem completion task, $t(59)=1.92$, $p=.06$. Only in the final study phase conducted for the stem-cued recall task had the performance of controls improved to match that of the ecstasy users, such that there was no difference in digit-monitoring task reaction times between the cohorts. All of these results were achieved while the accuracy attained by ecstasy users matched or even slightly exceeded that attained by controls, both on the primary task (digit-monitoring, see Figure 4.3b) and secondary task (word-learning, see Table 4-5).
Covariate analyses were conducted to evaluate the effect of potential covariates on the significant results obtained above. As outlined in section 4.2.1, the ecstasy users group had a higher proportion of males, and a slightly lower estimated IQ, than the control group. In order to investigate the impact of these possible covariates on the reaction times, a one-way ANCOVA of reaction time as a function of cohort was conducted for each divided attention task in Figure 4.3a, including the backward elimination of estimate IQ, sex, and all interactions. Estimated IQ was the only significant covariate to remain significant for the first and second set of divided attention practice trials, $F(1,57)=14.10$, $\text{MSE}=25799$, $p<.001$, and $F(1,57)=8.86$, $\text{MSE}=22381$, $p=.004$, respectively, such that a higher IQ was generally associated with faster reaction times. Once differences in estimated IQ were taken into account, the previous non-significant trend towards ecstasy users having faster reaction times than controls in the first set of divided attention practice trials became significant, $F(1,57)=10.26$, $\text{MSE}=25799$, $p=.002$, and the significance of the difference between the cohorts on the second set of trials increased to $F(1,57)=16.34$, $\text{MSE}=22381$, $p<.001$. These changes are consistent with the fact that controls on average had a higher estimated IQs than ecstasy users. For the stem completion study phase data, the only significant covariate was a two-way interaction between cohort and estimated IQ. Once the effect of that interaction was taken into account (using regression modelling to overcome the violation of assumption of classical ANCOVA caused by the interaction) the significance of the difference between the cohorts increased to $p=.005^{11}$. While this study was not designed to test this effect, the reaction time results indicated that ecstasy users were able to perform faster than controls on a secondary task under dual task conditions.

4.4 Discussion

The broad aim of the current study was to investigate the possible consequences of recreational ecstasy use on implicit and explicit memory for lists of single unrelated words. Stem-cued recall and stem completion tasks under full- and divided attention conditions were used to dissociate implicit- from explicit memory within a group of ecstasy users, and within a group of non-drug using controls. The possible effects of

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$^{11} \beta=-.338, t(58)=-2.947$
drug use were then investigated using between group comparisons of their implicit and explicit memory performance.

4.4.1 Summary of findings in the present study

Within each experimental group, dividing attention at study resulted in a significant decrease in performance on the stem-cued recall task (used to reveal explicit memory), and relatively little or no decrease in performance on the stem completion task (used to reveal implicit memory). These replications of the pattern of results commonly reported in literature confirms that the stem-cued recall task under full attention largely reflected explicit memory, while the stem completion task (especially under divided attention conditions) largely reflected implicit memory.

In the between-groups comparison, there was no difference between the ecstasy users and non-drug using controls on either explicit or implicit memory performance. The results were clear for implicit memory, as the trend was in the opposite direction to that expected for an ecstasy-related deficit (i.e., the performance of ecstasy users was slightly higher than controls by a non-significant amount). This is a novel finding, in that at the time of writing no previous reports could be identified of an investigation regarding the implicit memory functioning of ecstasy users.

The results were less clear regarding explicit memory. The performance of ecstasy users was not significantly different from that of the non-drug using controls. However, there was a tendency towards poorer performance in ecstasy users in the stem-cued recall task under full attention conditions. In addition, there was some evidence of explicit contamination of the stem completion task (implicit memory) performance for non-drug using controls but not for ecstasy users. One possible explanation for this is that ecstasy users had a slight explicit memory deficit that was just large enough to prevent explicit contamination of their stem completion task performance, but not large enough to cause a statistically significant difference in their stem-cued recall (explicit memory) task performance under full attention. The presence of these trends means that it is not possible from the current data to confidently conclude whether or not ecstasy use is associated with explicit memory deficits for lists of unrelated words.
4.4.2 The consistency of the results compared to previous literature, and the interpretation of findings in the present study

4.4.2.1 Implicit memory

The finding of intact implicit memory in ecstasy users is consistent with similar findings for other recreational drugs, including no association between implicit memory performance and the long-term effects of alcohol and cocaine, and no association between implicit memory and the acute and residual effects of ketamine and cannabis (Brunfaut & d'Ydewalle, 1996; Curran et al., 2002; Curran & Morgan, 2000; Jasiukaitis & Fein, 1999). However, this finding differs from the only study to examine the effects on implicit memory of disruption to the serotonin system by tryptophan depletion. That study found a tryptophan depletion-related deficit in implicit memory, as revealed by repetition priming (Burgund, Marsolek, & Luciana, 2003). One possible explanation for the difference between the findings in the present study and the tryptophan depletion study is that ecstasy use may not cause sufficient damage to the serotonin system to cause a noticeable difference in implicit memory performance. As outlined in the introduction to the present study, tryptophan depletion can be a useful tool for identifying cognitive functions that may be sensitive to ecstasy-related changes to the serotonin system. However, there is insufficient evidence to directly compare the cognitive consequences of ecstasy-related disruptions to the serotonin system to that caused by tryptophan depletion. In particular, the chronic nature of serotonergic disruptions in ecstasy users may enable compensatory neural changes in allied brain systems (e.g., the up-regulation of post-synaptic serotonin receptors, see Buchert et al., 2003; Reneman, Booij et al., 2000; Reneman, Endert et al., 2002; Reneman, Habraken et al., 2000; Terriere et al., 1995). Such changes may reduce the size of otherwise significant functional deficits. It is therefore conceivable that implicit memory may be more sensitive to the severe acute disruption of serotonin synthesis in tryptophan depletion, than the chronic effects on the serotonin system caused by recreational ecstasy use.

A second possible explanation for the finding of intact implicit memory in the present study, compared to an implicit memory deficit in the tryptophan depletion study (Burgund et al., 2003), is that the divergence of the results reflects the same pattern of
variability between studies as obtained for long-term explicit memory (outlined earlier in this chapter). An implication of this explanation is that future studies using other methodologies and/or samples may yield a significant ecstasy-related implicit memory deficit. This seems unlikely, however, as the slight non-significant trends in the data were in the opposite direction to what would be predicted for an ecstasy-related deficit.

4.4.2.2 Explicit memory

The lack of a statistically significant long-term explicit memory deficit in the current study may simply reflect the pattern of results found in the literature review, that explicit memory deficits for lists of unrelated words in ecstasy users are small and difficult to reliably detect. Assuming that ecstasy does in fact cause explicit memory deficits, there are several plausible explanations why a statistically significant deficit was not detected in the current study. One possible explanation is that a deficit may have been found in the present study if the power of the experiment to detect an effect had been greater. Power calculations suggested that an effect of the size obtained would have been statistically significant had approximately 80 people been tested in each cohort. However, there was insufficient time and resources available to test that number of participants. Furthermore, there is no guarantee that the effect size and variability of performance within cohorts of 80 participants would have remained the same as those obtained from the sample of 29 ecstasy users and 32 controls tested in the present study.

A different way of increasing the power of the study to detect an effect may be to increase the average lifetime ecstasy use within the sample. If there is a dose dependant relationship between ecstasy use and explicit memory for lists of single unrelated words, then a sample with a larger mean lifetime dose of ecstasy should have poorer explicit memory performance, thus increasing the likelihood of detecting a statistically significant difference between ecstasy users and non-drug using controls. This was implemented in the second memory study in the following chapter by attracting more people with higher lifetime ecstasy dose to the study, and also by excluding potential participants who had used relatively small lifetime doses of ecstasy.

A second possible explanation for the non-significant explicit memory result in the present study is that the use of two learning trials at study, and/or the provision of stem-cues at recall, inadvertently assisted ecstasy users more than controls. This could be the case if the ecstasy users formed a poorer memory trace of the words compared to
controls on the first learning trial, and thereby receive more assistance from the second learning trial and/or the stem-cues at recall. These possibilities are explored further in the following chapter, which includes an experimental comparison of the effect of varying the number of learning trials (one v. two) and the level of cueing (stem-cued v. free recall) on the difference between ecstasy users and non-drug using controls on stem-cued recall for a list of single unrelated words.

A third possible explanation for the non-significant explicit memory result in the present study is that ecstasy does not cause reliable hippocampal-related deficits on memory for lists of single unrelated words, and therefore that deficits observed in some published studies are due to other factors. The present study was based on delayed recall for lists of single unrelated words because that type of test was thought to be more specific to hippocampal functioning than any other cognitive test (as outlined in Chapter 3). While there is some doubt about the reliability of the explicit memory deficit in the present study, it is clear that if explicit deficits for lists of unrelated words do exist in the ecstasy using population that the sample in the present study was drawn from, that the deficits are very small at best. This brings into question the attribution of long-term explicit memory deficits in ecstasy to changes in hippocampal functioning (e.g., as argued by Gouzoulis-Mayfrank et al., 2003). In comparison to standard neuropsychological word-list learning tasks, the study phases in the current study were implemented in a way to specifically limit the extent of elaborative and/or associative processing, as well as mental rehearsal (by always quickly moving onto the next task; by alternating between learning different sets of words during study; and by always having an interference task between study and test). However it may be these processes that produce the ecstasy-related deficits in other studies. This possibility was tested in the following chapter by contrasting group performance on standard neuropsychology tests that allow for greater elaborative processing at study, with stem-cued recall.

4.4.2.3 Reaction times under divided attention

An interesting subsidiary result obtained in the present study was that, under divided-attention conditions, ecstasy users had a faster mean reaction time compared to non-drug using controls on the ‘digit-monitoring’ task. In contrast to the present study, no published studies were identified at the time of writing in which faster reaction times had been obtained for ecstasy users. Previous divided attention studies have either
shown no effect of ecstasy on reaction times (Wareing, Murphy, & Fisk, 2004), or slower reaction times for ecstasy users (Gouzoulis-Mayfrank et al., 2000; Jacobsen, Mencl, Pugh, Skudlarski, & Krystal, 2004). Even under full attention conditions, previous studies have either found no effect of ecstasy on reaction times (Daumann, Fimm et al., 2003; Daumann, Fischermann, Heekeren, Thron, & Gouzoulis-Mayfrank, 2004; Daumann, Schnitker et al., 2003; Fox, Toplis et al., 2001; Gouzoulis-Mayfrank et al., 2000; Morgan, 1998; Parrott, Lees, Garnham, Jones, & Wesnes, 1998; Rodgers, 2000), or slower reaction times in ecstasy users (Curran & Verheyden, 2003; Jacobsen et al., 2004; Verkes et al., 2001). The long-term effects of amphetamines by ecstasy users also does not appear to cause faster reaction times (Daumann, Schnitker et al., 2003). In conclusion, further research is required to clarify the origin of the apparent conflict between the results of the present study and previous literature.

### 4.4.3 Summary of discussion

With regard to the components and processes of memory, the results of the present study clearly show for the first time that implicit memory remains intact in recreational ecstasy users. The results are less clear regarding explicit memory, but no significant deficits in ecstasy users were found for lists of single unrelated words. In light of the localisation of these components of memory outlined in the previous chapter, this pattern of results raises some doubt in the veracity of attributing long-term memory deficits specifically to hippocampal dysfunctions, and raises the possibility that explicit memory deficits obtained in other studies are due to other brain regions and/or memory components and processes. The second memory study in the following chapter begins to explore the possibility of ecstasy-related deficits in elaborative and/or associative processing in long-term memory tasks, as well as seeking to clarify the contribution of the number of learning trials and the use of stem-cues at recall to the explicit memory results in the present study.
Chapter 5. The effects of the number of learning trials, level of cueing, and the opportunity for elaborative processing on long-term explicit memory

5.1 Introduction to the present study

In the discussion of the first memory experiment in the previous chapter, a number of possible explanations were explored regarding aspects of the experimental design that could have contributed to the finding that explicit memory performance in ecstasy users was not significantly different from that of controls. These possibilities are explored both theoretically and empirically in the current chapter to clarify and extend the findings of the first memory study. Towards that end, the main aims of the present study were to evaluate the influence of the number of learning trials and level of cueing on the difference between ecstasy users and controls on explicit memory for lists of unrelated words, and to test elaborative and associative processing in the current sample of ecstasy users using standard neuropsychological tests. An additional aim of the present study was to increase the likelihood of detecting an ecstasy-related deficit by testing a sample of ecstasy users who had a higher lifetime dose of ecstasy than those in the first memory study. The following sections address each of these aims in turn by reviewing relevant literature, describing the memory tasks used in the present study, and outlining the components of memory that are tapped by those tasks.

5.1.1 Aim: To evaluate the effect of the number of learning trials on the explicit memory performance of ecstasy users compared to controls

It has long been known that “practice makes perfect”, and that repetition can be an important facet of learning new material. The role of repetition in learning is clearly demonstrated in the word-list learning tasks reviewed in the previous chapter, in which recall improves following each successive study trial (e.g., see Figure 1 in Fox, Parrott et al., 2001). Repetition was used in the previous study to increase recall performance for the lists of unrelated words to a level that was sufficiently high enough above baseline response rates for performance deficits to be detectable.

Of concern in the present study is the possibility that the repetition of the learning trials in the previous study inadvertently assisted the ecstasy users more than the controls, thus reducing the likelihood of detecting a significant difference between the groups. A
tendency for the recall performance of ecstasy users and controls to converge over successive trials has been observed on memory for lists of single unrelated words (Fox, Toplis et al., 2001; Thomasius et al., 2003). However, the convergence of recall in those studies occurred as the performance of the participants approached the upper limit, or ‘ceiling’. In contrast, recall in the previous study after two learning trials was still well below ceiling, and therefore it is unclear if any difference between the groups would have been reduced by the second learning trial. Furthermore, not all studies which have compared ecstasy users and controls on word-learning tasks have found that the difference in memory performance between ecstasy users and controls has significantly narrowed over successive trials (e.g., Curran & Verheyden, 2003; McCardle et al., 2004).

In the present study, the effect of the number of learning trials on the difference between ecstasy users and controls on stem-cued recall was tested empirically. The recall of the groups was compared following both one and two learning trials, using a stem-cued recall task very similar to that used to reveal explicit memory under full attention in the previous study. Since implicit memory was not being tested in the present study, it was not necessary to conduct the divided attention condition that had been used in the previous study to check the dissociation of implicit and explicit memory processes. The omission of the divided attention condition improved overall performance to the extent that recall after one learning trial was sufficiently above baseline response rates for performance deficits to be detected.

If ecstasy users perform worse than controls following one learning trial, but not following two learning trials, this would suggest that the use of two learning trials in the previous study possibly had assisted ecstasy users more than controls, and that under one-trial learning ecstasy use is associated with explicit memory deficits for lists of single unrelated words. Alternatively, if the performance of ecstasy users and controls are not significantly different on either task, this would suggest that the use of two learning trials in the previous study did not inadvertently nullify an otherwise significant difference between the groups.
5.1.2  **Aim: To evaluate the effect of the level of cueing on the explicit memory performance of ecstasy users compared to controls**

The provision of stem-cues at test in the first memory study was a necessary part of the procedure used to dissociate implicit from explicit memory. This was achieved by using identical study, distractor and tests phases for each test, except that the to reveal implicit memory participants were asked to complete the word stems at test with the first word that came into their minds, whereas to reveal explicit memory they were asked to complete the word stems with words from the study list. Thus, any performance difference between the tasks could only be due to the test instructions designed to reveal the different types of memory.

However, of concern in the present study is the possibility that the provision of stem-cues at test may have inadvertently aided memory retrieval in ecstasy users more than controls. It is possible that ecstasy users had relatively poor memory traces for the studied words compared to controls after the learning trials, but were able to retrieve sufficient words from memory with the aid of cues at test so that there was no significant performance difference between the groups. In contrast, the controls may have formed relatively good memory traces at study, and therefore received relatively little benefit from the cues at test.

The effect of the level of cueing on recall performance in ecstasy users compared to controls has not been assessed using word-stems in previous literature, but has been assessed using recognition of studied items amongst distractors. Reneman, Lavalaye et al. (2001) found significant delayed recall deficits in ecstasy users, but not delayed recognition deficits. This particular pattern of results is consistent with the provision of cues at test reducing the significance of the difference between ecstasy users and controls. However, other studies have found different patterns of results, including significant deficits in ecstasy users on both delayed recall and delayed recognition (e.g., Yip & Lee, 2005), and deficits in controls compared to ecstasy users on delayed recognition, but no difference between the groups on delayed recall (e.g., Back-Madruga et al., 2003). Therefore, from previous studies it is not possible to be confident regarding the possible impact of providing stem-cues on the group differences in the first memory study.
In the present study, the effect of the level of cueing on the difference between ecstasy users and controls was empirically tested by comparing the performance of the groups on both stem-cued recall and free (‘un-cued’) recall at test. If ecstasy users perform worse than controls on free recall, but not on stem-cued recall, this would suggest that the provision of stem-cues at test in the first memory study may have assisted ecstasy users more than controls, and that ecstasy use is associated with explicit memory deficits for lists of single unrelated words under free recall conditions. Alternatively, if the performance of ecstasy users and controls is not significantly different on either task, this would suggest that the use of stem-cues at test in the previous study did not inadvertently nullify an otherwise significant memory deficit in ecstasy users, and therefore that ecstasy use is not associated with explicit memory deficits for lists of single unrelated words.

5.1.3 **Aim: To evaluate the effect of elaborative and associative processing on long-term memory test performance, as revealed by standard neuropsychological tests**

The first memory study and the follow-up memory tests outlined above are all concerned with the implicit and explicit components of long-term memory. In this section the focus of this thesis is turned towards evaluating the impact of ecstasy use on elaborative and associative processing in tests of long-term explicit memory. As defined in Chapter 3, elaborative processing refers to any process that involves the active use of word meanings. Associative processing is a special case of elaborative processing, in which meaningful associations between stimuli are generated. The possible role of these processes in ecstasy-related long-term memory deficits was examined in the present study by comparing ecstasy users and non-drug using controls on selected standard neuropsychological tests, namely the Auditory Verbal List Learning task (AVLT described in Lezak et al., 2004; Mitrushina et al., 1999) and prose recall (Wechsler, 1997a). These tasks are described in the following sections, along with an outline of the processes of memory that they tap which have not been examined so far, and reviews relevant literature.

5.1.3.1 **The Auditory Verbal List Learning task (AVLT)**

As outlined in the previous two chapters, the AVLT involves successive study and immediate test phases for a list of single unrelated words, generally followed by a
delayed recall and/or recognition test without any further exposure to the study materials. The AVLT has fewer restrictions on the use of elaborative and associative processing at study compared to the stem-cued and free recall tasks used in the current and previous chapters. Processing at study in the stem-cued and free recall tasks was limited by quickly moving from the study phase onto an interference task between study and test. Furthermore, in the previous study the attention of participants was quickly alternated between learning one word list under full attention conditions, and learning a second word list under difficult divided attention conditions. In contrast, in the AVLT the participants’ attention remains constantly on a single list of words throughout the successive immediate study and test phase of the test. This means that participants have much greater opportunity to engage in the strategic use of elaborative and/or associative processing of the studied items, during which time reasonably elaborate semantic structures could be generated in order to help them remember the words. Such processing may include associating the words into a smaller number of different composite images or sentences, each representing a few of the words, and thereby effectively reducing the number of items to be remembered (as outlined in Chapter 3).

The performance of ecstasy users on AVLT-type tasks (‘memory for lists of unrelated words’) was reviewed in the introduction to the first memory study in the previous chapter. That review found that some researchers have found statistically significant deficits in ecstasy users on AVLT-type tasks, which in some cases were dose dependent on some aspect of ecstasy use. However, the results are far from consistent across studies. In light of the variability of previous findings, a secondary reason for conducting the AVLT in the present study was to see if the current sample of ecstasy users would show a deficit on this task compared to controls.

In the present study, a deficit in ecstasy users on the AVLT but not on the stem-cued and free recall task would suggest that long-term memory deficits in ecstasy users may be principally due to deficits in the strategic use of elaborative and/or associative processing, rather than deficits in the consolidation of information into explicit memory per se. In terms of the localization of components of memory discussed in Chapter 3, this pattern of results would suggest that long-term explicit memory deficits in ecstasy users originate from changes in frontal lobe functioning, rather than from the hippocampus alone.
5.1.3.2 Prose recall

Prose recall is different from all of the word-list learning tasks outlined so far, because the use of elaborative processing at study is required rather than optional. In word-list learning tasks there is no requirement or suggestion to the participant that they should engage in elaborative processes. If participants choose to engage in strategic associative processing to generate images or sentences to help them remember the words, then they must generate the semantic structure of the composite image and/or sentences themselves. In contrast, prose recall requires elaborative processing in order to follow the story, and the semantic structure (i.e., the story) is provided to the participant, rather than them having to generate it themselves. Thus, comparing prose recall to word-list learning performance provides a means of assessing the use of elaborative processing under these conditions.

Table 5-1 and Table 5-2 summarise previous findings regarding ecstasy-related performance on prose recall, with the studies divided between the tables according to the degree of specificity with which any differences between cohorts can be attributed to ecstasy, as distinct from the use of other drugs. The division of the studies was conducted using the same criteria used in the previous chapter for the review of studies regarding memory for lists of single unrelated words. Of the eleven studies listed in Table 5-1, only three found that ecstasy users had poorer prose recall than other drug users (Bhattachary & Powell, 2001; Morgan, 1999b; Morgan, McFie, Fleetwood, & Robinson, 2002). However, the strength of the evidence for an ecstasy-related deficit in all of those was strengthened by the presence of dose dependent relationships between prose recall and some aspect of ecstasy use. These findings are supported by two studies which found non-significant trends towards prose recall deficits in ecstasy users (Curran & Verheyden, 2003; Daumann, Fischermann, Pilatus et al., 2004), one of which also found a dose dependant relationship between prose recall and ecstasy use (Curran & Verheyden, 2003). In contrast, the remaining six studies found no significant difference between ecstasy users in comparison to other drug users (Dafters et al., 2004; Gouzoulis-Mayfrank et al., 2003; Halpern et al., 2004; Rodgers, 2000; Simon & Mattick, 2002; Thomasius et al., 2003). Studies that exercised relatively weaker control over the influence of other drugs also produced inconsistent results Table 5-2, with two of the for studies finding a deficit in ecstasy users (Hanson & Luciana, 2004; Ward et al., in press) and the remaining two studies not finding any significant difference
### Table 5-1 Prose recall test results in literature for studies with relatively strong control over the influence of drugs apart from ecstasy.

<table>
<thead>
<tr>
<th>Study</th>
<th>Immediate recall</th>
<th>Delayed recall</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Bhattachary &amp; Powell, 2001)</td>
<td>sig.+DD</td>
<td>sig.+DD</td>
<td></td>
</tr>
<tr>
<td>(Curran &amp; Verheyden, 2003)</td>
<td>No+DD</td>
<td>.ns trend+DD</td>
<td>pre-treatment results</td>
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<tr>
<td>(Dafters et al., 2004)</td>
<td>.ns</td>
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<tr>
<td>(Daumann, Fischermann, Pilatus et al., 2004)</td>
<td>.ns trend</td>
<td>.ns trend</td>
<td>Probed recall</td>
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<tr>
<td>(Gouzoulis-Mayfrank et al., 2003)</td>
<td>.ns</td>
<td>.ns</td>
<td>Probed recall</td>
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<tr>
<td>(Halpern et al., 2004)</td>
<td>.ns</td>
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</tr>
<tr>
<td>(Morgan, 1999b)</td>
<td>sig. (DD p=.071)</td>
<td>sig.</td>
<td></td>
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<tr>
<td>(Morgan et al., 2002)</td>
<td>sig.+DD</td>
<td>sig.+DD</td>
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<tr>
<td>(Rodgers, 2000)</td>
<td>.ns</td>
<td>.ns</td>
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<tr>
<td>(Simon &amp; Mattick, 2002)</td>
<td>.ns</td>
<td>.ns</td>
<td>Test scores not reported, but no significant deficits or DD on WMS-III auditory or visual memory index scores (immediate or delayed)</td>
</tr>
<tr>
<td>(Thomasius et al., 2003)</td>
<td>.ns</td>
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</tbody>
</table>

Note. **sig.** = significant deficit in ecstasy users compared to controls, p<.05. Unless otherwise stated, the findings shown are in comparison to a control group of drug users who don’t use ecstasy. **ns** = no significant difference between ecstasy users and controls. **ns#** = no difference between ecstasy users and other drug users, but significantly different from non-drug using controls. **DD** = Dose Dependence to some measure of ecstasy use.

between the experimental groups (Back-Madruga et al., 2003; Fox, Parrott et al., 2001). In summary, while dose dependent evidence for ecstasy-related deficits have been found in some studies, the findings are far from consistent across studies.

### 5.1.4 Aim: To increase the power of the study to detect an ecstasy-related deficit

One of the possible reasons for the performance difference between ecstasy users and controls not being statistically significant in the first memory study was that the experiment lacked sufficient power to detect a difference. This was supported by analysis that showed that the difference between the groups on stem-cued recall under full attention may have been statistically significant had 80 participants been tested in each group. Given that insufficient resources were available for the current series of studies to test a significantly larger number of participants, an attempt to increase the
The likelihood of significant effects being detected in the present study was made by using a sample of ecstasy users who had a higher average lifetime dose of ecstasy. Measures of ecstasy use vary widely between studies, and there is no clear threshold of ecstasy use which is associated with cognitive deficits. For example, explicit memory deficits have been detected with average lifetime doses as low as 35.8 tablets (SD=13.21) (Yip & Lee, 2005), and 50 tablets (SD unreported) (Morgan, 1999b). Others have found explicit deficits with lifetime doses of 93.4 tablets (SD=119.9) (Gouzoulis-Mayfrank et al., 2000) and 166 tablets (SD=171) (median=104 tablets, Hall, 2001; Ward et al., in press). However, the first memory study in the current thesis failed to detect a significant deficit in ecstasy users with a lifetime dose of 115.5 tablets (SD=130.4), while Gouzoulis-Mayfrank et al. (2003) did not detect significant explicit memory deficits in ecstasy users with a lifetime doses of 503.2 (SD=555.5). Despite the apparent lack of a clear threshold for ecstasy-related cognitive deficits, findings of dose dependent relationships in a number of the prose recall studies reviewed above, as well as some of the word-list learning studies reviewed in the previous chapter, support the general principle that larger differences between ecstasy users and controls are likely to be found as the average lifetime dose of the sample is increased.

**Table 5-2 Prose recall test results in literature for studies with relatively weak control over the influence of drugs apart from ecstasy (c.f. Table 5-1)**

<table>
<thead>
<tr>
<th></th>
<th>Immediate</th>
<th>Delayed</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Back-Madruga et al., 2003)</td>
<td>.ns</td>
<td>.ns</td>
<td></td>
</tr>
<tr>
<td>(Fox, Parrott et al., 2001)</td>
<td>.ns</td>
<td>.ns</td>
<td></td>
</tr>
<tr>
<td>(Ward et al., in press)</td>
<td>sig.</td>
<td>sig.</td>
<td>Good control over non-drug covariates</td>
</tr>
<tr>
<td>(Hanson &amp; Luciana, 2004)</td>
<td>sig.</td>
<td>sig.</td>
<td>In comparison to expected performance, according to a comparison between their vocabulary test performance and a normative sample Also used a weak method to control for other drug use.</td>
</tr>
</tbody>
</table>

*Note. Where possible, findings shown are in comparison to drug users who don’t use ecstasy. sig. = significant deficit, p<.05, in ecstasy users compared to controls. ns = no significant difference between ecstasy users and controls.*

Table 5-2 Prose recall test results in literature for studies with relatively weak control over the influence of drugs apart from ecstasy (c.f. Table 5-1)

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</tr>
</tbody>
</table>

*Note. Where possible, findings shown are in comparison to drug users who don’t use ecstasy. sig. = significant deficit, p<.05, in ecstasy users compared to controls. ns = no significant difference between ecstasy users and controls.*
5.2 Method

5.2.1 Participants

The participants were the same as those used for the visual perception study reported in Chapter 7. They were recruited using the methods, as well as inclusion and exclusion criteria, described for the previous memory study (Chapter 4). The only exception was that in order to increase the average lifetime dose of ecstasy, the minimum ecstasy use criterion was increased to 20 tablets. Also, efforts were made to attract drug users who had used a relatively higher lifetime dose of ecstasy compared to those in the first memory study. The planned testing of a cannabis-control group to help control for the use of other drugs was not conducted, due to the lack of any statistically significant differences between the ecstasy users and non-drug using controls.

Potentially important characteristics of each group are summarised in Table 5-3 (for more detail see Appendix A: Table A-2). In summary, sixty-four people were allocated to a cohort on the basis of their drug use history. The groups were closely matched on sex, age and level of education, but ecstasy users had a significantly lower average estimated IQ compared to controls. On personality and mental health measures, ecstasy users scored significantly higher than controls on the Experience Seeking and Disinhibition subscales of the Sensation Seeking Scale, and the Somatization and Obsessive-Compulsive subscales of the Brief Symptom Inventory, but not on the other subscales of those measures. The elevated reports of somatoform symptoms in ecstasy users is consistent with a large longitudinal study of 2462 teenagers which found somatoform disorders/syndromes were one of the most common mental disorders in teenagers who used ecstasy\(^\text{12}\) (Lieb, Schuetz, Pfister, von Sydow, & Wittchen, 2002).

A drug use history was collected from all participants using the semi-structured “time line” interview described in detail in Chapter 2 (section 2.6.2). Some incidental use of cannabis was tolerated in the control group due to the difficulty in finding people who had never tried cannabis (n=11, lifetime dose: mean=2.9 times (SD=2.67) [range 1-9 times]. Last use=mean 1591 days prior to testing (SD=1650) [range 127-6125 days]).

---

\(^{12}\) Interestingly, the study also found that 73% of the ecstasy users reported that the onset of the somatoform disorder/syndrome occurred prior to their first use of ecstasy.
Table 5-3 Selected characteristics of ecstasy users and controls in the second (follow-up) memory study

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=34)</th>
<th>Ecstasy (n=30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>sex (male %)</td>
<td>65</td>
<td>63</td>
<td>0.91</td>
</tr>
<tr>
<td>age (years)</td>
<td>Mean (SEM)</td>
<td>Mean (SEM)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>23.24 (0.69)</td>
<td>23.23 (0.68)</td>
<td>.ns</td>
</tr>
<tr>
<td>highest level of education attained¹</td>
<td>3.35 (0.09)</td>
<td>3.23 (0.10)</td>
<td>.ns</td>
</tr>
<tr>
<td>estimated IQ</td>
<td>107.35 (0.82)</td>
<td>104.15 (0.95)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Ecstasy
- lifetime dose (tablets): - vs 394.54 (123.01)
- abstinence (days): - vs 55.81 (15.94)

Alcohol
- lifetime dose (standard drinks): 1023 (226) vs 4846 (771) <.001
- maximum monthly dose: 27.0 (5.9) vs 122.4 (17.5) <.001
- maximum ever dose: 14.2 (1.54) vs 20.9 (1.40) 0.002

Sensation Seeking Scale
- experience seeking: 5.53 (0.31) vs 7.90 (0.23) <.001
- Disinhibition: 4.74 (0.37) vs 6.87 (0.35) <.001

Brief Symptom Inventory
- somatization: 47.21 (1.10) vs 51.60 (1.72) 0.03
- obsessive compulsive: 56.29 (1.37) vs 61.03 (1.73) 0.03

Note. SEM = Standard Error of the Mean. (.ns indicates p>.05). For more detail see Appendix A: Table A-2.

¹ 1=Year 10 (middle secondary education); 2=Year 12 (upper secondary education); 3=Bachelor undergraduate degree; 4=post-graduate degree

Ecstasy users exceeded controls on several alcohol use measures, including: a larger lifetime dose; a large maximum dose in a one month period; a larger maximum dose; and non-significant tend towards having used it more recently.

5.2.2 Experimental design

A retrospective cohort study design was used to examine the effects of ecstasy use on explicit memory, by comparing ecstasy users with non-drug using controls on five different memory tests. Three of the tests were designed to clarify the influence of level of cueing and number of learning trials on memory for lists of unrelated single words (the ‘follow-up’ memory tests). These tests were stem-cued recall and free recall with one learning trial, and stem-cued recall with two learning trials, which resembled the...
test of explicit memory under full attention in the previous chapter. The dependent variable for the stem-cued recall tests were the number of target word responses to the stems of studied words. The dependent variable for the free recall test was the number of studied words recalled.

The remaining two tests were standard neuropsychology tests selected for this study to evaluate some aspects of elaborative processing at study. The tests used were the Auditory Verbal Learning Task (AVLT) and prose recall tasks. The dependent variables for the AVLT were the number of words recalled on each of the immediate learning trials. The dependent variables for the prose recall task were the number of ‘story units’ correctly recalled for each story, according to the Wechsler criteria (Wechsler, 1997a).

5.2.3 Experimental procedure and stimuli

The sequence of events during the testing session is outlined in Table 5-4. The three follow-up stem-cued recall and free recall memory tests each consisted of a study phase, distractor phase and a test phase, as outlined in the following sections.

5.2.3.1 Follow-up tests: Study phase

The study phase of each follow-up memory tests consisted of reading aloud and learning a list of words. The study phase was immediately repeated without disruption in the stem-cued recall with two learning trials test.

The stimuli in all of the study phases consisted of one of the lists of target words used in the first memory study in the previous chapter that the participant had not previous been exposed to. Prior to the commencement of each test, participants were advised if they would see each word once or twice in the study phase. Also, if the participants had previously completed one or more stem recall tasks and were about to do a free recall task, they were advised that they would not be given the words stems during the test phase. Pilot testing had revealed that this was necessary to avoid anxiety-related performance deficits in participants when they did not receive the words stems they had learnt to expect in the test phase.
At study, each participant read aloud the list of words, which were presented on a PC at a rate of one word every 3.5 seconds in lower case letters by Inquisit software (Draine, 2003). The number of errors and omissions were recorded. Each participant received training and practice with the word-learning task before the first memory test commenced. The word-learning task was demonstrated with three trials using words from the practice list, and the participant was required to say each word aloud. Participant was instructed to keep their eyes fixated on the words while they were being displayed, to read each word aloud when it appeared, and to try to remember as many words as possible.

5.2.3.2 Follow-up tests: Distractor phase

Each distractor phase consisted of a computerised “face memory experiment”. The reasons for selecting this distractor task included that the task took the same fixed amount of time for all participants, and required sufficient concentration to effectively prohibit the continuous rehearsal of words between the study and test phases of the follow-up memory study. Also, the use of non-verbal stimuli minimised the opportunity...
for interference between the distractor phase and experimental stimuli. The “experiment” comprised a go/no-go task in which participants studied a series of faces presented at a rate of one face every five seconds for a total of three minutes (a total of 36 face exposures). It was implemented on the same computer and software used for the study phase, such that it started immediately after the study phase was completed. The face for each presentation was randomly selected with replacement from a set of 16 grey-scale photographs of male faces with neutral expressions. Participants were required to press a key if they thought a face had been displayed previously. A different set of face images was used for the distractor phase in each memory experiment. The results of this distractor task are not reported because the design of the “experiment” was not sufficiently robust to make valid comparisons between cohorts.

5.2.3.3 Follow-up tests: Test Phase

The test phase consisted of either a stem-cued recall task or a free recall task. For the stem-cued recall task, participants were given a sheet of paper containing a randomly ordered list of three-letter word stems corresponding to the 12 studied words (e.g., “cal” for the word “calendar”). Participants were instructed to complete as many stems as they could with words from the study list. Stems from unstudied word lists were not included. They were considered unnecessary in the present study because the baseline rates obtained in the previous study did not differ significantly between conditions and cohorts. For the free recall task, participants were given a sheet of paper containing a row of 12 vertical dots (one for each word in the study phase). Participants were instructed to write down as many words as they could remember from the study list.

5.2.3.4 Prose recall and Auditory Verbal List Learning (AVLT) tests

Participants were also tested on two standard neuropsychological long-term memory tests, namely a prose recall task (Wechsler Memory Scales-III (WMS-III) Logical Memory I as described in Wechsler, 1997a) and a word list learning test (Auditory Verbal Learning Test using 'List A' as described in Lezak et al., 2004). For the prose recall task, Story A was read aloud by the experimenter. The participant was then immediately asked to recall as much of the story as they could. This procedure was then repeated two more times, but using Story B. For the AVLT test, the list of words was read aloud by the experimenter at a rate of approximately one word per second in a monotone voice. The participant was then asked to recall as many of the words they
could, in any order. Once they had exhausted their responses, the learning and testing procedure was repeated a further four times (make a total of five repetitions). Prior to commencing these tests, verbal permission was obtained from each participant to make an audio recording of their responses in the prose recall and AVLT tests. These recordings were only used if the experimenter had reason to believe they may have missed or misunderstood one or more responses. No delay-recall tests were conducted.

5.3 Results

5.3.1 Follow-up stem-cued recall tests

The data from the three follow-up stem-cued recall and free recall tests consisted of the number of words correctly recalled from the study list for each type of memory test. The mean performance on each test was calculated and is displayed in Figure 5.1 as a function of cohort (ecstasy users, controls). A mixed-model ANOVA analysis of test type (stem-cued recall following one learning trial, stem-cued recall following learning trials, and free recall) and cohort (ecstasy users, controls) revealed that the interaction between test type and cohort was not significant, $F<1$, $\text{MSE}=1.95$, $p>.05$. This suggests that the number of learning trials and the use of a stem-cued recall task did not have a significantly different affect on the performance of ecstasy users compared to controls. The analysis also revealed that there was no main effect of cohort, $F<1$, $\text{MSE}=11305$, $p>.05$, which indicates that a history of ecstasy use was not associated with poorer explicit memory performance. Calculations revealed that the power of the current study to detect an effect of the sizes observed for each test was 0.17 for one-trial learning, 0.10 for two-trial learning, 0.19 for free-recall, which corresponds to probability of a Type II error of 0.83, 0.90, and 0.81 respectively.\(^\text{13}\)

As expected, the main effect of test type was highly significant, $F(2,124)=142.68$, $\text{MSE}=1.95$, $p<.001$. Collapsed across cohort, repeated measures t-tests revealed that compared to stem-cued recall with one trial learning, participants performed better on the stem-cued recall with two learning trials, $t(63)=6.84$, $p<.001$, and worse on free recall.

\(^\text{13}\) Further calculations revealed that a difference of the magnitude obtained in the one-trial learning task may have been statistically significant had 121 participants been tested in each group. For the two trial learning task 1054 participants would have been required in each group, and for the free recall task 213 participants would have been required in each group.
5.3.2 Standard clinical neuropsychological tests of long-term memory

5.3.2.1 Prose recall

The prose recall data consisted of the number of ‘story units’ correctly recalled, according to the Wechsler criteria (Wechsler, 1997a). The mean performance on each test was calculated and is displayed in Figure 5.2 as a function of cohort (ecstasy users and controls). A mixed-model ANOVA analysis of test type (Story A, Story B1, Story B2) and cohort (ecstasy users, controls) revealed that there was no significant interaction between test type and cohort, $F(2,124)=1.16, \text{MSE}=5.89, p=.31$, and no significant main effect of cohort, $F(1,62)=1.43, \text{MSE}=33.51, p=.24$, respectively.
Follow-up contrasts revealed that even when the cohorts were compared on each test separately, that the difference in recall between controls and ecstasy users did not reach statistical significance, Story A, $t(62)=1.62$, $p=.11$, Story B1, $t(62)=.62$, $p=.53$, Story B2, $t(62)=.81$, $p=.42$.

5.3.2.2 Word list learning (AVLT)

The AVLT data consisted of the number of words correctly recalled following each repetition of the study list. The mean performance on each test was calculated and is displayed in Figure 5.3 as a function of trial (1st...5th) and cohort (ecstasy users and controls). Inspection of Figure 5.3 suggests that in general ecstasy users performed slightly worse than controls, especially on the 1st and 3rd trials. A mixed-model ANOVA analysis of trial (1st...5th) and cohort (ecstasy users, controls) revealed that the interaction between trial and cohort was not statistically significant, $F(4,248)<1$, $MSE=2.42$, $p=.41$, which indicates that the performance of ecstasy users did not vary compared to controls as a function of how many trials had been completed. In contrast, the main effect of cohort was significant, $F(1,62)=4.41$, $MSE=13.23$, $p=.04$, which suggests that there may have been an overall effect of ecstasy use on word list recall.
expected, the main effect of trial was highly significant, $F(4,248)=199.03$, $\text{MSE}=2.42$, $p<.001$. Repeated measures t-tests confirmed that recall significantly improved between the 1st and 5th trials for ecstasy users and controls, $t(29)=15.15$, $p<.001$, $t(33)=12.51$, $p<.001$, respectively.

In order to evaluate the specificity of the apparent effect of ecstasy on recall, bivariate correlations were conducted between the sum of AVLT recall over all trials (‘total AVLT recall’) and possible covariates, including estimate IQ, age, Brief Symptom Inventory indexes and sub-scale scores, and Sensation Seeking Scale (SSS) total and subscale scores. The correlations for which $p<.10$ are shown in Table 5-5.

The influence of these covariates was evaluated using a backward elimination procedure in a repeated measures ANCOVA analysis of trial (1st…5th) and cohort (ecstasy users, controls). The only significant covariate to remain in the model was estimated IQ, such that there was a significant main effect of estimated IQ, $F(1,61)=10.141$, $\text{MSE}=11.53$, $p=.002$. When this was taken into account, the previously reported main effect of cohort was no longer significant, $F(1,61)=1.310$, $\text{MSE}=11.53$, $p=.26$. In addition, further bivariate correlations showed that there was no indication of a dose dependant
Table 5-5 Covariates of the total AVLT score, \( p < .10 \)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>( r(64) )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>estimated IQ</td>
<td>.427</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>SSS Disinhibition</td>
<td>.249</td>
<td>.047</td>
</tr>
<tr>
<td>SSS Experience Seeking</td>
<td>-.217</td>
<td>.086</td>
</tr>
<tr>
<td>BSI Depression</td>
<td>.212</td>
<td>.093</td>
</tr>
<tr>
<td>BSI Phobia</td>
<td>.229</td>
<td>.068</td>
</tr>
</tbody>
</table>

relationship between any ecstasy use measure and total AVLT recall, and no significant dose dependant relationships between total AVLT recall and the use of any other drugs measured. In combination these results suggests that apparent difference between the ecstasy users and controls in Figure 5.3 is best accounted for by estimated IQ rather than the use of illicit drugs.

### 5.4 Discussion

In order to clarify the findings of the first memory study, two aims of the present study were to evaluate the influence of the number of learning trials at study and the level of cueing at test, on the difference between ecstasy users and controls on explicit memory for lists of unrelated words (the ‘follow-up’ memory tests). In order to extend the findings of the first memory test, a third aim of the present study was to test elaborative and associative processing in the current sample of ecstasy users using standard neuropsychological tests. In order to increase the likelihood of detecting significant cognitive deficits, the sample of ecstasy users who were accepted into the present study had used a larger average lifetime dose of ecstasy (i.e., they were ‘heavier ecstasy users’) compared to the ecstasy users in the first memory study.

#### 5.4.1 Summary of findings in the present study

Overall, in the present study there were no statistically significant deficits in long-term explicit memory for lists of single unrelated words, or prose, once significant covariates were taken into account. In particular, the follow-up memory tests showed that there was no significant difference between ecstasy users and controls regardless of the level of cueing at test (stem-cued recall v. free recall) or the number of learning trials (one v. two). On the standard neuropsychological tests, initial analysis showed that average recall on the AVLT was significantly lower for ecstasy users compared to controls, but that apparent deficit was no longer significant once estimated IQ was taken into
account. For prose recall, there was a tendency for ecstasy users to recall less story items than controls, but this effect did not reach statistical significance. All of these results were obtained in a sample of ecstasy users who had used more ecstasy, over a longer period of time, with a higher maximum monthly dose than the ecstasy users in the previous study.

5.4.2 Interpretation of the combined findings from the present and previous memory studies in the current thesis

The interpretation of the findings from the present and previous memory studies relies on the rationale for the selection and design of the tests used. As outlined in the previous chapters, published studies have examined long-term memory using either word list learning and/or prose recall tasks, and have either found no statistically significant deficits in ecstasy users, or where deficits have been found they are generally quite small. However, such studies invariably used standard neuropsychological and clinical research tests that confound the performance of different components of memory. The approach taken in the current series of studies was that a more consistent pattern of results may emerge if each component of memory was considered separately.

The follow-up memory tests in the current chapter, as well as the explicit memory tests in the previous chapter, were designed to be as specific as possible to long-term explicit memory. Even using these more specific measures, there was no evidence of explicit memory deficits for lists of single unrelated words in the current samples of ecstasy users. In particular, even though the present study tested ecstasy users with a relatively high average lifetime dose of ecstasy, the results of the stem-cued recall task following two learning trials did not reproduce the non-significant trend on a very similar task (‘explicit memory under full attention’) in the first memory study. Furthermore, analysis suggested that it was unlikely that significant deficits would have been detected even if three or four times as many participants had been tested. It is clear from these results that, in the current samples of ecstasy users at least, there was no evidence of significant ecstasy-related deficits on long-term explicit memory for lists of single unrelated words.

Another aspect of the follow-up memory tests in the present study was that they were designed to be as specific as possible in a cognitive test to hippocampal functioning. This was achieved by restricting the use of frontal lobe processing as much as possible during both the study and distractor phases of the tests. In light of this, the lack of
significant deficits in ecstasy users on these tests calls into question whether recreational ecstasy use causes significant long-term memory deficits that are specifically related to changes in hippocampal functioning. In addition, the finding in the first study of intact implicit memory, which is thought to largely rely on information stored in the sensory areas of the brain, suggests that any ecstasy-related long-term memory deficits do not specifically originate from damage to the sensory areas of the brain either. Therefore, if long-term memory deficits do exist in the current samples of ecstasy users – noting that such deficits have not yet been detected in this thesis – then the results obtained so far suggest that either those deficits are specifically related to some area of the brain other than the hippocampus or sensory areas, or else emerge from generalised changes in neural functioning throughout the brain without being specifically related to any one brain region.

The frontal lobes are another brain region that could underlie the ecstasy-related long-term memory deficits reported in some published studies based on standard neuropsychological tests. Amongst other functions, the frontal lobes are known to be critically involved in elaborative and associative processing. The two tests that have been used to show long-term memory deficits in published studies, i.e., AVLT and prose recall, both allow greater opportunity for elaborative and/or associative processing at study than the follow-up memory tasks in the current study, and the similar stem-cued recall tasks in the first memory study. As outlined in the introduction to the present study, this is because in the immediate memory phase of the AVLT the attention of participants remains constantly on a single list of words throughout the successive immediate study and test phases, and in the prose recall task elaborative processing is required to follow the plot of the story.

If deficits had been found on the AVLT and prose recall tasks, but not on the follow-up memory studies, that pattern of results would have suggested that long-term explicit memory deficits were related to the elaborative processing requirements of the AVLT and prose recall tasks. However, in the present study, neither the AVLT nor prose recall tasks revealed significant explicit memory deficits in the current sample of ecstasy users once covariates were taken into account. These non-significant results are more difficult to interpret. Given that the ecstasy users appeared to have intact performance on long-term explicit memory tasks related to hippocampal and sensory areas of the brain, one plausible explanation of these results is that the ecstasy users also did not have
significant deficits in frontal lobe elaborative processing, as revealed by these tasks. With regard to the AVLT, the use of elaborative processing in that task is optional. However, since the AVLT does not include any direct measures of elaborative processing, it is not possible to know the extent to which participants actually engaged in such processing. Therefore, another possible explanation for the lack of AVLT deficits in the present study is that neither the controls nor ecstasy users engaged in a significant amount of strategic elaborative processing, and consequently that the results cannot reveal any deficits in elaborative processes. It is not possible to tell from the present study which of these possible explanations of the non-significant difference between the groups on the AVLT is the correct interpretation.

The use of elaborative processing in tests of explicit memory in ecstasy users was more directly tested in the present study by the prose recall task. In contrast to the AVLT, prose recall requires elaborative processing at study to follow the story. In light of this, the prose recall results suggest that even when elaborative processing is required at study, that the current sample of ecstasy users still did not appear to have long-term explicit memory deficits compared to controls. However, in prose recall the semantic structure used in elaborative processing is provided within the stimuli itself (i.e., the ‘story’). Therefore, the possibility remains that explicit memory deficits in ecstasy users may be revealed in tasks that require elaborative processing at study, and also require participants to generate a semantic structure for the stimulus items.

The possibility that ecstasy-related explicit memory deficits may be related to the generation of semantic structures was tested in the third and final memory study in this thesis, reported in the following chapter. The first memory task completed by participants in that study measures memory for a list of semantically related single words, using a test that includes a measure of elaborative processing. The remaining memory tasks are all list-learning tests for multi-component items, which require the use of elaborative processing to generate a semantic structure for the stimuli at study, and which vary in the level of cognitive demands at study.
Chapter 6. Ecstasy-related effects on associative processing in list learning memory tests using multi-component items

6.1 Introduction to the present study

The results obtained in the previous memory studies in this thesis suggest that, in tests designed to limit the use of frontal lobe processes, ecstasy-related deficits in long-term memory are not revealed using lists of single unrelated words. In the previous chapter, the focus of this thesis was turned to the possibility that long-term explicit memory deficits obtained by some other researches may reflect ecstasy-related deficits in elaborative processing, rather than deficits in the retention of long-term memories per se. In relation to this possibility, the results suggested that ecstasy use was not associated with explicit memory deficits on a memory task in which the semantic structure was provided at study (i.e., prose recall). However, the results regarding the strategic use of elaborative processing (i.e., AVLT) in a list learning task could not be interpreted because it was not possible to tell from the results if the ecstasy users or controls had elected to use elaborative processing.

The aim of the present study was to clarify and extend the findings of the previous study about the possible role of elaborative processing deficits in long-term explicit memory performance in ecstasy users. This was achieved using a number of tests that differed in their associative processing demands, mainly based on lists of multi-component items. The tests used include the California Verbal Learning Test (CVLT, Delis et al., 1987), Verbal Paired Associates (from Wechsler Memory Scales III (WMS-III), Wechsler, 1997a), Visual Paired Associates (from Wechsler Memory Scales - Revised (WMS-R), Wechsler, 1987), and a novel test developed specifically for this study called Verbal Triplet Associates. These tests are outlined in the following sections, with particular emphasis on the components and processes of memory which they reveal in the context of the present study, as well as literature reviews of the performance of ecstasy users on those tests.

6.1.1 The California Verbal Learning Test

The California Verbal Learning Test (CVLT, Delis et al., 1987) is a test of explicit memory for a list of single words, much like the AVLT used in the previous chapter,
except that in the CVLT the words are drawn from four distinct semantic categories (clothing, tools, fruit, spices-and-herbs). The test commences with five immediate trials, each of which commences with the experimenter reading aloud a single list of 16 words, immediately followed by a verbal free-recall test of the studied words. No reference is made to the semantic categories represented in the word list at this stage\textsuperscript{14}. An interference trial is then conducted using a different word list, which is based on two of the original semantic categories (fruit, spices-and-herbs) and two new categories (appliances, fish). Following a free recall test on the interference trial word list, two ‘short delayed’ tests of the participants recall of the original word list are conducted. The first of these is a verbal free recall test. The second is a category-cued recall test in which the experimenter names each of the semantic categories in turn, and for each category the participant responds with all of the words they can recall from that category. This is the first reference made by the experimenter to the presence of the semantic categories in the studied word list. Following a filled delay of approximately 20-30 minutes, without any further exposure to the word list, the participant is again tested on their free- and category-cued recall of the original word list, as well as a verbal recognition test for the words from the original word list amongst distracters.

Similar to the AVLT, the CVLT does not require the use of associative processing at study or test, but associative processing can be used strategically to combine the words into meaningful sentences or images, thereby effectively reducing the number of individual items that need to be remembered. This strategic use of associative processing is made easier in the CVLT compared to the AVLT, because all of the studied words belong to one of four distinct semantic categories. However, since no reference is made to the categories until after the learning trials have been completed, it is up to the participant to notice and use the categories if they wish. Of particular interest to the present study is that, unlike the AVLT, the CVLT includes a measure of the degree to which participants group words by semantic category at test. This measure, called the semantic clustering index, provides an indication of the extent to which the participants have noticed and used the categories.

\textsuperscript{14} However, it has been shown that providing explicit instructions regarding categories prior to learning had no significant effect on recall within each trial, or on the semantic cluster ratios in controls (Shear, Wells, & Brock, 2000; van Spaendonck, Berger, Horstink, Borm, & Cools, 1996)
At the time of writing, only two ecstasy studies could be identified which applied the CVLT as a memory performance measure. However, neither of the studies reported the delayed recall results or the semantic clustering index. Semple, Ebmeier, Glabus, O'Carroll, and Johnstone (1999) reported an overall finding that ecstasy users performed significantly worse than controls who had not used ecstasy, but who had similar use of other drugs. However, the authors did not report the results of any specific memory measure or the semantic clustering index. In a separate study, Halpern et al (2004) compared 23 ecstasy users who had minimal use of other drugs to 16 non-drug using controls from the same ‘rave’ population. Ecstasy users tended to have lower recall on the immediate trials, especially those who had used more than 60 tablets in their lifetime (‘heavy ecstasy users’, \(n=11\)), but these deficits did not reach statistical significance. The lack of significant deficits in this study may have been due to a lack of statistical power because of the small number of participants in each group. Furthermore, this study did not test short- or long- delayed recall, or report results of the semantic clustering index. So, while these studies generally provide some evidence for ecstasy-related deficits on the CVLT, the main variables of theoretical interest in the present study have not yet been reported in literature.

In the present study, if ecstasy users have a significantly lower CVLT semantic clustering index score compared to controls, and also recall fewer words, this would suggest that they utilised elaborative processing less than controls, and gained less benefit from the presence of the semantic categories in the word list. Alternatively, if ecstasy users have significantly lower semantic clustering index scores, but are not significantly different on recall, this would suggest that ecstasy users have been able to achieve the same recall performance as controls using strategies other than elaborative processing, such as rote learning. Finally, if the groups do not differ on the semantic clustering index, this would suggest that ecstasy use is not associated with a decline in elaborative processing on memory for lists or related words.

6.1.2 The Verbal Paired Associates test

The present study included three learning tasks for a list of multi-component items. The first of these was the Verbal Paired Associates task (Wechsler, 1997a) in which the stimuli consists of pairs of words that would not normally be associated (e.g., Truck-Arrow). The task commences with four immediate recall trials, followed by a delayed
cued-recall test. Each immediate learning trial starts with a study phase in which the experimenter reads aloud a list of eight word-pairs. In the subsequent cued-recall task, the experimenter reads aloud the first word from each word-pair, and the participant verbally responds with the paired word from the study phase. To inhibit the utility of rote learning the second words in each pair, the order to the word-pairs at study and the word-cues at test are varied for each trial. After a filled delay of approximately 20-30 minutes, the delayed cued-recall test is repeated without any further exposure to the study list.

In contrast to the list learning explicit memory tasks conducted and outlined in this thesis so far, the Verbal Paired Associates task specifically requires the use of elaborative processing (in this case associative processing) at study and test in order to store and recall the word-pairs. The prose recall task reported in the previous memory study also required elaborative processing at study, however, in that test the semantic structure of the stimuli is supplied at study as part of the stimuli itself (i.e., the story). In contrast, in the Verbal Paired Associates test the semantic structure of each word-pair must be generated by the participant themselves.

Previous studies that have applied a list-learning task for word-pairs are listed in Table 6-1. For immediate recall, most of the studies only considered a composite recall score rather than reporting performance on individual trials (Bolla et al., 1998; Daumann, Fischermann, Pilatus et al., 2004; Gouzoulis-Mayfrank et al., 2003; Rodgers, 2000; Simon & Mattick, 2002). None of these studies found a significant deficit in ecstasy users compared to controls on immediate recall performance. This possibly reflects a general limitation of the Verbal Paired Associates test when used in research on participants who do not exhibit gross cognitive deficits, such as ecstasy users and non-drug using controls. As the performance of participants improves over successive trials, the opportunity for them to further improve is curtailed by the upper performance limit (i.e., a marked 'ceiling' effect. e.g., Ward et al., in press). On composite measures of immediate recall, this causes an under-estimation of the overall difference in performance between the groups, thus decreasing the likelihood of a statistically significant group effect being detected. Therefore, it is unsurprising that all of the studies in Table 6-1 that used a composite immediate recall score failed to detect any significant difference between the performance of ecstasy users and controls.
In contrast, two of the studies in Table 6-1 reported results for the first trial in isolation (Montgomery et al., 2005; Ward et al., in press) both found a significant recall deficit in ecstasy users on that trial. When considered with the results for composite immediate recall scores outlined above, these findings suggest that ecstasy users initially recall fewer word-pairs compared to controls, at least on the first immediate trial, but that the difference between the groups on subsequent trials becomes non-significant as the performance of the participants approach ceiling.

Turning to the delayed recall findings on word-pair list learning studies in Table 6-1, the pattern of results is less consistent across studies. Two studies have found significant differences on delayed recall compared to controls who had used other drugs (Gouzoulis-Mayfrank et al., 2003; Rodgers, 2000). These findings are supported by two other studies, one of which reported a non-significant trend towards a deficit in ecstasy
users in a study with a small sample size (n = 13) (Daumann, Fischermann, Pilatus et al., 2004), and one of which found that delayed recall was correlated with the average monthly dose of ecstasy, but also reported that there was no significant difference between the groups on the number of word-pairs recalled (Bolla et al., 1998). However, given the ceiling effects in the immediate trials outlined above, the failure of this study, as well as the remaining studies in Table 6-1, to detect significant differences in delayed recall between the groups is also unsurprising.

In the present study, the results of each immediate trial is reported in order to gather further evidence regarding the possibility that ecstasy users have reliable immediate cued-recall deficits for word pairs, at least after the first learning trial. If the ecstasy users do have deficits on the first trial, this would also confirm the existence of long-term explicit memory deficits in a sample of ecstasy users that had been drawn from the same population as those who participated in the other studies in this thesis.

### 6.1.3 The Visual Paired Associates test

The Visual Paired Associates test is another list-learning test for pairs of items, which was used to gather more evidence regarding the effects of ecstasy use on elaborative processing in explicit memory tasks. It is similar to the Verbal Paired Associates test, except that the stimuli consists of six pairs of visual items. Each paired item consists of one simple line diagram and one colour square. At study, in each of the four immediate learning trials, the experimenter presents each pair of items in turn. At test, the experimenter then displays a card showing all of the coloured squares. The experimenter then shows the participant the line diagrams one at a time, and for each diagram asks the participant to point to the coloured square that it was associated with it at study.

The validity of the Visual Paired Associates test as a test of visual memory has been questioned because of the tendency for participants to verbally encode the line diagrams used, and because the test has been shown to be no more sensitive to lesions in the visual centres in the brain than verbal tests (Loring, 1989; Tulsky, Chiaravalloti, Palmer, & Chelune, 2003; Wechsler, 1997b). However, for the purposes of the present study, the Visual Paired Associates task is still a valid test of explicit memory for multi-component items that require associative processing at study. Also, this test enabled further evidence to be gathered regarding associative processing in ecstasy users,
without significantly increasing any interference between tests, which may have occurred had further tests based on word-stimuli been used.

At the time of writing, only two ecstasy studies could be identified which had administered Visual Paired Associates. Rodgers (2000) found a deficit in ecstasy users on delayed recall, but not immediate recall, compared to both cannabis-controls and non-drug using controls. In contrast, Bolla et al. (1998) did not find any significant group deficits in ecstasy users on either immediate or delayed recall compared to cannabis-controls, despite finding significant dose dependent effects between the average monthly ecstasy use and both immediate and delayed recall. These studies suggest that ecstasy use is associated with Visual Paired Associate delayed performance, and possibly immediate performance, but that this does not necessarily lead to a statistically significant decrement in the performance of ecstasy users. However, the pattern of results is inconsistent across the two studies that have reported administering the test.

6.1.4 The Verbal Triplet Associates tests

The Verbal Triplet Associates test is a novel test, developed specifically for this study, to overcome the ceiling effect in the Verbal Paired Associates task. For the purposes of the present study, the ceiling effect on that test substantially reduces the likelihood of detecting statistically significant performance deficits on immediate trials 2 to 4. Also, the ceiling effect reduces the learning rate of each group, especially for the higher performing groups, such that a valid investigation of the comparative learning rates cannot be conducted. The Verbal Triplet Associates test was developed to overcome these problems by significantly increasing the cognitive demands at study, thereby lowering overall performance and eliminating the ceiling effect in earlier trials, and significantly reducing it in later trials.

The Verbal Triplet Associates task is similar to the Verbal Paired Associates task, except the multi-component items are triplets of words rather than word-pairs, and less time is provided to remember each item (approximately 1.5 seconds per word-triplet v. approximately 2 seconds per word-pair in Verbal Paired Associates). Also the list length is two items longer (10 triplets v. 8 word-pairs in Verbal Paired Associates), with one additional immediate trial (5 immediate trials v. 4 in Verbal Paired Associates). With these alterations, relatively few participants were able to achieve perfect scores. This
enabled for the first time a valid investigation of the difference between ecstasy users and controls across multiple trials, in a test that requires participants to generate semantic structures using associative processing at study.

Some research suggests that reliable ecstasy-related cognitive deficits may only emerge under relatively high cognitive demand conditions, such as those produced in the Verbal Triplet Associates task, while performance under low cognitive demands may remain relatively intact. In rats, neuroendocrine challenge studies have found that the behavioural consequences of the inhibition of some types of 5-HT receptors are only apparent in memory tasks when cognitive demands are high (outlined in Buhot, 1997; Buhot, Martin, & Segu, 2000). In humans, Jacobsen, Mencl, Pugh, Skudlarski, and Krystal, (2004) used fMRI to examine hippocampal functioning in ecstasy users while they were engaged in a working memory task. They found that correlations between ecstasy use and hippocampal functioning were only significant under relatively high cognitive demand conditions. In combination, these studies raise the possibility that reliable explicit memory deficits in humans may also emerge under high cognitive load conditions. If this is the case, then the Verbal Triplet Associates task may be a more reliable instrument for detecting ecstasy-related deficits than standard neuropsychological memory tests.

In accordance with the literature for the Verbal Paired Associates test, it was expected that ecstasy users in the present study would show a deficit on at least the first learning trial of the Verbal Triplet Associates task. This would again add further evidence of long-term explicit memory deficits in the population from which the samples of ecstasy users in this thesis were drawn. In addition, the relative lack of ceiling effects obtained in the first three trials of the Verbal Triplet Associates task enabled - for the first time on an association task - an evaluation of the relative rate of improvement of ecstasy users and controls over successive trials in the absence of ceiling effects.

### 6.1.5 The present study

The present study compared the performance of ecstasy users to controls on the above memory tests. The results were then interpreted in light of both the previous findings in the current thesis and published literature, and also with regard to the different opportunities and requirements for associative processing across the various tasks. For example, a deficit in ecstasy users on the CVLT semantic clustering index, but not on
any of the associative tasks, would suggest that ecstasy use is associated with deficits in the strategic use of associative processing rather than when associative processing is required by the task. Alternatively, deficits on all or most tasks in the present study, in light of intact recall on the various list learning tasks for single unrelated words, as well as prose recall, in the previous chapters, would suggest a general ecstasy-related deterioration in associative processing, but not in other elaborative processes such as those used in prose recall. Finally, the results of the novel Verbal Triplet Associates task may provide evidence regarding the effects of ecstasy on learning rate in associative tasks.

In contrast to the previous studies, the immediate phase of learning tasks is of specific interest in the present study. The emphasis in the previous studies, at least in part, was to expose behavioural consequences of ecstasy-related damage to the hippocampus. Thus, emphasis was placed on tests of delayed recall, which were designed to severely limit the role of frontal lobe processes in recall performance. In contrast, the emphasis of the present study is specifically on the involvement of frontal lobe processes – in this case associative processing. Consequently, immediate recall performance is now of particular interest. However, the delayed conditions of the standard neuropsychological tests used were still administered (CVLT; Verbal- and Visual-Paired Associates) to provide further evidence regarding long-term memory functioning.

6.2 Method

6.2.1 Participants

Participants were recruited using the methods as used for the previous memory studies (Chapters 4 and 5), and according to the same inclusion and exclusion criteria. The only exception was that the minimum ecstasy use criterion was increased to 75 tablets. However, only four out of the 32 ecstasy users reported a lifetime dose of less than 100 tablets. In contrast to the previous studies, significant differences between ecstasy users and non-drug using controls were detected on the main variables of interest, and therefore the planned testing of a cannabis-control group was conducted to aid in the assessment of the specificity of the results to ecstasy. The cannabis-control group met the same inclusion criteria as other cohorts, except that they were required to have never binged on, or regularly used ecstasy, and to have used cannabis on at least ten separate occasions, including at least once in the past six months. Some incidental use of ecstasy
was tolerated in the cannabis-control cohort due to the difficulty in finding drug users who had never tried ecstasy (details below).

6.2.1.1 Demographic, personality, and mental health characteristics

Potentially important demographic, personality, and mental health characteristics of each group are summarised in Table 6-2 (for more details see Appendix A: Table A-3)

In summary, ninety-seven people were allocated to a cohort on the basis of their drug use history. Of these participants, 19 ecstasy users and 16 non-drug using controls had also participated in the previous study (Chapter 5). A comparison between these participants and those who participated in only one of the studies is conducted in the results section of this chapter. In the present study, the ecstasy users and non-drug using control groups were closely matched on sex and age, but there were non-significant trends towards ecstasy users having a lower estimated IQ, $t(63)=0.94$, $p=0.07$, and a lower level of education, $t(63)=0.94$, $p=0.07$, compared to non-drug using controls.

On the personality measure, namely the Sensation Seeking Scale (Zuckerman, 1994), the three cohorts had distinctly different profiles. The cohorts did not differ significantly on the Thrill and Adventure subscale, although cannabis-controls tended to score slightly lower than ecstasy users, $t(64)=0.92$, $p=.10$, and non-drug using controls, $t(63)=.90$, $p=.12$. The drug using cohorts (i.e., cannabis-controls and ecstasy users) both scored significantly higher than non-drug using controls on the Experience Seeking subscale, but there was no significant difference between the different drug using cohorts. However, the Disinhibition subscale did distinguish between all three cohorts, such that ecstasy users had the highest level of Disinhibition, cannabis-controls had a relatively moderate level of Disinhibition, whereas non-drug using controls had the lowest level of Disinhibition (see Table 6-2).

With regard to mental health, the Brief Symptom Inventory (BSI, Derogatis, 1993) indicated that ecstasy users had significantly higher scores on the Anxiety sub-scale, as well scores on the Global Severity Index and Positive Symptom Total index, and a non-significant trend towards higher scores on the Depression sub-scale compared to non-drug using controls, $t(63)=0.93$, $p=0.09$. Ecstasy users and cannabis-controls did not differ significantly on any BSI index or subscale, except for a non-significant trend
Table 6-2 Selected characteristics of ecstasy users and controls in the third memory study

<table>
<thead>
<tr>
<th></th>
<th>Non-drug using Controls (n=33)</th>
<th>Cannabis-Controls (n=32)</th>
<th>Ecstasy (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>sex (male %)</td>
<td>64</td>
<td>66</td>
<td>66</td>
</tr>
<tr>
<td>age (years)</td>
<td>Mean (SEM)</td>
<td>Mean (SEM)</td>
<td>Mean (SEM)</td>
</tr>
<tr>
<td>highest level of education attained&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.42 (0.09)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3.22 (0.09)</td>
<td>3.16 (0.12)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>estimated IQ</td>
<td>106.46 (0.89)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>106.80 (1.01)</td>
<td>104.11 (0.93)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Brief Symptom Inventory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Global Severity Index</td>
<td>50.03 (1.84)&lt;sup&gt;Ep&lt;/sup&gt;</td>
<td>54.75 (2.04)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>55.94 (2.04)&lt;sup&gt;C&lt;/sup&gt;</td>
</tr>
<tr>
<td>Positive Symptom Total</td>
<td>51.94 (1.72)&lt;sup&gt;E&lt;/sup&gt;</td>
<td>55.75 (2.01)</td>
<td>57.00 (1.53)&lt;sup&gt;C&lt;/sup&gt;</td>
</tr>
<tr>
<td>Depression</td>
<td>52.55 (1.52)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>54.78 (2.04)</td>
<td>56.69 (1.86)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Anxiety</td>
<td>49.52 (1.68)&lt;sup&gt;E&lt;/sup&gt;</td>
<td>53.34 (2.03)</td>
<td>55.25 (1.82)&lt;sup&gt;C&lt;/sup&gt;</td>
</tr>
<tr>
<td>Paranoid Ideation</td>
<td>48.24 (1.53)&lt;sup&gt;E&lt;/sup&gt;</td>
<td>50.91 (2.08)</td>
<td>53.81 (1.76)&lt;sup&gt;C&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Sensation Seeking Scale</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>thrill and adventure</td>
<td>7.27 (0.34)</td>
<td>6.38 (0.46)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>7.34 (0.35)&lt;sup&gt;P&lt;/sup&gt;</td>
</tr>
<tr>
<td>experience seeking</td>
<td>5.64 (0.31)&lt;sup&gt;Ep&lt;/sup&gt;</td>
<td>7.72 (0.26)&lt;sup&gt;C&lt;/sup&gt;</td>
<td>7.19 (0.29)&lt;sup&gt;C&lt;/sup&gt;</td>
</tr>
<tr>
<td>disinhibition</td>
<td>4.03 (0.39)&lt;sup&gt;Ep&lt;/sup&gt;</td>
<td>5.81 (0.26)&lt;sup&gt;CE&lt;/sup&gt;</td>
<td>6.81 (0.33)&lt;sup&gt;EP&lt;/sup&gt;</td>
</tr>
<tr>
<td>boredom susceptibility</td>
<td>3.21 (0.32)&lt;sup&gt;e&lt;/sup&gt;</td>
<td>3.38 (0.34)</td>
<td>4.13 (0.36)&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Note. SEM = Standard Error of the Mean. (.ns indicates p>.05). For more detail see Appendix A: Table A-3.

<sup>a</sup> 1=Year 10 (middle secondary education); 2=Year 12 (upper secondary education); 3=Bachelor undergraduate degree; 4=post-graduate degree

<sup>c</sup> p<.05 compared to non-drug using controls; <sup>Ep</sup> p<.05 compared to cannabis-controls; <sup>E</sup> p<.05 compared to ecstasy users
<sup>e</sup> p<.10 compared to non-drug using controls; <sup>P</sup> p<.10 compared to cannabis-controls; <sup>e</sup> p<.10 compared to ecstasy users

Towards a difference between cannabis-controls and the non-drug using controls on the Global Severity Index, t(63)=0.93, p=0.09.

6.2.1.2 Drug use

A drug use history was collected from all participants using the semi-structured “time line” interview described in detail in Chapter 2 (section 2.6). A summary of the use of ecstasy, alcohol, cannabis and amphetamines use by each cohort is provided in Table 6-3. As with the previous studies in Chapters 4 and 5, some incidental use of cannabis was tolerated in the control group due to the difficulty in finding people who had never tried cannabis (n=14, lifetime dose: mean=4.79 times (SD=1.02) [range 1-10 times].
Table 6-3 Selected drug use measures by non-drug using controls, cannabis-controls, and ecstasy users (Standard Error of the Mean in brackets)

<table>
<thead>
<tr>
<th></th>
<th>Non-drug using Controls (n=33)</th>
<th>Cannabis-Controls (n=32)</th>
<th>Ecstasy (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ecstasy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lifetime dose</td>
<td>-</td>
<td>u</td>
<td>384.72 (109.37)</td>
</tr>
<tr>
<td>(tablets)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>abstinence (days)</td>
<td>-</td>
<td>u</td>
<td>37.02 (6.75)</td>
</tr>
<tr>
<td>Alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lifetime dose</td>
<td>749 (208)^{EP}</td>
<td>3060 (557)^{Ce}</td>
<td>4748 (791)^{CP}</td>
</tr>
<tr>
<td>(std. drinks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>maximum monthly dose</td>
<td>24.64 (6.18)^{EP}</td>
<td>76.25 (9.82)^{CE}</td>
<td>123.84 (16.78)^{CP}</td>
</tr>
<tr>
<td>maximum ever dose</td>
<td>11.94 (1.49)^{EP}</td>
<td>18.72 (1.37)^{CE}</td>
<td>27.29 (2.09)^{CP}</td>
</tr>
<tr>
<td>Cannabis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lifetime administrations(^a)</td>
<td>-</td>
<td>1208 (303)^{e}</td>
<td>2694 (780)^{p}</td>
</tr>
<tr>
<td>maximum monthly dose</td>
<td>u</td>
<td>43.84 (8.19)^{E}</td>
<td>102.80 (25.37)^{P}</td>
</tr>
<tr>
<td>maximum ever dose</td>
<td>5.03 (0.46)^{E}</td>
<td>7.56 (1.08)^{i}</td>
<td></td>
</tr>
<tr>
<td>Amphetamines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lifetime dose</td>
<td>-</td>
<td>5.54 (3.69)^{E}</td>
<td>59.05 (15.41)^{P}</td>
</tr>
<tr>
<td>(grams(^a))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>maximum monthly dose</td>
<td>-</td>
<td>0.53 (0.46)^{E}</td>
<td>2.97 (0.73)^{P}</td>
</tr>
<tr>
<td>maximum ever dose</td>
<td>-</td>
<td>0.53 (0.18)^{e}</td>
<td>1.64 (0.39)^{P}</td>
</tr>
</tbody>
</table>

Note. For more detail see Appendix A: Table A-3.

\(^a\) dose measurements explained in Chapter2, section 2.6.2
\(^c\) p<.05 compared to non-drug using controls; \(^e\) p<.05 compared to cannabis-controls; \(^E\) p<.05 compared to ecstasy users
\(^P\) p<.10 compared to cannabis-controls; \(^e\) p<.10 compared to ecstasy users
\(^i\) the means and SEMs relate to that subset of 14 cannabis-controls who had used amphetamines, and not the entire cannabis-control group.
\(^u\) some incidental use - see text in section 6.2.1.2.

Last use=mean 1427 days prior to testing (SD=450) [range 31-6223 days]). Similarly, some use of ecstasy was tolerated in the cannabis-control group due to the difficulty in finding drug users who had never tried ecstasy (n=16, lifetime dose: mean=5.58 tablets (SD=0.79) [range .3-13 tablets]. Last use: mean=350 days prior to testing (SD=84) [range 21-1210 days]).

The cohorts had significantly different levels of alcohol use. Ecstasy users exceeded cannabis-controls, who in turn exceeded non-drug using controls, on their average lifetime dose, largest ever dose in a one month period, and largest ever dose on a single occasion. The only exception to this was that the greater lifetime dose of alcohol by ecstasy users compared to cannabis-users failed to reach significance, t(63)=0.94,
p=0.08. In addition, ecstasy users had a greater use of cannabis and amphetamine compared to cannabis-controls. In particular, only about half of the cannabis-control group had used amphetamines, and amongst those participants their lifetime dose of amphetamines was very low compared to ecstasy users.

6.2.1.3 Summary of group characteristics

The non-drug users, cannabis-control and ecstasy user groups in the current study were well matched on sex and age. In contrast to the previous studies, the difference in estimate IQ between non-drug users and ecstasy users failed to reach significance, although there were trends towards ecstasy users have a lower estimated IQ and lower level of eduction.

There were significant differences between the groups on indicators of personality, mental health, and alcohol use. In addition the cannabis-controls and ecstasy users also differed on cannabis and amphetamine use. The influence of these group differences were investigated and controlled for by statistical means.

6.2.2 Experimental design

A retrospective cohort study design was used to examine the effects of ecstasy use on the use of elaborative processing in explicit memory. All participants completed a series of memory tests, which varied in the elaborative processing requirements at study and test. As outlined in the introduction to this study, three of the memory tests were standard neuropsychological tests, being the California Verbal Learning Test (CVLT, Delis et al., 1987), Verbal-Paired Associates (from Wechsler Memory Scales III (WMS-III), Wechsler, 1997a), Visual Paired Associates (from Wechsler Memory Scales - Revised (WMS-R), Wechsler, 1987). The remaining test was the Verbal Triplet Associates, which is a novel test designed for this study. The dependent variables for each test were some combination of immediate and delayed recall, and delayed recognition. The between-subjects independent variable was drug cohort (ecstasy users, non-drug using controls, cannabis-control).

6.2.3 Experimental stimuli

The stimuli for the standard neuropsychology tests were those supplied with the tests. For the novel Verbal Triplet Associates task, the stimuli consisted of a list of 10 triplets
of words (see Figure 6.1). The triplets were constructed from words selected from the semantic category word lists in Casey and Heath (1988). The words were selected on the basis that they were not used in any of the other tests being conducted, not in categories used in the CVLT, and not related to drug use. The words were grouped into triplets, such that each triplet consisted of words from a different subset of the semantic categories represented, (e.g., an animal, an occupation, and a tree), and ordered within the triplet to least resemble any other triplet. An initial set of eight triplets was pilot tested on an independent group of eight people. An appreciable ceiling effect could be observed as early as the third trial (out of five trials). In order to reduce this effect, a further two triplets were added. This expanded set of 10 triplets was pilot tested on a further 15 participants, and was found to be suitable for use in the present study.

6.2.4 Experimental procedure

The full sequence of events that took place with each participant is shown in Table 6-4. The standard neuropsychological tests (CVLT, Visual Paired Associates, and Verbal Paired Associates) were conducted according to the manufacturers instructions supplied with each test, as summarised in the introduction to this study.

The Faces I (Wechsler, 1997a) test was included for the sole purpose of keeping the participants occupied during the filled delay between the immediate and delayed trials of the standard neuropsychological tests. This particular test was chosen because it used non-verbal stimuli (i.e., pictures of faces), and therefore would not introduce any unnecessary interference with verbal material stored for the other tests. Since there was

Goat – Plumber – Willow
Shoulder – Tulip – Seagull
Rugby – Bike – Pistol
Finch – Ballet – Fridge
Lily – Elbow – Boat
Tram – Rabbit – Dentist
Lamp – Blocks – Maple
Clerk – Cannon – Tango
Jazz – Baseball – Snake
Lego – Neck – Wattle

Figure 6.1 Stimuli for the Verbal Triplet Associates test
Table 6-4 The sequence of events that took place with each participant

1. Informed consent
2. Drug use history interview
3. Immediate recall tests:
   - CVLT (including short delay)
   - Visual Paired Associates I (WMS-R)
   - Verbal Paired Associates I (WMS-III)
   - Faces I (WMS-III)
4. Brief Symptom Inventory
5. Delayed retrieval tests:
   - CVLT (recall and recognition)
   - Visual Paired Associates II (recall only)
   - Verbal Paired Associates II (recall and recognition)
6. Verbal Triplet Associates (immediate recall only)
7. Contextual AusNART if not already completed in the 1st or 2nd study
8. Sensation Seeking Scale if not already completed in the 1st or 2nd study
9. Explanation, debrief, and answer participant questions about the study

For the Verbal Triplet Associates task, the study phase of each trial consisted of the experimenter reading aloud the list of word-triplets in Figure 6.1 in a monotone voice. A moderately fast reading tempo was used, such that it took approximately 1.5 seconds to read each triplet, with a pause of approximately 1.5 seconds between each triplet, such that it took about 30 seconds to read the entire list. The triplets were read in a set order, which was the same for all participants, but different for each trial. The test phase for each trial consisted of the experimenter reading aloud the first word in each triplet (the ‘cue’) in the same order they had been read in that study phase. For each cue, the participant was given five seconds to verbally recall either, or both, of the remaining two words in the triplet. To be scored as a correctly matched response, the participant was required to say the exact form of the word used in the study phase, within the 5 seconds allowed for that cue. The study and test phases were then repeated for the remaining trials.

6.2.5 Statistical Analysis

For repeated measures variables, such as the multiple immediate recall trials used in all of the memory tests, statistical analyses commence with a mixed model ANOVA, in
which the repeated-measures variable is learning trial, and the between subjects variable is cohort (ecstasy users, cannabis-controls, non-drug using controls). For single measure variables, such as delayed recall, statistical analysis commences with a univariate ANOVA of the memory measure as a function of cohort (ecstasy users, cannabis-controls, non-drug using controls). In either case, potential covariates are then identified from amongst the demographic, mental health, and personality variables. For repeated measures variables, this was achieved by conducting bivariate correlations between the total score of the immediate recall trials and the demographic, mental health, and personality variables. The influence on recall of all variables with correlations with the total recall score of $p < .10$ included in an ANCOVA analysis of the same design as used in the initial ANOVA, except for the inclusion of the potential covariates. The backward elimination of the covariates was then conducted, by repeatedly applying the ANCOVA analysis (based on the backward elimination of variables in regression modelling, as outlined in Kleinbaum et al., 1988). At the end of each analysis, the covariate with the largest $p$ value was eliminated from the model until either all of the potential covariates had been eliminated from the model, or all of the remaining covariates had a significance level of $p < .05$. In models which include a repeated measures variable (e.g., multiple immediate recall trials), covariates were only eliminated if the interaction between the covariate and the repeated measures variable/s were $p > .05$, in addition to significance of the main effect of the covariate being $p < .05$. The covariates that remain in the ANCOVA model, along with the significance of the main effect of cohort and follow-up contrasts between cohorts (as reported by SPSS, 2004) are then reported.

If an effect of cohort was indicated by either the main effect or the follow-up contrasts, then the potential influence of alcohol and cannabis use variables was then assessed using the same procedure of bivariate correlations, followed by ANCOVA analysis with the backward elimination of potential covariates. For alcohol, since most participants in all of the cohorts used alcohol, all three cohorts were included in the analysis. For cannabis, since there was only incidental use of cannabis in the non-drug using control groups, the influence of cannabis was assessed using the cannabis-controls and ecstasy users only.

Simple effects analysis within one level of a repeated measures variable (e.g., a particular trial) was conducted if the above analysis revealed a significant interaction between cohort and some other variable, or if the simple effects analysis suggests a
different pattern of significant effects than obtained in the repeated-measures analysis. The simple effects analysis was conducted following the same procedure outlined above using univariate ANOVA and ANCOVA of memory performance as a function of cohort (ecstasy users, cannabis, controls).

Following the completion of the between group analysis of the results for all tests, the dose dependence of the results of all tests is examined for measures of both ecstasy and amphetamine use. The effects of amphetamines could not be validly examined using ANCOVA because of the low use of amphetamines in the cannabis-control group, and absence of amphetamine use in the non-drug using control group. Therefore, the influence of amphetamines was assessed using bivariate correlations, and where possible, regression analysis. This analysis for all memory tests is reported in the last sub-section of the results.

6.3 Results

The aim of the present study was to evaluate the possible role of elaborative processing on the long-term memory performance of ecstasy users. This was achieved by comparing ecstasy users to both cannabis-controls and non-drug using controls on a number of memory tests that differed in their level of demand for associative processing.

6.3.1 Immediate recall

6.3.1.1 California Verbal Learning Test (CVLT)

The immediate recall data from the California Verbal Learning Test (CVLT) consisted of the number of words from the main study list that were correctly recalled following each trial in the immediate phase of the test. The mean recall for each trial is displayed in Figure 6.2 as a function of cohort (ecstasy users, cannabis-controls, non-drug controls). Inspection of the figure suggests that ecstasy users recalled less words on every trial compared to the non-drug controls, and that the performance of the cannabis-controls fell in between that of the ecstasy users and non-drug controls, with a tendency towards being more similar to the non-drug controls.

A mixed model ANOVA analysis of recall as function of cohort and trial revealed a main effect of cohort, $F(1,94)=3.58$, $\text{MSE}=15.38$, $p=.03$, and no significant interaction
between cohort and trial, F(8,376)<1, MSE=1.71, p=.64. Follow-up contrasts confirmed that the difference between cannabis-controls and non-drug controls was not significantly different, p=.39, but that ecstasy users performed significantly worse than cannabis-controls, p=.01, and non-drug using controls, p=.01.

Bivariate correlations revealed a number of covariates, shown in Table 6-5. When introduced into ANCOVA analysis using the backward elimination of covariates, the only significant covariate to remain in the model was the BSI Obsessive-Compulsive subscale, F(1,93)=4.46, MSE=14.83, p=.037. When this covariate was taken into account the main effect of cohort was no longer significant, F(2,93)=2.85, MSE=14.83, p=.06, and the interaction between cohort and trial remained non-significant, F(8,372)<1, MSE=1.70, p=.66. However, contrasts still showed the same pattern that the difference between cannabis-controls and non-drug controls was not significant, p=.56, and that ecstasy users performed worse than both cannabis-controls, p=.02 and non-drug using controls, p=.02.
Further bivariate correlations reveal that total CVLT recall was uncorrelated with any alcohol use measure. Also, within the cannabis-control and ecstasy users groups, CVLT recall was uncorrelated with any cannabis use measure.

6.3.1.2 Verbal Paired Associates

The immediate recall data from the Verbal Paired Associates test consisted of the number of words recalled in response to the experimenter reading aloud the word it was paired with in the study list. The mean recall for each trial is displayed in Figure 6.3 as a function of cohort (ecstasy users, cannabis-controls, non-drug controls). Inspection of the figure suggests the same pattern of results found for the CVLT, that ecstasy users performed worse than cannabis and non-drug controls, and that the performance of the two control groups did not differ from each other. The reduced length of the error bars, and the progressive decrease slope of the lines between each trial, indicates an appreciable ceiling effect increasingly influences the data as performance approaches the total number of studies pairs (eight), possibly as early as the second trial. This created significant skewing in the data, and greatly reduced variability. For instance, a perfect score of 100% items correct on the fourth trial (i.e., 8 out of 8 items) was achieved by all but two of the non-drug using controls (n=33) and all but one of the cannabis-controls (n=32). To minimise the impact of the ceiling effect, and to avoid significant violations of the assumptions of ANCOVA, the initial analysis only included first two Verbal Paired Associates trials.

A mixed model ANOVA analysis of recall as function of cohort and trial revealed a non-significant trend towards a main effect of cohort $F(2,94)=2.65, \text{MSE}=6.33, p=.08$, and no significant interaction between cohort and trial, $F(2,94)=1.51, \text{MSE}=1.19, p=.23$. Follow-up contrasts revealed that the difference between non-drug using controls and cannabis-controls was not significant, $p=.97$, but that ecstasy users performed.

<table>
<thead>
<tr>
<th></th>
<th>(r(97))</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSI Global Severity Index (GSI)</td>
<td>-.21, (p=.04)</td>
</tr>
<tr>
<td>BSI Obsessive-Compulsive</td>
<td>-.24, (p=.02)</td>
</tr>
<tr>
<td>BSI Depression</td>
<td>-.23, (p=.02)</td>
</tr>
<tr>
<td>BSI Paranoid Ideation</td>
<td>-.24, (p=.02)</td>
</tr>
<tr>
<td>BSI Psychotocism</td>
<td>-.22, (p=.04)</td>
</tr>
<tr>
<td>estimated IQ</td>
<td>-.19, (p=.06)</td>
</tr>
</tbody>
</table>

Table 6-5 Bivariate correlations of total CVLT immediate recall across trials 1...5, \(p<.10\)
significantly worse than both cannabis-controls, \( p = .02 \), and non-drug using controls, \( p = .05 \).

Bivariate correlations between the total of the first two trials and demographic, mental health, and personality variables revealed a number of potential covariates, shown in Table 6-6. When introduced into ANCOVA analysis using the backward elimination of covariates, the only significant covariate to remain in the model was the BSI Positive Symptom Distress Index, \( F(1, 93) = 6.18, \text{MSE} = 6.00, p = .02 \). When this covariate was taken into account, the trend towards a main effect of cohort weakened to \( F(2, 93) = 2.09, \text{MSE} = 6.00, p = .13 \), and the interaction between cohort and trial remained non-significant, \( F(2, 93) = 1.19, \text{MSE} = .95, p = .31 \). The follow-up contrasts revealed that the difference between non-drug using controls and cannabis-controls remained non-significant, \( p = .81 \), and that ecstasy users recalled significantly less than cannabis-controls, \( p = .05 \). However, the significant difference between ecstasy users and non-drug users was reduced to a non-significant trend, \( p = .10 \).

Further bivariate correlations reveal that total Verbal Paired Associates recall for trials 1 and 2 was uncorrelated with any alcohol use measures. However, within the cannabis-controls and ecstasy user groups, it was correlated with the lifetime dose of cannabis,
When the lifetime dose of cannabis was introduced to the ANCOVA model, the effect of BSI Positive Symptom Distress Index remained significant, $F(1, 60) = 5.97$, $MSE = 6.07$, $p = .02$, and the lifetime dose of cannabis remained in the model as a marginally significant covariate, $F(1, 60) = 3.98$, $MSE = 6.07$, $p = .051$. The follow-up contrast revealed that the significant difference between ecstasy users and cannabis-controls in the previous analysis was no longer significant, $p = .18$.

An a priori simple effects analysis on Trial 1 was conducted to see if ecstasy users differed from either of the control groups on that trial. A univariate ANOVA of recall on trial 1 as a function of cohort (ecstasy users, cannabis-controls, non-drug users) revealed a non-significant trend towards an effect of cohort, $F(2, 96) = 2.78$, $MSE = 5.03$, $p = .07$. Follow-up contrasts showed that there was no significant difference between cannabis-controls and non-drug using controls, $p = .73$ and that ecstasy users performed significant worse than cannabis-controls, $p = .02$, and non-drug using controls, $p = .03$. Bivariate correlations reveal that total Verbal Paired Associates recall for trial 1 had very similar potential covariates as those for the total of trials 1 and 2, as shown in Table 6-6. When introduced into a univariate ANCOVA analysis using the backward elimination of covariates, the only significant covariate to remain in the model was again the BSI Positive Symptom Distress Index, $F(1, 97) = 5.55$, $MSE = 4.80$, $p = .02$. Once this covariate was taken into account, the main effect of cohort was now clearly not significant, $F(1, 97) = 2.15$, $MSE = 4.80$, $p = .12$. The follow-up contrasts revealed a similar pattern of results to the previous analysis, that there was no significant difference between cannabis-controls and non-drug using controls, $p = .92$, and that ecstasy users performed significant worse than cannabis-controls, $p = .04$, but the difference between
ecstasy users and non-drug using controls, was reduced to a non-significant trend, $p=.07$.

Further bivariate correlations showed that Verbal Paired Associates recall on the first trial was correlated with the maximum monthly dose of alcohol, $r(93)=-.22$, $p=.03$, and the maximum ever dose of alcohol, $r(93)=-.20$, $p=.06$, across alcohol users in all three cohorts. When introduced into the ANCOVA model with the backward elimination of covariates, neither alcohol variable remained in the model as a significant covariate.

When cannabis use was assessed across the cannabis-control and ecstasy user cohorts, there were no significant bivariate correlations between the first trial of Verbal Paired Associates and any cannabis use measure. Therefore, the results obtained above remain unaltered, that on the first trial of Verbal Paired Associates ecstasy users recalled significantly less words than cannabis-controls, and there was a non-significant trend towards them also recalling less than non-drug using controls. This is in contrast to the earlier analysis, which found that when trials 1 and 2 where considered together there was no statistically significant difference ecstasy users and either control group once the effect of mental health and cannabis use covariates were taken into account.

Figure 6.4 Mean number of correct colour associations in the Visual Paired Associates test as a function of trial (1...3) and cohort (ecstasy users, cannabis-controls, non-drug controls). Error bars = standard errors
The immediate recall data from the Visual Paired Associates test consisted of the number of pictures for which the participant pointed to the same colour panel that it was associated with in the study phase. The mean number of correctly recalled and matched words for each trial is displayed in Figure 6.4 as a function of trial (1...3) and cohort (ecstasy users, cannabis-controls, non-drug controls). Inspection of the figure suggests that all drug users, consisting of both ecstasy users and non-drug using controls, perform relatively poorly compared to non-drug controls on all trials, but that cannabis-controls possibly do a little better than ecstasy users on the third trial.

A mixed model ANOVA analysis of recall as function of cohort and trial revealed a non-significant trend towards a main effect of cohort $F(2,94)=2.73$, $MSE=3.97$, $p=.07$, and no significant interaction between cohort and trial, $F(4,188)<1$, $MSE=1.07$, $p=.60$. Follow-up contrasts revealed that ecstasy users performed significantly worse than non-drug using controls, $p=.02$, with non-significant trends towards cannabis-controls performing worse than non-drug using controls, $p=.11$, and better than ecstasy users, $p=.10$.

Bivariate correlations between the total Visual Paired Associates recall and demographic, mental health, and personality variables revealed a number of potential covariates. The only correlations for which $p<.10$ were sex, $r(97)=.34$, $p=.001$, and the BSI Obsessive-Compulsive subscale, $r(97)=-.19$, $p=.07$. When introduced into ANCOVA analysis using the backward elimination of covariates, the only significant covariate to remain in the model was sex, $F(1, 93)=12.72$, $MSE=3.53$, $p=.001$. Since the cohorts were well matched on sex, it is unsurprising that the significance level of the main effect of cohort remained largely unchanged, $F(2,93)=2.90$, $MSE=3.53$, $p=.06$, and the interaction between cohort and trial remained non-significant, $F(4,184)<1$, $MSE=1.03$, $p=.57$. The results of follow-up contrasts between the cohorts still showed ecstasy users recall significantly less than non-drug using controls, $p=.02$, and that there were non-significant trends for cannabis-controls to perform worse than non-drug using controls, $p=.08$ and better than ecstasy users, $p=.06$.

Further bivariate correlations showed that Visual Paired Associates recall on the first trial was correlated with lifetime dose of alcohol, $r(97)=-.22$, $p=.03$, and the maximum ever dose of alcohol, $r(93)=-.19$, $p=.07$. When introduced into the ANCOVA model,
Table 6-7 Summary of the simple effects analysis for each trial of Visual Paired Associates controlling for sex, lifetime dose of alcohol and maximum ever dose of alcohol (standard drinks) as a function of cohort (ecstasy users, cannabis-controls, and non-drug using controls)

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sex</th>
<th>Lifetime dose</th>
<th>Max. ever dose</th>
<th>Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F(1,93)</td>
<td>MSE</td>
<td>p</td>
<td>F(1,93)</td>
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<tr>
<td>Trial 1</td>
<td>4.94</td>
<td>2.08</td>
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<td>2.08</td>
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<td>Trial 3</td>
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Before elimination of non-significant covariates

<table>
<thead>
<tr>
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<td>.01</td>
<td>8.91</td>
<td>1.68</td>
<td>.004</td>
<td>6.342</td>
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<td>.01</td>
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<td>Lifetime dose</td>
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After backward elimination of covariates

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<th></th>
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<th>p</th>
<th>F(1,93)</th>
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<tr>
<td>Cohort</td>
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<td>1.68</td>
<td>.50</td>
<td>3.279</td>
<td>1.63</td>
<td>.04</td>
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</tbody>
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Follow-up contrasts

<table>
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<th></th>
<th>p</th>
<th>p</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>C v. CC</td>
<td>.25</td>
<td>.29</td>
<td>.16</td>
</tr>
<tr>
<td>CC v. E</td>
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<td>.31</td>
<td>.03</td>
</tr>
<tr>
<td>E v. C</td>
<td>.35</td>
<td>.31</td>
<td>.01</td>
</tr>
</tbody>
</table>

Note. C=Non-drug using controls; CC=Cannabis-controls; E=Ecstasy users

there was a significant interaction between trial and lifetime dose of alcohol F(2,174)=3.43, MSE=1.01, p=.04, and non-significant trend toward an interaction between trial and the maximum ever dose of alcohol, F(2,174)=2.511, MSE=1.01, p=.09. When these covariates were taken into account the main effect of cohort was clearly not significant, F(2,87)=1.2, MSE=3.71, p=.31, as was the difference between ecstasy users and controls in the follow-up contrasts, p=.27.

In order to better understand the interactions between trial and the alcohol use measures, simple effects analysis was conducted on each trial using univariate ANCOVA of recall as a function of cohort (ecstasy users, cannabis-controls, and non-drug using controls) controlling for sex, lifetime dose of alcohol and maximum ever dose of alcohol. The results of the analysis are summarised in Table 6-7. For all three trials, sex remained in the model as a significant covariate after the backward elimination procedure. With regard to the alcohol measures, the lifetime dose of alcohol was a significant covariate in the second trial, and not in the first and third trials. The maximum ever dose of alcohol was not a significant covariate in any trial. The main effect of cohort and
follow-up contrasts show that the only significant difference between the cohorts occurred in the third trial, where there was no significant difference between the two control groups, and that ecstasy users performed significantly worse than both control groups. Further bivariate correlations did not reveal any significant associations between cannabis use measures and recall within the combined group of cannabis-controls and ecstasy users.

Overall the analyses of Visual Paired Associates indicate that after accounting for covariates, the performance of ecstasy users in the first and second trials did not differ significantly from that of either cannabis-controls or non-drug using controls. However, on the third trial the performance of ecstasy users was significantly lower than both of those control groups.

6.3.1.4 Verbal Triplet Associates

The main immediate recall data from Verbal Triplet Associates test consisted of the number of words correctly recalled and matched to the first word of a triplet (the ‘cue’) from the study list read aloud by the experimenter. Since there were a maximum of two
Table 6-8 Bivariate correlations between total Verbal Triplet Associates recall, \( p \leq 10 \)

<table>
<thead>
<tr>
<th></th>
<th>( r ) ( 92 )</th>
<th>( p )</th>
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</thead>
<tbody>
<tr>
<td>Estimated IQ</td>
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<td>.01</td>
</tr>
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<td>BSI Global Severity Index</td>
<td>-.22</td>
<td>.04</td>
</tr>
<tr>
<td>BSI Positive Symptom Distress Index</td>
<td>-.22</td>
<td>.04</td>
</tr>
<tr>
<td>BSI Depression</td>
<td>-.24</td>
<td>.02</td>
</tr>
<tr>
<td>BSI Psychoticism</td>
<td>-.22</td>
<td>.04</td>
</tr>
<tr>
<td>BSI Interpersonal Sensitivity</td>
<td>-.17</td>
<td>.10</td>
</tr>
</tbody>
</table>

words which could be matched to the cue word from each of the 10 triplets in the study list, a maximum of 20 words could be correctly recalled and matched\(^{15}\). The mean number of correctly matched words is displayed in Figure 6.5 as a function of trial (1...5) and cohort (ecstasy users, cannabis-controls, and non-drug controls). From the figure it appears that on the first trial that both ecstasy users and cannabis-controls performed worse than non-drug controls, but that cannabis-controls improved at a faster rate across trials than ecstasy users, such that the performance of cannabis-controls converged with non-drug controls as the performance of the non-drug controls approached ceiling. In contrast, performance of the ecstasy users appears to remain consistently lower than non-drug controls over all of the trials. This pattern was largely confirmed by statistically analysis.

A mixed model ANOVA analysis of word recall as a function of trial (1...5) and cohort (ecstasy users, cannabis-controls, and non-drug controls), found that there was a significant main effect of cohort, \( F(2,90)=4.70, \text{MSE}=180.76, p=.01 \), and significant interaction between cohort and trial, \( F(8, 218)=2.56, \text{MSE}=8.33, p=.03 \). Follow-up contrasts revealed that ecstasy users performed significant worse than cannabis-controls, \( p=.015 \), and non-drug using controls, \( p=.003 \). There was also a non-significant trend towards cannabis-controls performing worse than non-drug using controls, \( p=.07 \).

Bivariate correlations revealed a number of covariates, shown in Table 6-8. When introduced into ANCOVA analysis using the backward elimination of covariates, the only significant covariate to remain in the model was estimated IQ, \( F(1,88)=5.94, \text{MSE}=103.84, p=.02 \). Once this covariate was taken into account, the main effect of

\(^{15}\) No attention was paid to the order in which correctly matched words were recalled.
cohort remained statistically significant, \( F(2,87)=3.64, \text{MSE}=103.84, p=.03 \), but the interaction between cohort and trial evident in the original analysis just failed to reach significance, \( F(8,217)=2.13, \text{MSE}=8.15, p=.06 \). Follow-up contrasts revealed that the difference between ecstasy users and non-drug using controls was still significant, \( p=.01 \), as was the difference between ecstasy users and cannabis-controls, \( p=.05 \). The non-significant trend between cannabis-controls and non-drug using controls remained unchanged, \( p=.07 \).

Further bivariate correlations showed that total Verbal Triplet Associates recall was correlated with the maximum lifetime dose of alcohol, \( r(89)=-.20, p=.05 \), and the maximum ever dose of alcohol, \( r(89)=-.23, p=.03 \). There was also a non-significant trend towards a correlation with the maximum monthly dose of alcohol, \( r(89)=-.19, p=.08 \). When these variables were introduced into the ANCOVA model, the main effect of estimated IQ remained significant, \( F(1,82)=7.55, p=.007 \), and there was a significant interaction between the maximum monthly alcohol dose and trial, \( F(4,328)=8.54, \text{MSE}=6.53, p<.001 \), and between lifetime dose of alcohol and trial, \( F(4,328)=3.64, \text{MSE}=6.53, p=.02 \). Also, the main effect of cohort was no longer significant, \( F(2,82)=2.82, \text{MSE}=99.56, p=.07 \). Follow-up contrasts revealed that the performance of ecstasy users remained significantly different from non-drug users, \( p=.03 \), and that the inclusion of the alcohol variables had further reduced the significance of the non-significant trend toward a difference between ecstasy users and cannabis-controls, \( p=.11 \). Conversely, accounting for alcohol had increased the significance of the difference between cannabis-controls and ecstasy users so that it was now just significant, \( p=.05 \).

In order to investigate the interactions between the alcohol use measures and trial, simple effects analysis was conducted for each trial using a univariate ANCOVA analysis of recall performance of a function of cohort (ecstasy users, cannabis-controls, non-drug users), along with the backwards elimination of estimated IQ, lifetime alcohol dose, and maximum monthly alcohol dose. The results of this analysis are summarised in Table 6-9. After accounting for covariates, this analysis indicates that ecstasy users consistently performed worse than controls over all of the trials. In contrast, cannabis-controls started on the first trial with a performance level that was very similar to ecstasy users, but with each successive trial improved their performance so that on the last two trials they recalled and correctly matched significantly more words than ecstasy
Table 6-9 Summary of simple effects analysis for each trial of the Verbal Triplet Associates test, including the backward elimination of estimated IQ, the lifetime dose of alcohol, and the maximum every monthly dose of alcohol.

<table>
<thead>
<tr>
<th>Trial 1</th>
<th>Trial 2</th>
<th>Trial 3</th>
<th>Trial 4</th>
<th>Trial 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>p</td>
<td>F</td>
<td>p</td>
<td>F</td>
</tr>
<tr>
<td>Before elimination of non-significant covariates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated IQ</td>
<td>3.20 .08</td>
<td>5.46 .02</td>
<td>7.04 .01</td>
<td>7.45 .01</td>
</tr>
<tr>
<td>Lifetime dose</td>
<td>0.20 .65</td>
<td>0.22 .64</td>
<td>2.34 .13</td>
<td>4.58 .04</td>
</tr>
<tr>
<td>Max. monthly dose</td>
<td>0.67 .42</td>
<td>0.30 .59</td>
<td>0.68 .41</td>
<td>4.14 .04</td>
</tr>
<tr>
<td>After backward elimination of covariates</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated IQ</td>
<td>- -</td>
<td>4.17 .04</td>
<td>5.04 .03</td>
<td>7.45 .01</td>
</tr>
<tr>
<td>Lifetime dose</td>
<td>- -</td>
<td>- -</td>
<td>- -</td>
<td>4.58 .04</td>
</tr>
<tr>
<td>Max. monthly dose</td>
<td>- -</td>
<td>- -</td>
<td>- -</td>
<td>4.14 .04</td>
</tr>
<tr>
<td>Cohort</td>
<td>4.51 .01</td>
<td>3.72 .03</td>
<td>3.75 .03</td>
<td>2.79 .07</td>
</tr>
</tbody>
</table>

Follow-up contrasts

| C v. CC | .01 | .06 | .06 | .13 | .22 |
| CC v. E | .25 | .05 | .06 | .04 | .03 |
| E v. C | .02 | .01 | .01 | .02 | .02 |

users, and were not significantly different from controls. Note that in Figure 6.5, it appears that the performance of controls in trials 4 and 5 may be subject to a slight ceiling effect, which may be part of the reason that the performance of non-drug using controls and cannabis-controls appears to be converging over the later trials (an analysis of the relative rates of learning (i.e. slopes of the lines) over the first three trials is reported below).

With regard to the potential impact of cannabis use on the results, further bivariate correlations showed that cannabis dose measures (lifetime dose, maximum monthly dose, maximum ever dose) were not significantly related to total Verbal Triplet Associates recall. This suggests that the lower performance of the ecstasy users compared to the cannabis-controls was not due to greater cannabis use by the ecstasy users.

The statistical significance of the apparent difference between the learning rate of cannabis-controls and ecstasy users was investigated. The learning slope was calculated by subtracting performance on the first trial from that of the third trial, and dividing by three. The third trial was used in this calculation because from Figure 6.5 it appears that
improvement of controls on the fourth and fifth trials was affected by a ceiling effect. Follow-up contrasts from a univariate ANOVA of the learning slope as a function of cohort (ecstasy users, cannabis-controls, and non-drug controls) revealed that the learning slope of ecstasy users (2.03 words per trial, SD=1.33) was significantly less than that of cannabis-controls, (2.67 words per trial, SD=1.17), p=.02, which was not significant different from the learning slope of non-drug controls (2.70 words per trial, SD=1.16), p=.92. Bivariate correlations revealed that learning slope was significantly correlated with estimated IQ, r(92)=.24, p=.02, and BSI Global Severity Index (GSI), r(93)=-.24, p=.02. When analysed using a backward elimination ANCOVA analysis, only BSI GSI remained as a significant covariate, F(1,89)=4.39, MSE=1.44, p=.04. However, accounting for the influence of BSI GSI did not change the pattern of results, such that the difference between the learning slopes of cannabis-controls and ecstasy users remained significant, p=.04, and the difference between cannabis-controls and non-drug using controls remained highly non-significant, p=.81. In addition, slope was uncorrelated with alcohol and cannabis use measures. Therefore, this analysis shows a clear learning deficit in ecstasy users compared to both cannabis-controls and ecstasy users.

In summary, this analysis shows that overall ecstasy users performed significantly worse than non-drug using controls on all trials, and learnt the triplets at a significantly slower rate, even after statistically controlling for the effects of mental health and alcohol. In comparison, cannabis-controls and ecstasy users appeared to perform at a similarly lower level compared to controls over the first couple of trials, but the performance of cannabis-controls improved at a rate that was not-significantly different from non-drug using controls, such that (with the possible assistance of a slight ceiling effect in the non-drug using control group) they were not significantly different from controls in the later trials. There was no indication that the group differences between ecstasy users and cannabis-controls, or the significantly lower learning rate in ecstasy users was attributable to cannabis use.

6.3.2 Delayed recall

6.3.2.1 Verbal and Visual Paired Associates

For the Verbal Paired Associates test, a perfect score of 8 items correctly recalled was achieved by 28 of the 33 non-drug using controls, 26 of the 32 cannabis-controls, and
23 of the 32 ecstasy users. This high incidence of perfect scores meant that group comparisons using ANOVA could not be validly conducted because of the extreme violation of the assumption of the normal distribution of scores. The tendency for less ecstasy to achieve perfect scores compared to the control groups did not reach statistical significance, $\chi^2(2, n=97)=1.77$, $p=.41$.

Similarly, for Visual Paired Associates, a perfect score of 6 items correctly matched to the correct colour was achieved by 29 of the 33 non-drug using controls, 26 of the 32 cannabis-controls, and 25 of the 32 ecstasy users. Again the tendency for less ecstasy to achieve perfect scores compared to the control groups did not reach statistical significance, $\chi^2(2, N=97)=1.12$, $p=.57$.

6.3.2.2 CVLT

In the CVLT test, free recall and category-cued recall were measured following a short time delay of approximately three minutes, which was filled by single learning trial and free recall of an interference word list. Later, free recall, category-cued recall, and correct recognition was measured following a long delay of approximately 20 minutes, which was filled with a range of other cognitive tests (as listed in Table 6-4). Results are displayed in Table 6-10.

For short-delayed free recall, a univariate ANOVA revealed a main effect of cohort, $F(2,94)=4.25$, $MSE=6.73$, $p=.02$, with follow-up contrasts showing that there was non-

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**Table 6-10 Mean number of words recalled in the California Verbal Learning Test (CVLT) as a function of test type (free recall, category-cued recall, correct recognition), duration of delay (short, long) and cohort (ecstasy users, cannabis-controls, non-drug using controls).**

<table>
<thead>
<tr>
<th></th>
<th>Non-drug using controls</th>
<th>Cannabis-controls</th>
<th>Ecstasy users</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (SEM)</td>
<td>Mean (SEM)</td>
<td>Mean (SEM)</td>
</tr>
<tr>
<td>Free recall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short delay</td>
<td>12.82 (0.38)$^E$</td>
<td>12.53 (0.46)$^E$</td>
<td>11.06 (0.53)$^CP$</td>
</tr>
<tr>
<td>Long delay</td>
<td>13.30 (0.39)$^E$</td>
<td>13.19 (0.38)$^E$</td>
<td>11.72 (0.53)$^CP$</td>
</tr>
<tr>
<td>Category-cued recall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short delay</td>
<td>13.30 (0.40)$^E$</td>
<td>12.88 (0.50)</td>
<td>11.97 (0.48)$^C$</td>
</tr>
<tr>
<td>Long delay</td>
<td>13.21 (0.53)</td>
<td>13.53 (0.39)$^E$</td>
<td>12.00 (0.52)$^P$</td>
</tr>
<tr>
<td>Correct recognition$^a$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long delay</td>
<td>43.06 (0.31)$^{EP}$</td>
<td>42.06 (0.45)$^C$</td>
<td>41.44 (0.58)$^C$</td>
</tr>
</tbody>
</table>

Note. The significance levels shown are for independent t-tests
$^a$ calculated as 44-(total number of errors) $^C p<.05$ compared to non-drug using controls; $^P p<.05$ compared to cannabis-controls
$^E p<.05$ compared to ecstasy users
### Table 6-11 Covariates of short and long delay, free recall and category-cued recall, p<.10

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Free recall</th>
<th></th>
<th>Category-cued recall</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Short</td>
<td>Long</td>
<td>Short</td>
<td>Long</td>
</tr>
<tr>
<td>Estimated IQ (n=96)</td>
<td>r(97)</td>
<td>p</td>
<td>r(97)</td>
<td>p</td>
</tr>
<tr>
<td>SSS Disinhibition</td>
<td>-.22</td>
<td>.03</td>
<td>-.23</td>
<td>.02</td>
</tr>
<tr>
<td>SSS Boredom Susceptibility</td>
<td>-.24</td>
<td>.02</td>
<td>-.27</td>
<td>.01</td>
</tr>
<tr>
<td>BSI Global Severity Index</td>
<td>-.22</td>
<td>.03</td>
<td>-.25</td>
<td>.01</td>
</tr>
<tr>
<td>BSI Positive Symptom Total index</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSI Positive Symptom Distress Index</td>
<td>-.21</td>
<td>.04</td>
<td>-.29</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>BSI Obsessive-Compulsive</td>
<td>-.25</td>
<td>.02</td>
<td>-.29</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>BSI Interpersonal Sensitivity</td>
<td>-.21</td>
<td>.04</td>
<td>-.26</td>
<td>.02</td>
</tr>
<tr>
<td>BSI Depression</td>
<td>-.28</td>
<td>.01</td>
<td>-.26</td>
<td>.01</td>
</tr>
<tr>
<td>BSI Phobic Anxiety</td>
<td>-.17</td>
<td>.09</td>
<td>-.20</td>
<td>.06</td>
</tr>
<tr>
<td>BSI Paranoid Ideation</td>
<td>-.24</td>
<td>.02</td>
<td>-.19</td>
<td>.06</td>
</tr>
<tr>
<td>BSI Psychoticism</td>
<td>-.25</td>
<td>.01</td>
<td>-.26</td>
<td>.01</td>
</tr>
</tbody>
</table>

Bivariate correlations revealed a number of possible covariates, shown in Table 6-11. When introduced into ANCOVA analysis using the backward elimination of covariates, the only significant covariate to remain in the model was BSI Depression, F(1,96)=4.85, MSE=6.27, p=.03. There was also a non-significant trend towards estimated IQ being a significant covariate, F(1,96)=3.58, MSE=6.27, p=.06, so it was also included in the initial model. Once these covariates were taken into account, there was a non-significant trend towards a main effect of cohort, F(2,96)=2.37, MSE=6.27, p=.10. Follow-up contrasts revealed that the pattern of differences between the cohorts remained unchanged, i.e., that there was no statistically significant difference between non-drug using controls and cannabis-controls, p=.74, but that ecstasy users performed significant worse than cannabis-controls, p=.03, and non-drug using controls, p=.04.

Further bivariate correlations revealed non-significant trends towards short delayed free recall being correlated with lifetime dose of alcohol, r(93)= -.18, p=.07. However, this variable did not remain in the model following the backward elimination of covariates (while estimated IQ and BSI Depression remained in the model as significant covariates). With regard to cannabis use in the cannabis-control and ecstasy user groups,
there were no significant bivariate correlations, $p<.10$, between any cannabis use variable and short delayed free recall.

For short-delayed category-cued recall, a univariate ANOVA revealed that the main effect of cohort was not significant, $F(2,94)=2.19, \text{MSE}=6.87, p=.12$. Follow-up contrasts showed that similar to the short delayed free recall, the cannabis-control and non-drug using control groups were not significantly different, $p=.65$, but that the ecstasy users were significantly worse than cannabis-controls, $p=.05$, and non-drug using controls, $p=.04$. Bivariate correlations revealed a number of possible covariates, shown in Table 6-11. When introduced into ANCOVA analysis using the backward elimination of covariates, the only significant covariate to remain in the model were estimated IQ, $F(1,91)=12.73, \text{MSE}=5.94, p=.001$, and BSI Boredom Susceptibility, $F(1,91)=4.36, \text{MSE}=5.94, p=.04$. With these covariates taken into account, there was clearly no significant main effect of cohort, $F(2,91)<1, \text{MSE}=5.84, p=.52$. Follow-up contrasts revealed that the difference between non-drug using controls and cannabis-controls remained not significant, $p=.40$, but that the differences between ecstasy users and cannabis-controls, $p=.43$, as well as non-drug using controls, $p=.28$, were now also not significant. This indicates that in contrast to the short-delay free recall results, that once covariates were taken into account ecstasy use did not have a significant effect on short-delayed category cued recall.

For long delayed free recall and category-cued recall, a similar pattern of results was obtained to that obtained following the short-delay (see means in Table 6-10). For long-delayed free recall, a univariate ANOVA revealed a main effect of cohort, $F(2,94)=4.03, \text{MSE}=6.24, p=.02$, with follow-up contrasts showing the usual pattern of no difference between cannabis-controls and non-drug using controls, $p=.85$, but significantly worse performance by ecstasy users compared to both cannabis-controls, $p=.01$, and non-drug using controls, $p=.01$. When the influence of the covariates in Table 6-11 was evaluated using a backward elimination ANCOVA, BSI Obsessive-Compulsive was the only statistically significant covariate to remain in the model, $F(1,97)=7.42, \text{MSE}=5.84, p=.01$. With this covariate taken into account, the main effect of cohort remained significant, $F(2,96)=3.39, \text{MSE}=5.84, p=.04$, and the pattern of the follow-up contrasts remained unaltered such that there was no significant difference between the non-drug using controls and cannabis-controls, $p=.87$, and the ecstasy users.
performed significantly worse than cannabis-controls, \( p = .01 \), and non-drug using controls, \( p = .03 \).

For long delayed category-cued recall on the CVLT, a univariate ANOVA revealed a non-significant trend towards a main effect of cohort, \( F(2, 94) = 2.75, \text{MSE} = 7.61, p = .07 \) (see means in Table 6-10). Unusually, the cannabis-controls recalled on average more words than non-drug using controls, however the difference did not approach statistical significance, \( p = .69 \). Ecstasy users performed significantly worse than the cannabis-controls, \( p = .02 \), but the difference between the ecstasy users and non-drug using controls was a non-significant trend, \( p = .08 \).

Bivariate correlations revealed a number of possible covariates for long-delayed category-cued recall, as shown in Table 6-11. When introduced into ANCOVA analysis using the backward elimination of covariates, the only significant covariate to remain in the model was BSI Obsessive Compulsive, \( F(1, 91) = 4.95, \text{MSE} = 7.09, p = .03 \). However, there was also a non-significant trend towards estimated IQ being a significant covariate, \( F(1, 96) = 2.89, \text{MSE} = 7.09, p = .09 \). With estimated IQ retained in the model, the main effect was not significant, \( F(2, 91) = 1.48, \text{MSE} = 7.09, p = .23 \), with follow-up contrasts showing that there was no statistically significant difference between non-drug using controls and cannabis-controls, \( p = .54 \), or between ecstasy users and cannabis-controls, \( p = .11 \), or non-drug using controls, \( p = .27 \). With estimated IQ removed from the model the trend towards a difference between cannabis-controls and ecstasy users increased slightly to \( p = .09 \). There were no significant correlations between long-delay category-cued recall and alcohol or cannabis use measures.

For CVLT long-delayed correct recognition (see means in Table 6-10), a univariate ANOVA revealed a significant main effect of cohort, \( F(2, 94) = 3.58, \text{MSE} = 6.10, p = .03 \). Follow-up contrasts showed a non-significant trend towards there being a difference between cannabis-controls and non-drug using controls, \( p = .11 \). In addition ecstasy users performed significantly worse than cannabis-controls, \( p = .04 \) and non-drug using controls, \( p = .01 \). Bivariate correlations revealed a large number of potential covariates, as shown in Table 6-12. When evaluated using ANCOVA with the backward elimination of the correlates shown the only covariates to remain in the model were estimated IQ, \( F(1, 91) = 6.72, \text{MSE} = 5.35, p = .01 \), and BSI Depression, \( F(1, 91) = 6.44, \text{MSE} = 5.35, p = .01 \). Once these variables were taken into account, the main effect of
The follow-up contrasts showed the difference between the cannabis-controls and non-drug using controls remained a non-significant trend, $p = .10$. However, the difference between ecstasy users and non-drug using controls was also reduced to a non-significant trend, $p = .07$, and the difference between ecstasy users and cannabis-controls was now clearly not significant, $p = .24$. Further bivariate correlations failed to reveal any significant associations between CVLT correct recognition and any alcohol or cannabis use measure.

In summary for the CVLT results, once covariates were taken into account, ecstasy users have statistically significant deficits in short- and long-delayed free recall. With regard to the provision of cues at retrieval, the provision of category-cues assisted the recall of ecstasy users to the extent that their performance was no longer significantly different from either control group after a short- or long- delay, except for a non-significant trend for there category-cued recall to be worse than the controls groups after a long delay.

### 6.3.3 Use of semantic strategies in the CVLT

#### 6.3.3.1 Immediate recall

The CVLT is the only test in the current series of studies that attempts to specifically measure the use of associative retrieval strategies at test. This was achieved by
calculating the List-Based Semantic Clustering Index (Stricker, Brown, Wixted, Baldo, & Delis, 2002) for each free recall test, which provides an index of the extent to which the participant clusters the words by semantic category.

For the immediate recall free recall tests, the total List-Based Semantic Clustering Index for the immediate trials was calculated and is shown in Table 6-13 as a function of cohort (non-drug using controls, cannabis-controls, and ecstasy users). A univariate ANOVA revealed a slight non-significant trend toward a main effect of cohort. Follow-up contrasts showed that semantic clustering at test by cannabis-controls was not significantly different than non-drug using controls, \( p = .78 \), but that ecstasy users used semantic clustering significantly less than both cannabis-controls, \( p = .04 \) and non-drug using controls, \( p = .05 \). The influence of the bivariate correlations listed in table 6-14 revealed a number of possible covariates. The influence of these possible covariates was evaluated using a backward elimination ANCOVA, with the only covariates to remain in the model being SSS Experience Seeking, \( F(1, 97) = 11.01, MS_E = 124.89, p = .001 \), and sex, \( F(1, 97) = 4.03, MS_E = 124.89, p = .05 \). There was also a non-significant trend towards BSI Obsessive-Compulsive being a significant covariate, \( F(1, 97) = 3.56, MS_E = 124.89, p = .06 \), so this variable was left in the model. Once these covariates were taken into account, the main effect of cohort was statistically significant, \( F(2, 97) = 4.11, MS_E = 124.89, p = .02 \). Follow-up contrasts revealed a slight trend towards lower semantic clustering score for cannabis user than non-drug using controls, and that ecstasy users were lower than both cannabis-controls, \( p = .01 \), and non-drug using controls, \( p = .005 \).

The total semantic clustering index score was uncorrelated (\( p < .10 \)) with any alcohol or cannabis use measure. Overall, this analysis of the total List-Based Semantic Clustering

<table>
<thead>
<tr>
<th></th>
<th>Non-drug using controls</th>
<th>Cannabis-controls</th>
<th>Ecstasy users</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
<td>15.33 (2.22)</td>
<td>14.50 (2.08)</td>
<td>9.33 (2.11)</td>
</tr>
<tr>
<td>Short delay</td>
<td>4.61 (0.56)</td>
<td>4.79 (0.54)</td>
<td>3.33 (0.48)</td>
</tr>
<tr>
<td>Long delay</td>
<td>5.48 (0.58)</td>
<td>5.47 (0.55)</td>
<td>4.14 (0.50)</td>
</tr>
</tbody>
</table>

Note. Immediate = total of the List-Based Semantic Clustering Index scores for trials 1 to 5.
Table 6-14 Bivariate correlations of the CVLT List-Base semantic Clustering Index (LBSCI) as a function of the delay (immediate, short-delay and long-delay) on the free recall tests, \( p < .01 \)

<table>
<thead>
<tr>
<th></th>
<th>Immediate</th>
<th>Short-delay</th>
<th>Long-delay</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( r(97) )</td>
<td>( p )</td>
<td>( r(97) )</td>
</tr>
<tr>
<td>Sex</td>
<td>.22</td>
<td>.03</td>
<td>.28</td>
</tr>
<tr>
<td>SSS Thrill and Adventure</td>
<td></td>
<td></td>
<td>-.19</td>
</tr>
<tr>
<td>SSS Experience Seeking</td>
<td>.23</td>
<td>.02</td>
<td>.20</td>
</tr>
<tr>
<td>SSS Boredom Susceptibility</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BSI Global Severity Index (GSI)</td>
<td>-.19</td>
<td>.06</td>
<td>-.23</td>
</tr>
<tr>
<td>BSI Positive Symptom Total (PST) index</td>
<td>-.18</td>
<td>.08</td>
<td>-.23</td>
</tr>
<tr>
<td>BSI Obsessive-Compulsive</td>
<td>-.24</td>
<td>.02</td>
<td>-.25</td>
</tr>
<tr>
<td>BSI Interpersonal Sensitivity</td>
<td>-.19</td>
<td>.07</td>
<td></td>
</tr>
<tr>
<td>BSI Depression</td>
<td>-.21</td>
<td>.04</td>
<td>-.22</td>
</tr>
<tr>
<td>BSI Phobic Anxiety</td>
<td>-.17</td>
<td>.09</td>
<td>-.17</td>
</tr>
<tr>
<td>BSI Paranoid Ideation</td>
<td>-.24</td>
<td>.02</td>
<td>-.24</td>
</tr>
<tr>
<td>BSI Psychoticism</td>
<td>-.17</td>
<td>.10</td>
<td>-.19</td>
</tr>
</tbody>
</table>

Note. Immediate = the total LBSCI score for the five immediate recall trials.

Index scores indicates that once covariates were taken into account, ecstasy users engaged in significantly less semantic clustering at test compared to both non-drug using controls and cannabis-controls.

6.3.3.2 Delayed recall

For the List-Based Semantic Clustering index on CVLT free recall after a short delay (see means in Table 6-13), a univariate ANOVA revealed that the main effect of cohort was not significant, \( F(2,94), \text{MSE}=8.98, p=.11 \). Follow-up contrasts showed that cannabis-controls were not significantly different from non-drug using controls, \( p=.81 \). There was a non-significant trend towards ecstasy users using less semantic clustering than non-drug using controls, \( p=.09 \), and significantly less than cannabis-controls, \( p=.04 \). The influence of the potential covariates listed in Table 6-14 were evaluated using a backward elimination ANCOVA, with the significant covariates remaining in the model being sex, \( F(1,91)=6.72, \text{MSE}=7.60, p=.01 \), SSS Experience Seeking, \( F(1,91)=7.31, \text{MSE}=7.60, p=.01 \) and the BSI Obsessive-Compulsive sub-scale, \( F(1,91)=3.84, \text{MSE}=7.60, p=.05 \). With these covariates taken into account, the main effect of cohort was just significant, \( F(2,91)=3.04, \text{MSE}=7.60, p=.05 \). Follow-up contrasts revealed that the semantic clustering score of ecstasy users was now significantly less than that of both cannabis-controls, \( p=.02 \), and non-drug using controls, \( p=.02 \), and that cannabis-controls and non-drug using controls were not
significantly different, \( p = .46 \). Further bivariate correlations showed that the only correlation (\( p < .10 \)) with any alcohol use measure was a non-significant trend with the maximum ever dose, \( r (93) = -.18, p = .08 \). However, when entered into the backward elimination ANCOVA, this variable did not remain in the model as a significant covariate. Also, there were no significant correlations (\( p < .10 \)) with any cannabis use measure.

For the List-Based Semantic Clustering index following the long delay (see Table 6-13), the pattern of results was very similar to that following the short delay, with a univariate ANOVA revealing that the main effect of cohort was not significant, \( F(2,94) = 2.00, \text{MSE} = 9.60, p = .14 \), and follow-up contrasts showing that cannabis-controls and non-drug using controls were not significantly different, \( p = .99 \). Ecstasy users at test used significantly less semantic clustering than cannabis-controls, \( p = .05 \), with ecstasy users also showing a non-significant trend towards less use of semantic clustering than non-drug using controls, \( p = .08 \). The influence of the covariates in Table 6-14 were evaluated using a backward elimination ANCOVA, with the significant covariates remaining in the model being BSI Phobic Anxiety, \( F(1,91) = 6.66, \text{MSE} = 8.27, p = .01 \), SSS Experience Seeking, \( F(1,91) = 7.81, \text{MSE} = 8.27, p = .01 \) and SSS Boredom Susceptibility, \( F(1,91) = 4.96, \text{MSE} = 7.60, p = .03 \). With these covariates taken into account, the main effect of cohort remained non-significant, \( F(2,91) = 2.03, \text{MSE} = 8.27, p = .14 \). The pattern of results in the follow-up contrasts change slightly, such that the difference between the ecstasy users and cannabis-controls was reduced to a non-significant trend, \( p = .11 \), and the difference between ecstasy users and non-drug using controls now being significant, \( p = .05 \). The difference between cannabis-controls and non-drug using controls remained not significant, \( p = .81 \). There were no significant correlations (\( p < .10 \)) between semantic clustering after a long delay and any alcohol or cannabis use measure.

Overall, once covariates were taken into account, the List-Based Semantic Clustering Index scores for short and long delayed free recall tests exhibited the same pattern as for the immediate recall test, with ecstasy users showing less semantic clustering at test than both cannabis- and non-drug using controls. The only exception was that for long-delayed recall, the trend toward a difference between ecstasy users and cannabis-controls failed to reach significance.
Table 6-15 Bivariate correlations between the principal memory measures in the present study and the number of days since the last use of alcohol (for all participants), as well as the number of days since the last use of cannabis (for cannabis-controls and ecstasy users only)

<table>
<thead>
<tr>
<th></th>
<th>Alcohol</th>
<th></th>
<th>Cannabis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r(93)(^a)</td>
<td>p</td>
<td>r(64)(^b)</td>
<td>p</td>
</tr>
<tr>
<td>CVLT Total Immediate recall</td>
<td>0.00</td>
<td>0.99</td>
<td>0.07</td>
<td>0.57</td>
</tr>
<tr>
<td>CVLT Short Delay free recall</td>
<td>0.04</td>
<td>0.68</td>
<td>0.11</td>
<td>0.39</td>
</tr>
<tr>
<td>CVLT Short Delay cued recall</td>
<td>0.05</td>
<td>0.66</td>
<td>0.11</td>
<td>0.40</td>
</tr>
<tr>
<td>CVLT Long Delay free recall</td>
<td>0.06</td>
<td>0.58</td>
<td>0.08</td>
<td>0.52</td>
</tr>
<tr>
<td>CVLT Long Delay cued recall</td>
<td>0.06</td>
<td>0.56</td>
<td>0.04</td>
<td>0.74</td>
</tr>
<tr>
<td>CVLT Correct recognition</td>
<td>-0.04</td>
<td>0.72</td>
<td>0.13</td>
<td>0.30</td>
</tr>
<tr>
<td>LB Semantic Cluster Immediate</td>
<td>0.10</td>
<td>0.36</td>
<td>0.13</td>
<td>0.31</td>
</tr>
<tr>
<td>LB Semantic Cluster Short Delay</td>
<td>0.07</td>
<td>0.48</td>
<td>0.03</td>
<td>0.81</td>
</tr>
<tr>
<td>LB Semantic Cluster Long Delay</td>
<td>-0.04</td>
<td>0.72</td>
<td>-0.27</td>
<td>0.13</td>
</tr>
<tr>
<td>Visual PA Immediate</td>
<td>0.03</td>
<td>0.75</td>
<td>0.14</td>
<td>0.26</td>
</tr>
<tr>
<td>Visual PA Delayed</td>
<td>0.03</td>
<td>0.74</td>
<td>0.04</td>
<td>0.77</td>
</tr>
<tr>
<td>Verbal PA Immediate</td>
<td>0.02</td>
<td>0.84</td>
<td>0.00</td>
<td>1.00</td>
</tr>
<tr>
<td>Verbal PA Delayed free recall</td>
<td>0.06</td>
<td>0.56</td>
<td>0.00</td>
<td>0.98</td>
</tr>
<tr>
<td>VTA Matched Words on trial 5</td>
<td>0.11</td>
<td>0.32</td>
<td>0.08</td>
<td>0.52</td>
</tr>
<tr>
<td>VTA Total Matched Words total</td>
<td>0.14</td>
<td>0.18</td>
<td>0.12</td>
<td>0.36</td>
</tr>
<tr>
<td>VTA Slope</td>
<td>-0.03</td>
<td>0.76</td>
<td>0.09</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Note. PA=Paired Associates; VTA= Verbal Triplet Associates
\(^a\) \(n=89\) for VTA
\(^b\) \(n=63\) for VTA

6.3.4 Recency of drug use: Correlations between memory performance and the last use of ecstasy, alcohol, cannabis and amphetamines

The focus of all of the studies in the current thesis is on the long-term effects of ecstasy use, as distinct from the acute or residual effects of the drug. In order to assess the likelihood that findings in the present study were due to residual or acute effects of relevant drugs, bivariate correlations were conducted between the principal memory measures and the number of days since participants had last used alcohol, cannabis, amphetamines and ecstasy (see Table 6-15 and Table 6-16).

There were no significant correlations between any of the principal memory measures and the recent use of any drug (Table 6-15 and Table 6-16). However, there were non-significant trends towards an effect of the number of days since the last use of amphetamines on both CVLT long delay free recall and ‘slope’ in the Verbal Triplet Associates test in the ecstasy users group. The potential influence of the recent use of amphetamines on these memory variables was explored using backward elimination
Table 6-16 Bivariate correlations between the principal memory measures in the present study and the number of days since the last use of amphetamines, as well as the number of days since the last use of ecstasy, in the ecstasy users group

<table>
<thead>
<tr>
<th></th>
<th>Amphetamines</th>
<th></th>
<th>Ecstasy</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CVLT Total immediate recall</td>
<td>0.17</td>
<td>0.35</td>
<td>0.14</td>
<td>0.44</td>
</tr>
<tr>
<td>CVLT Short delay free recall</td>
<td>0.11</td>
<td>0.55</td>
<td>0.11</td>
<td>0.55</td>
</tr>
<tr>
<td>CVLT Short delay cued recall</td>
<td>0.10</td>
<td>0.58</td>
<td>0.08</td>
<td>0.65</td>
</tr>
<tr>
<td>CVLT Long delay free recall</td>
<td>0.29</td>
<td>0.11</td>
<td>0.18</td>
<td>0.34</td>
</tr>
<tr>
<td>CVLT Long delay cued recall</td>
<td>0.24</td>
<td>0.19</td>
<td>0.14</td>
<td>0.43</td>
</tr>
<tr>
<td>CVLT Correct recognition</td>
<td>0.15</td>
<td>0.42</td>
<td>0.19</td>
<td>0.30</td>
</tr>
<tr>
<td>LB Semantic Cluster Immediate</td>
<td>0.18</td>
<td>0.34</td>
<td>-0.10</td>
<td>0.59</td>
</tr>
<tr>
<td>LB Semantic Cluster Short Delay</td>
<td>0.23</td>
<td>0.22</td>
<td>-0.13</td>
<td>0.49</td>
</tr>
<tr>
<td>LB Semantic Cluster Long Delay</td>
<td>0.03</td>
<td>0.86</td>
<td>-0.27</td>
<td>0.13</td>
</tr>
<tr>
<td>Visual PA Immediate</td>
<td>0.23</td>
<td>0.22</td>
<td>0.08</td>
<td>0.67</td>
</tr>
<tr>
<td>Visual PA Delayed</td>
<td>0.09</td>
<td>0.65</td>
<td>0.09</td>
<td>0.64</td>
</tr>
<tr>
<td>Verbal PA Immediate</td>
<td>0.01</td>
<td>0.95</td>
<td>0.04</td>
<td>0.83</td>
</tr>
<tr>
<td>Verbal PA Delayed free recall</td>
<td>0.12</td>
<td>0.52</td>
<td>0.18</td>
<td>0.32</td>
</tr>
<tr>
<td>VTA Matched Words on trial 5</td>
<td>0.14</td>
<td>0.47</td>
<td>0.09</td>
<td>0.64</td>
</tr>
<tr>
<td>VTA Total Matched Words total</td>
<td>0.15</td>
<td>0.42</td>
<td>0.07</td>
<td>0.73</td>
</tr>
<tr>
<td>VTA Slope</td>
<td>0.31</td>
<td>0.10</td>
<td>0.06</td>
<td>0.77</td>
</tr>
</tbody>
</table>

Note. PA=Paired Associates; VTA= Verbal Triplet Associates.

Regression analysis, which included the potential covariates identified in sub-sections 6.3.2.2 and 6.3.1.4, respectively. For both memory variables, the number of days since the last use of amphetamines was eliminated from the regression model as not being a significant predictor of memory performance.

6.3.5 Dose dependence: Correlations between memory performance and measures of ecstasy and amphetamine use

In quasi-experimental studies such as the present study, one of Hill’s (1965) criteria for inferring causal relationships is biological gradient, which in the context of drug research refers to the expectation that if a drug causes an effect, then the effect should be larger for increased doses of the drug (‘dose dependence’). This provides an additional method to the group comparisons and covariate analysis (above) for assessing drug effects in the present study. Furthermore, in the between group comparisons in the present study, it was not possible to exercise statistical control over the potential influence of amphetamines on memory performance because of the minimal use of
amphetamines in the cannabis-control group. Therefore, examination of dose
dependence in the present study also provides a means for examining the potential
influence of amphetamines on memory performance.

Bivariate correlations were conducted between the principal memory performance
measures and dose measures of ecstasy use for participants in the ecstasy users group.
The results are shown in Table 6-17. There were no significant correlations with any
ecstasy dose measure for any memory test. Similar bivariate correlations were also
conducted between the same memory performance measures and dose measures of
amphetamine use by ecstasy users. The results are shown in Table 6-18. Significant
negative correlations were found between most CVLT variables and the maximum
monthly dose of amphetamines. These correlations were explored using backward
elimination regression for all of the CVLT measures, including the potential covariates
for each test listed in Table 6-5, Table 6-12 and Table 6-14. For all of the analyses, the
maximum monthly dose of amphetamines was eliminated from the regression model as
not being a significant predictor of the memory performance measure. In combination
these analyses failed to find any significant dose dependant relationships between either
Table 6-18 Dose dependence of amphetamines: Bivariate correlations between the main memory measure in the present study and lifetime dose of amphetamines, maximum monthly dose of amphetamines, and the maximum ever dose of amphetamines in a single session, for all amphetamine users in the cannabis-control and ecstasy user groups

<table>
<thead>
<tr>
<th></th>
<th>Lifetime dose</th>
<th>Max. monthly dose</th>
<th>Max. ever dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>r(45)</td>
<td>p</td>
<td>r(45)</td>
</tr>
<tr>
<td>CVLT Immediate recall</td>
<td>-0.15 0.33</td>
<td>-0.33 &lt;0.01**</td>
<td>-0.05 0.74</td>
</tr>
<tr>
<td>CVLT Short Delay free recall</td>
<td>-0.26 0.08*</td>
<td>-0.43 &lt;0.01**</td>
<td>-0.09 0.54</td>
</tr>
<tr>
<td>CVLT Short Delay cued recall</td>
<td>-0.03 0.86</td>
<td>-0.38 0.01**</td>
<td>0.00 1.00</td>
</tr>
<tr>
<td>CVLT Long Delay free recall</td>
<td>-0.20 0.20</td>
<td>-0.55 &lt;0.01**</td>
<td>-0.17 0.28</td>
</tr>
<tr>
<td>CVLT Long Delay cued recall</td>
<td>-0.27 0.07*</td>
<td>-0.56 &lt;0.01**</td>
<td>-0.14 0.34</td>
</tr>
<tr>
<td>CVLT Correct recognition</td>
<td>0.08 0.61</td>
<td>-0.21 0.17</td>
<td>0.09 0.54</td>
</tr>
<tr>
<td>LB Semantic Cluster Immediate</td>
<td>-0.23 0.14</td>
<td>-0.32 0.03**</td>
<td>-0.27 0.08*</td>
</tr>
<tr>
<td>LB Semantic Cluster Short Delay</td>
<td>-0.21 0.18</td>
<td>-0.24 0.12</td>
<td>-0.09 0.54</td>
</tr>
<tr>
<td>LB Semantic Cluster Long Delay</td>
<td>-0.03 0.84</td>
<td>-0.31 0.04**</td>
<td>-0.08 0.59</td>
</tr>
<tr>
<td>Visual PA Immediate</td>
<td>0.16 0.28</td>
<td>0.05 0.72</td>
<td>-0.04 0.81</td>
</tr>
<tr>
<td>Visual PA Delayed</td>
<td>0.03 0.83</td>
<td>0.19 0.20</td>
<td>0.08 0.61</td>
</tr>
<tr>
<td>Verbal PA Immediate</td>
<td>0.12 0.41</td>
<td>-0.12 0.43</td>
<td>0.11 0.46</td>
</tr>
<tr>
<td>Verbal PA Delayed free recall</td>
<td>-0.19 0.20</td>
<td>-0.17 0.26</td>
<td>0.07 0.65</td>
</tr>
<tr>
<td>VTA Matched Words on trial 5</td>
<td>0.05 0.74</td>
<td>-0.11 0.47</td>
<td>0.14 0.36</td>
</tr>
<tr>
<td>VTA Total Matched Words total</td>
<td>0.04 0.81</td>
<td>-0.05 0.74</td>
<td>0.19 0.23</td>
</tr>
<tr>
<td>VTA Slope</td>
<td>-0.15 0.33</td>
<td>-0.23 0.13</td>
<td>-0.04 0.79</td>
</tr>
</tbody>
</table>

Note: PA=Paired Associates; VTA= Verbal Triplet Associates
* p<.05, ** p<.01
\( \bar{n}=30 \) for VTA

ecstasy or amphetamines and the principal memory measures used in the present study, once other covariates had been taken into account.

6.3.6 The validity of comparing results across the second and third memory studies: Are the results due to sample or test characteristics?

Significant memory deficits were detected in ecstasy users in the present study, but not in the first or second memory experiments (Chapters 4 and 5, respectively). One likely reason for this is that ecstasy users have deficits on the tasks used in the present study, but not on those used in the first and second memory study. However, another possibility is that in general ecstasy users have deficits on all the memory tasks used in all of the studies, and that the different patterns of results are due to differences in the characteristics of the ecstasy users in each study. For example, the deficits in the present study may not be due to the tasks used, as expressed above, but rather may result from the greater use of ecstasy and cannabis by the drug users in this study. This possibility was explored in the present section by comparing 19 ecstasy users who participated in both the present and previous (‘second’) memory studies with those who only
participated in the second memory study, as well as those who only participated in the present study.

In Table 6-19, the 19 ecstasy users who participated in both the second and present memory studies are compared to those who only participated in the second memory study. There was no significant difference between these groups of ecstasy users on demographic variables, estimated IQ, or drug use, although the group that returned to the third memory study tended to be heavier ecstasy users than those who did not return. Importantly, the groups of ecstasy users also did not differ in their performance on the main memory tests in the second memory study. This indicates that the group of participants who chose to return to participate in the present study was not an inadvertently self-selected group of people with particularly poor memories.
The same 19 ecstasy users who participated in both of the second and third memory study (the “old” ecstasy users) were also compared to ecstasy users in the third memory study who had not participated in any of the previous studies (the “new” ecstasy users; see Table 6-20). These groups of ecstasy users were also not significantly different on demographic, estimated IQ and drug use variables, although there were very slight non-significant trends for the new ecstasy users to be slightly younger, and less educated, with less lifetime use of ecstasy. With regard to memory measures, the new and old ecstasy users did not differ on their mean performance on the CVLT and Verbal Paired Associates tests, especially in the delayed conditions. However, the deficits in new ecstasy users compared to non-drug using controls on the immediate recall trials had a much greater level of statistical significance than the old ecstasy users compared to the same group of non-drug using controls. Furthermore, on Visual Paired Associates, the new ecstasy users performed significantly worse than the old ecstasy users. These differences between the new and old ecstasy users suggest that the deficits in ecstasy users on these tasks in the present study may have been due, at least in part, to the new ecstasy users lowering the overall performance of the whole sample. However, it is not clear what difference between the new and old ecstasy users could have caused the lower performance in the new ecstasy users group. As outlined above, the groups are not significantly different on any demographic or drug use variable. While there were trends towards the new ecstasy users being younger with lower lifetime ecstasy use than the old ecstasy users, these trends are in the direction that would predict new ecstasy users having better rather than worse performance. With regard to the trends towards lower education and higher cannabis use in the new ecstasy users, education was shown to be uncorrelated with results in the statistical analysis, and cannabis use was statistically controlled for whenever it was found to be a significant covariate. In summary, it is unclear why the new ecstasy users in the present study performed worse on immediate CVLT and Verbal Paired Associates recall, as well as Visual Paired Associates, compared to ecstasy users who had also participated in the previous study.

Turning to the Verbal Triplet Associates test, the results are much clearer (Table 6-20). On all of the trials, as well as for the total score, there is clearly no significant difference between the performance of new and old ecstasy users. This indicates that, for this task at least, the deficits in ecstasy users in the final memory study appear to be due to characteristics of the task, rather than any difference between the new ecstasy users included in the study and those who have participated in the previous study. This
evidence supports the validity of using the pattern of results obtained across the second and third memory studies (at least with regard to the Verbal Triplet Associates test), to evaluate the role of the hippocampus and other brain regions in ecstasy-related memory deficits.

### Table 6-20 Comparison of ecstasy users who participated in both the second and third memory studies (Study 2 & 3, 'Old'), with ecstasy users who only participated in the third study (Study 3 only, 'New') and non-drug using controls in the third memory study ('C')

<table>
<thead>
<tr>
<th></th>
<th>Study 3 controls “C” (n=33&lt;sup&gt;a&lt;/sup&gt;)</th>
<th>Study 2 &amp; 3 ecstasy users “Old” (n=19&lt;sup&gt;a&lt;/sup&gt;)</th>
<th>Old v. C</th>
<th>Study 3 only ecstasy users “New” (n=13)</th>
<th>New v. C</th>
<th>Old v. New</th>
</tr>
</thead>
<tbody>
<tr>
<td>sex (male %)</td>
<td>63</td>
<td>63</td>
<td>.97</td>
<td>69</td>
<td>.72</td>
<td>.72</td>
</tr>
<tr>
<td>age (years)</td>
<td>Mean (SEM)</td>
<td>Mean (SEM)</td>
<td>.54</td>
<td>Mean (SEM)</td>
<td>.39</td>
<td>.22</td>
</tr>
<tr>
<td>highest level of education attained&lt;sup&gt;c&lt;/sup&gt;</td>
<td>3.42 (0.1)</td>
<td>3.26 (0.17)</td>
<td>.40</td>
<td>3.00 (0.16)</td>
<td>.03</td>
<td>.27</td>
</tr>
<tr>
<td>estimated IQ</td>
<td>106.5 (0.9)</td>
<td>104.1 (1.1)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>.10</td>
<td>104.2 (1.7)</td>
<td>.20</td>
<td>.96</td>
</tr>
<tr>
<td>Ecstasy lifetime dose (tablets)</td>
<td>521.2 (186.9)</td>
<td>207.7 (51.2)</td>
<td>.12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstinence (days)</td>
<td>40.47 (10.69)</td>
<td>31.96 (5.93)</td>
<td>.54</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol lifetime dose (std. drinks)</td>
<td>749 (208)</td>
<td>5591 (1118)</td>
<td>&lt;.001</td>
<td>4599 (1232)</td>
<td>.01</td>
<td>.56</td>
</tr>
<tr>
<td>Abstinence (days)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>170 (104)</td>
<td>5.6 (1.7)</td>
<td>.12</td>
<td>64.0 (43.6)</td>
<td>.50</td>
<td>.21</td>
</tr>
<tr>
<td>Cannabis lifetime “administrations”</td>
<td>1941 (560)</td>
<td>3793 (1736)</td>
<td>.33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstinence (days)</td>
<td>189.6 (91.7)</td>
<td>183.0 (167.3)</td>
<td>.97</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVLT-total immediate</td>
<td>61.1 (1.4)</td>
<td>56.7 (2.3)</td>
<td>.09</td>
<td>53.4 (2.4)</td>
<td>.01</td>
<td>.34</td>
</tr>
<tr>
<td>- delayed</td>
<td>13.3 (0.4)</td>
<td>11.7 (0.8)</td>
<td>.08</td>
<td>11.8 (0.6)</td>
<td>.04</td>
<td>.93</td>
</tr>
<tr>
<td>CVLT LBSCI&lt;sup&gt;f&lt;/sup&gt; immediate</td>
<td>15.3 (2.2)</td>
<td>11.2 (2.9)</td>
<td>.26</td>
<td>6.6 (3.0)</td>
<td>.03</td>
<td>.30</td>
</tr>
<tr>
<td>- short delayed</td>
<td>4.6 (0.6)</td>
<td>4.0 (0.6)</td>
<td>.50</td>
<td>2.3 (0.7)</td>
<td>.03</td>
<td>.09</td>
</tr>
<tr>
<td>- long delayed</td>
<td>5.5 (0.6)</td>
<td>3.9 (0.7)</td>
<td>.10</td>
<td>4.5 (0.7)</td>
<td>.33</td>
<td>.60</td>
</tr>
<tr>
<td>Verbal PA-total immediate</td>
<td>28.3 (0.8)</td>
<td>26.4 (1.5)</td>
<td>.21</td>
<td>25.1 (1.8)</td>
<td>.07</td>
<td>.56</td>
</tr>
<tr>
<td>- delayed</td>
<td>7.8 (0.1)</td>
<td>7.3 (0.3)</td>
<td>.20</td>
<td>7.3 (0.4)</td>
<td>.30</td>
<td>.93</td>
</tr>
<tr>
<td>Visual PA-total immediate</td>
<td>14.2 (0.5)</td>
<td>13.4 (0.8)</td>
<td>.37</td>
<td>10.5 (1.2)</td>
<td>.01</td>
<td>.04</td>
</tr>
<tr>
<td>- delayed</td>
<td>5.8 (0.1)</td>
<td>5.8 (0.1)</td>
<td>.05</td>
<td>5.2 (0.4)</td>
<td>.09</td>
<td>.10</td>
</tr>
<tr>
<td>Verbal Triplets A - total</td>
<td>63.9 (4.1)</td>
<td>47.9 (6.1)</td>
<td>.03</td>
<td>42.7 (7.4)</td>
<td>.01</td>
<td>.59</td>
</tr>
<tr>
<td>- trial 1</td>
<td>6.1 (0.8)</td>
<td>4.0 (0.9)</td>
<td>.11</td>
<td>3.2 (1.0)</td>
<td>.05</td>
<td>.59</td>
</tr>
<tr>
<td>- trial 2</td>
<td>10.7 (1.0)</td>
<td>6.8 (1.2)</td>
<td>.02</td>
<td>6.2 (1.4)</td>
<td>.02</td>
<td>.74</td>
</tr>
<tr>
<td>- trial 3</td>
<td>14.2 (1.0)</td>
<td>10.2 (1.5)</td>
<td>.02</td>
<td>9.2 (1.8)</td>
<td>.01</td>
<td>.66</td>
</tr>
<tr>
<td>- trial 4</td>
<td>15.8 (0.9)</td>
<td>12.3 (1.6)</td>
<td>.05</td>
<td>11.5 (1.7)</td>
<td>.02</td>
<td>.72</td>
</tr>
<tr>
<td>- trial 5</td>
<td>17.1 (0.7)</td>
<td>14.6 (1.3)</td>
<td>.10</td>
<td>12.6 (1.7)</td>
<td>.03</td>
<td>.38</td>
</tr>
</tbody>
</table>

<sup>a</sup> Demographic and drug use data at Study 3

<sup>b</sup> Median abstinences: non-drug using controls=7, “old” ecstasy users=3, “new” ecstasy users=3 days

<sup>c</sup> estimated IQ was measured during the second study, and that data transferred to the third study because the test could not be validly repeated. Only new participants were tested in the third study. This also applied between the first and second studies.

<sup>d</sup> except for Verbal Triplet Associates for which n=30, and for alcohol use n=29

<sup>e</sup> 1=Year 10 (middle secondary education); 2=Year 12 (upper secondary education); 3=Bachelor undergraduate degree; 4=post-graduate degree

<sup>f</sup> LBSCI = List-Based Semantic Clustering Index
6.4 Discussion

The main aim of the present study was to investigate the impact of possible ecstasy-related changes in elaborative processing, on the performance of ecstasy users on long-term explicit memory tests. This was achieved by comparing ecstasy users to both cannabis-controls and non-drug using controls on a number of tests that differed in their elaborative processing demands, including the California Verbal Learning Test (CVLT, based on a list of single words from four distinct semantic categories, Delis et al., 1987), Verbal Paired Associates (based on a list of word-pairs, from the Wechsler Memory Scales III (WMS-III), Wechsler, 1997a), Visual Paired Associates (based on pairs of diagrams and colour squares, from Wechsler Memory Scales - Revised (WMS-R), Wechsler, 1987), and a novel test called Verbal Triplet Associates developed specifically for the current study (based on a list of word-triplets).

6.4.1 Summary of findings in the present study

The most common pattern of results obtained for tests in the present study was that ecstasy users had significant performance deficits compared to both cannabis-controls and non-drug using controls, and that there was no significant performance difference between the two control groups. Before controlling for possible covariates, this pattern of results was found for immediate recall in the CVLT test (including the semantic clustering index), Verbal Paired Associates (for repeated measures analysis on trials 1 & 2, as well as simple effects analysis of trial 1) and Verbal Triplet Associates, as well as for a simple effects analysis on the third trial of Visual Paired Associates. On delayed recall, this same pattern of results was obtained for CVLT recall, including free recall and category-cued recall after both short and long delays, as well as recognition after the long delay, and the semantic clustering index. For multi-component items, there were no interpretable measures of delayed performance on any test because of considerable ceiling effects in the Verbal Paired Associates and Visual Paired Associates test results, and there was no delayed condition on the Verbal Triplet Associates test.

The possible explanations for these deficits in ecstasy users included a number of variables on which the groups differed, apart from the difference on their ecstasy use status. The groups were well matched on sex and age, but there were trends towards ecstasy users having a lower estimated IQ and a lower level of eduction than non-drug
using controls. There were significant differences between the groups on indicators of personality, mental health, and alcohol use. In addition, the cannabis-controls and ecstasy users also differed on cannabis and amphetamine use. The influence of these group differences were investigated and controlled for by statistical means.

After controlling for significant covariates, the pattern of results in which ecstasy users performed significantly worse than both cannabis-controls and non-drug using controls remained unchanged for most tests, including: CVLT immediate free recall, CVLT short and long delayed free recall, and the CVLT immediate and short delayed semantic clustering index, as well as the third trial of the Visual Paired Associates test. On Verbal Paired Associates immediate recall, ecstasy users performed significantly worse than cannabis-controls, and there was a non-significant trend towards ecstasy users also having poorer performance than non-drug using controls. In contrast, the performances of ecstasy users and the control groups on CVLT short- and long-delayed category-cued recall were no longer significantly different after controlling for covariates. Also, on the long-delayed CVLT semantic clustering index, controlling for covariates reduced the difference between ecstasy users and cannabis-controls to a non-significant trend.

The results for the Verbal Triplet Associates test were more complex. After statistically controlling for covariates, including alcohol, ecstasy users performed significantly worse than non-drug using controls on all trials. The recall of cannabis-controls on the first trial was not significantly different from ecstasy users. However, the cannabis-controls improved their performance across trials at a rate significantly greater than ecstasy users, such that by the fifth trial, the performance of the cannabis-controls was no longer significantly different from that of the non-drug using controls, but was significantly better than ecstasy users.

6.4.2 The consistency of the results compared to previous literature

In general, the results obtained in the present study for the standard neuropsychological tests are consistent with those in previous literature. For the CVLT, the significant deficits found in ecstasy users in the present study were consistent with the only two reports in published literature of this test having been applied to ecstasy users. (Halpern & LaMay, 2000; Semple et al., 1999). Since neither of those studies reported delayed recall or the semantic clustering index, the present study is the first known report of those measures in ecstasy users.
With regard to the Verbal Paired Associates test, the significant recall deficit in ecstasy users compared to cannabis-controls on the first trial is consistent with the only other studies to report results on individual trials (Montgomery et al., 2005; Ward et al., in press). For the delayed condition, most ecstasy users and non-drug using controls in the present study achieved perfect scores, and consequently there was very little difference in the average delayed recall between the groups. This is consistent with results obtained by Ward et al (in press) and Bolla et al. (1998)\(^\text{16}\), but in contrast to Rodgers (2000) who reported significantly worse delayed recall in a group of 15 relatively light ecstasy users (average use of 20 times over the previous 5 years) in comparison to both cannabis-controls (who were well matched on cannabis use) and non-drug using controls.

For Visual Paired Associates, the lack of a statistically significant deficit on the overall immediate recall performance is consistent with Bolla et al. (1998), but in contrast to a significant deficit found by Rodgers (2000). Published studies have only ever reported composite immediate recall measures for the Visual Paired Associate test, so the significant deficit on the third trial in the present study is the first known report of a deficit on an individual trial.

In summary, with the exception of the Rodgers (2000) study, the results for all of the standard neuropsychology tests in the present study are consistent with published studies which also reported results of the same variables. It is unclear why the findings of Rodgers (2000) are in contrast with the delayed Verbal Paired Associates recall and the Visual Paired Associates immediate recall results in the present study. The more significant deficits in the Rodgers study suggest that the ecstasy users had greater cognitive impairment, despite having used ecstasy relatively few times compared to ecstasy users in the present study.

\(^{16}\) Bolla et al. (1998) reported that there were no statistically significant differences between ecstasy users and controls on any memory measure, but did find a significant dose dependence between delayed recall on the Verbal Paired Associates and the average monthly dose of ecstasy once this variable was introduced into a regression model.
6.4.3 Interpretation of findings

6.4.3.1 The CVLT semantic clustering index

All of the experimental tasks in the present study were selected to reveal some aspect of the role of elaborative processing in long-term explicit memory performance. The only specific measure of such processing in any test was the CVLT semantic clustering index, which measures the extent to which participants group the list of single words at recall into the four distinct categories represented in the word list. Since the CVLT tests memory for a list of single unrelated words, the use of elaborative processing at study is not specifically required to do the task. However, participants can choose to use elaborative processing to their strategic advantage, which is encouraged by the four distinct semantic categories represented in the word list.

The CVLT semantic clustering index results indicates that ecstasy users made significantly less strategic use of the semantic categories in the immediate and short-delayed tests, compared to both cannabis-controls and non-drug using controls. There was also a trend towards ecstasy users having made less use of the semantic categories on the long-delayed test. Interestingly, when provided with the category names in the short-delayed category-cued recall test, the performance of ecstasy users was no longer significantly different from controls. However, the ecstasy users still had a significant deficit compared to the control groups on the subsequent long-delayed free recall task, before once again being not significantly different from controls on the long-delayed category-cued task. This suggests that ecstasy users had trouble remembering or using the categories (and words) in the free recall tasks, but that ecstasy users were able to use the categories to recall approximately as many words as controls whenever the experimenter provided the category names (i.e., in the category-cued recall tasks). To be able to do this, the ecstasy users had to have identified the categories at study, and then used them to generate semantic associations between the words and categories for later use in the category-cued recall tasks. However, the return of the ecstasy users to a significant free recall deficit following the long delay (i.e., after having had no deficit on the short-delayed cued recall task), suggests that the consolidation of the semantic structures of the category information into long-term memory by ecstasy users at study was relatively weak compared to controls. This could have resulted from either slower elaborative processing, or the slower transfer of information between the processing and
memory centres of the brain. Either of these changes in processing speed would reduce the time available to consolidate the semantic structures into memory.

6.4.3.2 Learning in ecstasy users compared to cannabis-controls

Evidence consistent with slower processing speed in ecstasy users was also obtained in the present study using the Verbal Triplet Associates task. That task was developed for the present study in order to overcome the significant ceiling effects obtained when using the Verbal Paired Associates test on research participants who do not have large cognitive deficits (e.g., Ward et al., in press). The ceiling effects on these tasks prevent a valid assessment of the learning rate of ecstasy users compared to controls. On the Verbal Triplet Associates task, ceiling effects were not apparent for the ecstasy users or cannabis-control group on any trial, and were only apparent for the non-drug using controls on the fourth and fifth trials. A comparison of the rate at which participants learnt the triplets over the first three trials revealed that despite having a similar deficit to ecstasy users on the first trial, that cannabis-controls improved across trials at a rate not significantly different from that of the non-drug using controls. In contrast, the ecstasy users improved at a rate significant less than both non-drug using controls and the cannabis-controls. Thus, only ecstasy users appear to have had a lower learning rate over successive trials, whereas cannabis users had a deficit in immediate recall but had unimpaired learning ability.

A similar pattern of results was obtained in the Visual Paired Associates test. On the first two trials, the recall of ecstasy users was not significantly different from either cannabis-controls or non-drug using controls. However, on the third (final) trial, the ecstasy users had improved less than the two control groups, such that they recalled significantly fewer items than either of the controls groups. This occurred despite the performance of the non-drug using control group approaching ceiling (see Figure 6.4). Like the results of the Verbal Triplets Associates test, this indicates that ecstasy users had the same initial performance as the cannabis-control group, and in this case the non-drug using control group as well, but that ecstasy users had a lower learning rate over successive trials.

One plausible explanation for the lower learning rate in ecstasy users is that they have a lower elaborative processing speed. In the Verbal Triplets Associates and Visual Paired Associates tests, the first trial differs from subsequent trials in that the participants are
exposed to the stimuli for the first time, and are still getting to know what the task involves through the experience of being exposed to the stimuli. They are also presumably having an initial attempt at forming memorable semantic associations, and have not yet been exposed to the test phase to help them refine the best strategy to use in the study phase. Under these conditions, ecstasy users and cannabis users appeared to be equally impaired compared to controls. However, on the subsequent trials, the initial exposure to the task and stimuli has passed, and they have already had an opportunity to develop their strategies for learning the triplets. Under these conditions, the cannabis users appear to improve at the same rate as the controls, however, the ecstasy users appear to have additional problems in improving their performance. As expected, the fact that ecstasy users are able to do the task at all, confirms that they are capable of forming semantic associations for multi-component stimuli. The ongoing lower learning rate in ecstasy users may therefore emerge for similar reasons to those proposed for the lower CVLT semantic clustering index scores, which were that either ecstasy users have slower elaborative processing, or the speed of transfer of information between the elaborative processing and memory centres of the brain. Either of these reductions in processing speed would reduce the time available to consolidate semantic structures into memory, and thus would reduce the rate at which new material is learnt.

6.4.3.3 The validity of interpreting the pattern of results across memory studies in the current thesis

The evaluation of elaborative processing involved in the recall measures in the present study (as distinct from the measures of learning and semantic clustering evaluated above) require comparisons to be made with the findings regarding other components of memory tested in the previous chapters. The tests used in the previous studies did not find any ecstasy-related deficits on any test of implicit or explicit memory for lists of single unrelated words. In contrast, the present study found significant explicit memory deficits for a list of words drawn from four semantic categories, and on lists of multi-component items. One obvious explanation for the different results between the studies is that they used different tasks, such that in general ecstasy users have deficits on the tasks in the present study, but not on those used in the previous studies. However, an alternative explanation is that the different patterns of results were due to differences between the samples of ecstasy users, rather than differences between the tasks that were applied. According to this explanation, the ecstasy users in the present study may
have been more impaired than those in the previous studies, and as such they would have also had deficits on the tasks in the previous studies had they been applied to them.

The basis for the different patterns of results obtained in the present study and previous chapter was evaluated by comparing the sample characteristics and memory performance of ecstasy users who participated in both studies, with those who only participated in one of the studies. For the previous study, there were no statistically significant differences between the 19 ecstasy users who went on to participate in the present study, and those who did not, on any demographic, drug use, or memory performance measure. This indicates that the ecstasy users who chose to participate in both studies were not an inadvertently self-selected group who were unrepresentative of the entire sample of ecstasy users in the previous chapter, or who had greater cognitive impairments than those who did not participate in the present study. In addition, in the present study, the 19 “old” ecstasy users who participated in both studies were also not significantly different on demographic, drug use, or memory performance measures from the “new” ecstasy users (i.e., those had not participated in the previous study). However, compared to the non-drug using controls in the present study, the new and old groups of ecstasy users had different patterns of results on the standard neuropsychological tests (CVLT, Verbal Paired Associates, Visual Paired Associates), such that the new ecstasy users tended to perform significantly worse than the non-drug using controls, whereas the 19 ecstasy users from the previous study did not. For example, on the short-delay CVLT semantic clustering index, there was a non-significant trend towards new ecstasy users having lower scores than the ecstasy users from the previous chapter. Also, compared to non-drug using controls, the new ecstasy users had a significant performance deficit, whereas the ecstasy users from the previous study clearly did not. Thus, the significant deficits on the standard neuropsychological tests in the present study may have been due, at least in part, to the inclusion of ecstasy users with higher levels of cognitive impairment on these particular tasks, rather than solely due to the demands of the task.

In contrast, the significant deficits on Verbal Triplet Associates recall in ecstasy users in the present study appear to be due to the nature of the task, rather than the inclusion of ecstasy users who performed significantly worse on this task. On Verbal Paired Associates, the new ecstasy users in the present study were clearly not significantly different from the 19 ecstasy users from the previous study, and both groups of ecstasy
users had the same pattern of results compared to non-drug using controls. Since this was not the case with the standard neuropsychological tests above, the comparison of results across the memory studies in the following section will focus on the interpretation of the findings from the Verbal Triplet Associates task in light of the previous studies.

6.4.3.4 The localisation of long-term memory deficits in the brain: The implications of the pattern of results across the memory studies in this thesis

In Chapter 3, it was outlined that the localisation of long-term memory deficits in ecstasy users in the current thesis would be evaluated by comparing tests designed to reveal different components and processes of memory, starting with tests that were as specific as possible in a cognitive study to a single component of memory, and comparing the findings on that test to other tests which were responsive to other components of memory. Within this framework, the previous studies did not find any ecstasy-related deficits on tests of implicit or explicit memory for lists of single unrelated words. In light of the literature regarding the components and processes of memory revealed by those tasks, those results were interpreted as being inconsistent with the attribution of deficits on tests of long-term memory to ecstasy-related changes in the hippocampus, and/or to implicit memory components localised in the sensory areas of the brain. The main difference between the Verbal Triplet Associates task in the present study, and the free recall tasks in the previous study (follow-up free recall, and AVLT) is that the Verbal Triplet Associates task required participants to generate semantic associations between words at study, whereas the tasks in the previous study did not. Since associative processes have been shown to be localised in the frontal lobes (Posner et al., 1988; Roskies et al., 2001; Schreckenberger et al., 1998; Shaywitz et al., 1995), this suggests that ecstasy-related deficits in long-term memory tasks may emerge either from deficits in frontal lobe processes, or from the aggregation of smaller deficits to many brain systems including the frontal lobes, which only cause significant behavioural deficits when several brain regions are loaded concurrently.

6.4.4 Evidence regarding slower processing speed in ecstasy users in previous literature

Earlier in this discussion, it was proposed that the pattern of results in the present study could be explained by elaborative processing being slower in ecstasy users compared to
controls. This proposal was inferred from ecstasy users having lower CVLT semantic clustering index scores, and a lower learning rate across trials on the Verbal Triplet Associates and Visual Paired Associates tasks, compared to the control groups. Anecdotally, some support for this proposal was provided by ecstasy users in the present study, who expressed frustration at their poor ability to do the Verbal Triplet Associates task by exclaiming that they could have done the task much better if the experimenter had read the triplets a little slower. While this was not formally tested in the present study, some direct evidence of slower processing in ecstasy users has been obtained using reaction time tasks. As outlined in the discussion in Chapter 4 (the first memory study), evidence of longer reaction times in ecstasy users have been obtained under both full- and divided-attention conditions (e.g., Daumann, Schnitker et al., 2003; Verkes et al., 2001). However, the pattern of results has been inconsistent across studies. Further research is required to clarify the conditions under which longer reaction times in ecstasy users reliably occurs, and to reveal the underlying cause of that effect.

Of particular interest to the present study are findings that indicate a relationship between slower processing and serotonergic functioning. Disruption to the serotonin system by tryptophan depletion has been shown to be associated with longer processing times (especially with increased task difficulty) and an increase in the number of trials required to learn visuo-spatial associations (i.e., learning rate), but with no overall effect on response accuracy or recall (Park et al., 1994; Sobczak et al., 2002). Also, a neuroendocrine challenge study conducted by Verkes et al. (2001) found that disruption to the serotonin system by administration of the indirect serotonin agonist dexfenfluramine had a significantly greater effect on cortisol levels in ecstasy users compared to cannabis-controls, and that cortisol levels were significantly correlated with working memory span. Other cognitive tests applied showed that ecstasy users also had longer reaction times, and poorer long-term memory recognition. While these tryptophan depletion and neuroendocrine studies have not tested the type of elaborative processing evaluated in the present study, the results indicate the presence of a link between serotonergic functioning and the speed of cognitive processing, as well as a link between serotonin and the number of trials required to learn novel stimuli.

If the deficits on the explicit memory tasks in the present study are due to slower processing speed, then the degree of slowing in ecstasy users may be considerable. The
Verbal Paired Associates task is less cognitively demanding and has more time available to learn each item than the Verbal Triplet Associates task. This suggests that if the deficits are due to slower processing speed in ecstasy users, then considerably more time at study would need to be allowed for ecstasy users to process the stimuli than is already allowed in Verbal Paired Associates. This could be tested in future research by varying the amount of time available at study in the Verbal Triplets Associates and Verbal Paired Associates tests. If the provision of substantially more time at study to learn the word-pairs and/or triplets did not significantly reduce or eradicate the difference between the groups, then this would suggest that the performance deficits on associative tasks in ecstasy users is not due to processing speed, but rather some other aspect of formation of the memory trace.

6.4.5 Summary of discussion

In summary, the present study found significant memory deficits in ecstasy users compared to both cannabis-controls and non-drug using controls. The deficits were found on tests of memory for lists of multi-component items, as well as on the use of elaborative processing strategies in a test of memory for single words drawn from a set of four distinct semantic categories (i.e., the CVLT). In addition, the performance of ecstasy users in the Verbal Triplets Associates test improved across trials at a lower rate than both cannabis-controls and non-drug using controls. Of particular interest was that ecstasy users and cannabis-controls showed immediate recall deficits after the first learning trial, but only ecstasy users had a significantly lower learning rate across trials compared to both controls groups. It was argued the pattern of deficits in the present study could be explained by slower elaborative processing speed in ecstasy users. This possibility is supported by published literature that has reported evidence of a relationship between acute disruption to the serotonin system and slower cognitive processing.

The significant results in the present study are in contrast with the lack of significant deficits in ecstasy users on memory for lists of single unrelated words, as well as prose recall, in the previous studies in this thesis. This pattern of results was interpreted in light of evidence from published literature about the localization of the components and processes of memory that were revealed by the various tests. Overall, the findings of the present series of studies suggest that deficits in ecstasy users on tests of long-term
memory may emerge either from deficits in frontal lobe processes, or from the aggregation of smaller deficits in many brain systems that appear non-significant when tested independently, but result in significant deficits on complex tasks which tax multiple brain regions concurrently. This is in contrast to the attribution of explicit memory deficits solely to central memory structures such as the hippocampus (e.g., Gouzoulis-Mayfrank et al., 2003).
Chapter 7. The consequences of ecstasy use on the behavioural functioning of the occipital lobe

7.1 Introduction to the present study

7.1.1 Overview

The empirical research reported in Chapters 4 to 6 investigated the nature of long-term memory deficits in ecstasy users in terms of the various components and processes of the memory system. The overall pattern of results across the studies was interpreted as indicating that memory deficits in ecstasy users either reflect elaborative processing deficits (thought to be localised in the frontal lobes), or emerge from aggregation of smaller deficits in many brain systems. This chapter turns to a somewhat different question by investigating possible ecstasy-related deficits in visual processes that reflect occipital lobe functioning. Some studies have reported changes in the neural functioning of the occipital lobes of ecstasy users, as indicated by altered electrical and blood-oxygen activity (e.g., Daumann, Schnitker et al., 2003; Gamma, Frei et al., 2000). However, there have been no studies published to date that have investigated if these changes result in alterations in the behavioural functioning of ecstasy users, indicated by performance differences between ecstasy users and controls on tasks which are thought to reflect occipital lobe processes.

The occipital lobe is primarily involved in the low-level processing of visual information, including simple orientation, motion and depth perception. All of these processes are potential targets for ecstasy studies. In the present study, I chose to investigate orientation perception because there is some evidence of serotonergic involvement in the processing of orientation, and particularly in a visual illusion called the tilt aftereffect.

The following section contains a review of studies published to date regarding ecstasy-related changes to the neural functioning of the occipital lobe. Overviews are then provided of: how orientation is encoded in the occipital lobe; how it can be investigated experimentally using the tilt aftereffect illusion; and the possible role of serotonin in limiting the size of the tilt aftereffect through narrowing the tuning bandwidth of orientation sensitive neurons. This leads to the prediction that ecstasy-related serotonergic changes in the occipital lobe would broaden the tuning of the neurons, and
thereby increase the magnitude of the tilt aftereffect in ecstasy users compared to non-drug using controls.

Evidence in support of this prediction is then reported in a study in which I compared the magnitude of the tilt aftereffect in 30 ecstasy users to that of 34 non-drug using controls at two adaptation angles, 15° and 40°. The results at 40° show for the first time increased magnitude of the tilt aftereffect in ecstasy users, after statistically controlling for an unexpected effect of recent amphetamine use. This is a novel result, and is consistent with the increase in the tilt aftereffect in ecstasy users (after controlling for amphetamine use) being mediated by serotonergic involvement in narrowing the tuning bandwidth of orientation sensitive neurons in the occipital lobe.

7.1.2 Evidence consistent with ecstasy having a long-term effect on the neural functioning of the occipital lobe

Like any other part of the brain, the effects of ecstasy on the occipital lobe can be thought of as having acute, residual and long-term effects. Ecstasy users report that the acute effects of ecstasy include a temporary increase in visual “clarity” (sic) and the intensity of colour perception, which later returns to normal (e.g., Liester et al., 1992). Some research suggests that a residual effect of ecstasy use is an increase in the excitability of neurons in the occipital lobe which lasts for at least three days, as indicated by an average lower phosphene threshold in ecstasy users compared to non-drug using controls following stimulation of the occipital lobe by Transcranial Magnetic Stimulation (TMS, Oliveri & Calvo, 2003). With respect to long-term effects, research outlined in the following sections includes a review of the only published case study in which an ecstasy user reported chronic visual perception distortions, as well as evidence from other studies in which ecstasy-related changes to occipital lobe neural functioning was indicated by measurements of electrical activity and blood-oxygen content.

7.1.2.1 Subjective report

There has been one published case report of a heavy ecstasy user who developed a persistent and continual distortion in his vision which was thought to result from his ecstasy use (Passie, Schneider, & Emrich, 2002). The afflicted person described his vision as being like a “snow-storm on a defective TV” when his eyes were open, which overlayed his otherwise normal vision. When his eyes were closed he reported seeing
colourless dots. An examination did not reveal any eye abnormalities. The reported distortions are consistent with a disturbance in low-level visual perception processes, such as those in the occipital lobe, rather than higher-order visual processes in the temporal and parietal lobes.

In terms of the dosage required to produce this effect, the person had reported that they had used ecstasy “almost daily”, consuming a total of over 350 tablets in 18 months, taking up to 8 tablets per day. However, it is worth noting that other studies (including those reported in this thesis) often include some users who have had much higher lifetime total doses of ecstasy, with periods of similar or greater frequency of use, but without any reported visual distortions (Fox, Toplis et al., 2001; Gouzoulis-Mayfrank et al., 2003). Thus, while it is possible that the distortions may have been caused by sustained periods of daily ecstasy use, it could also be that the person in the Passie et al. (2002) study was either particularly sensitive to ecstasy-related damage, or that their ecstasy use exacerbated some other pre-existing problem. The effects may also have been due to an unusual contaminant in the ecstasy tablets that they had administered, or some unrelated neurological condition. This would explain why the effects are not commonly reported in other ecstasy users.

7.1.2.2 Electroencephalography (EEG)

Gamma and Frei et al. (2000) investigated long-term ecstasy-related changes to the electrical activity of the occipital lobe. Measurements were taken on the surface of the head by electroencephalography (EEG). They found significantly greater electrical power over the occipital lobe and temporooccipital lobe of ecstasy users compared to other drug users who had not used ecstasy. Interestingly, the lateralisation (left or right) of the power differences varied according to whether the eyes were open or closed. This suggests that the changes in electrical activity in the occipital region were related to cohort differences in the processing visual inputs, at least when the eyes were open.

Further evidence of ecstasy-related EEG changes were obtained by Dafters, Duffy, O'Donnell, and Bouquet (1999). They found greater EEG power in many parts of the frontal lobe.

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17 The participants were apparently not required to perform any tasks when their eyes were closed, or to view any specific stimuli when their eyes were open (Gamma, Frei et al., 2000).
brain in ecstasy users who had reportedly been free of illicit drugs for at least a week. Of particular relevance to the present study is that ecstasy use over the previous year was negatively correlated with specific EEG measures thought to indicate the functioning of the main visual association pathways between the occipital lobe and parietal-temporal lobes, such that greater ecstasy use was associated with lower visual association pathway activity. The results remained significant after statistically accounting for the use of other drugs.

Each of the above studies shows ecstasy-related changes in electrical activity in a different part of the visual system. The contrasting direction of the findings – that ecstasy use was associated with both an increase in activity in the occipital lobe and a decrease in visual association pathway functioning – are not necessarily conflictual. Different types of serotonin receptors can perform excitatory and inhibitory functions (Barnes & Sharp, 1999), and so one plausible explanation of the different directions of the results is that the two effects reflect damage to different types of serotonin receptors. Another possible explanation is that the increased electrical activity within the occipital lobe may inhibit the signalling between the occipital lobe and higher-order centres later in the visual association pathway in the parietal and temporal lobes.

7.1.2.3 Functional Magnetic Resonance Imaging (fMRI)

Daumann et al. (2003) used functional Magnetic Resonance Imaging (fMRI) scans to compare the occipital lobe blood-oxygen content in ecstasy users to that of non-drug using controls. In a repeated measures design, the fMRI scans were obtained while participants were engaged in a visual sequential “n-back” task, in which they were required to press a button when the current letter in a sequence matched the previous letter (1-back condition), the letter from two-trials earlier (2-back condition), or a previously specified target letter (0-back condition). There were no behavioural performance differences between the ecstasy users and controls on any condition of the n-back task. However, the fMRI scans showed the blood-oxygen content in the primary visual cortex of ecstasy users was significantly lower than that of the controls, as indicated by a lower Blood Oxygenation Level-Dependent (BOLD) contrast signal. This suggests that ecstasy use was associated with changes in the neural functioning of the occipital lobe.
As with the EEG studies, the exact neural mechanism underlying these changes is currently unknown. The interpretation of the BOLD signal is complex and not fully understood, especially with regard to the relationship between BOLD and inhibitory neural circuits, such as those proposed later in this chapter regarding serotonergic involvement in visual line orientation processing (Logothetis & Wandell, 2004; Tagamets & Horwitz, 2001). It is possible that the lower BOLD signal reflects decreased competition between excitatory and inhibitory signals brought about by a decrease in serotonergic inhibitory signals in the occipital lobe.

Of particular relevance to results obtained in the present study, the reduction in the BOLD signal detected by Daumann et al. (2003) was only detected in ‘pure’ ecstasy users, and not in ecstasy users who had also used other drugs. The authors suggested that this may have occurred because other drugs had a contrary effect to ecstasy. That is, the use of a variety of drugs could have damaged a range of both excitatory and inhibitory systems such that no overall detectable change occurred in the competition between exhibitory and inhibitory systems. This raises the possibility that the use of other drugs, in addition to ecstasy, may also have contrary effects on the behavioural functions of the occipital lobe as tested in the present study.

7.1.2.4 Summary of published research to date regarding the effect of ecstasy on the operation of the occipital lobe

The evidence outlined in this section from EEG and fMRI studies, as well as the single case study, suggests that ecstasy results in detectable changes in the operation of the occipital lobe. Given the evidence of the long-term effects of ecstasy on the serotonin system (see Chapter 1), it is likely that these neural changes reflect ecstasy-related changes to the serotonin system within that lobe.

If these changes impact important visual perception processes, then it should be possible to detect associated changes in the behavioural responses of ecstasy users in a visual perception experiment, if appropriate stimuli and response requirements are used. However, no study published to date has experimentally investigated such changes in the behavioural functioning of ecstasy users. In order to identify a suitable method to investigate this in the present study, the following sections look briefly at what visual perception functions are carried out in the occipital lobe, and the theory underlying the method selected for the present study.
7.1.3 The functions of the occipital lobe which can be observed experimentally

The occipital lobe contains the primary visual processing area of the brain, commonly designated as “V1”. Area V1 receives input from the eyes via subcortical brain structures, and projects outputs to other parts of the visual cortex along various neural pathways (Engel et al., 1994; Heimer, 1994; Hubel & Wiesel, 1974). As visual information is transferred along these pathways, the type of information represented by the activation of neurons in each area increases in complexity. Information that is directly processed in V1 is limited to basic visual attributes like the detection of the orientation of lines and edges, as well as simple motion and stereoscopic depth extraction (for review see Zeki, 1993). Cortical areas further along the visual pathways use the results of these V1 processes to extract more complex visual information, such as the three-dimensional shapes of objects. V1 also receives feedback from these processing areas, through which these higher-order functions can moderate V1 neuronal activity.

Of the basic visual functions directly carried out within the occipital lobe, there is some evidence for the involvement of serotonin in simple orientation perception (Masini, Antonietti, & Moja, 1990). Also, orientation detection is relatively simple to test in laboratory experiments. Since this was the first known study to investigate the behavioural functioning of the occipital lobe in ecstasy users, it was decided to focus the present study on investigating whether ecstasy-related changes to the serotonin system in the occipital lobe causes long term changes in orientation processing.

7.1.4 How orientation is encoded in the occipital lobe

Neurons in area V1 of the occipital lobe are sensitive to light falling within a small specific region of the visual field. This region is called the ‘receptive field’ of the neuron. In order to activate a particular neuron, the precise stimulus attribute that the neuron is tuned to must fall within its receptive field. In area V1, many neurons are tuned to detect a particular orientation (Hubel & Wiesel, 1974; Tootell et al., 1998). The level of activation of these neurons decreases sharply for lines angled away from the orientation it is tuned to (the ‘preferred’ orientation). This produces a characteristic tuning curve for that neuron, as illustrated in Figure 7.1. The range of orientations that a particular neuron responds to is called its bandwidth, often represented by the width of the tuning curve at half of the maximum height of the curve, also shown in Figure 7.1.
Neurons in V1 are arranged in a highly organised columnar structure. All of the neurons within a single column share the same receptive field, and respond to the same preferred orientation, although vary in their response according to other attributes of the stimulus, such as spatial frequency, colour, and luminance polarity. Columns are grouped into ‘hypercolumns’. All columns in a hypercolumn respond to the same receptive field, but to different preferred orientations, such that the entire range of possible orientations are represented within each hypercolumn.

Within a hypercolumn, the preferred orientation of columns progresses uniformly from 0° to 180°, with the difference between successive columns being approximately 10° to 15°. Single-cell recording experiments in primates have shown that the tuning bandwidth for most individual neurons is between 20° and 50° (Ringach, Shapley, & Hawken, 2002; Schiller, Finlay, & Volman, 1976). As a consequence, a line of any given orientation in a particular receptive field produces a pattern of activation across of population of neurons, each having a level of activation proportional to the difference between its preferred orientation and the orientation of the stimulus, as illustrated in Figure 7.2. The broader the bandwidth of individual neurons, the greater the range of

Figure 7.1 An example tuning curve for an orientation sensitive neuron in the occipital lobe. The sample neuron shown responds with its maximum level of activation for vertical lines (i.e. its preferred orientation), with a bandwidth of approximately 50°, as determined at the width of the curve at half the height of the curve (from Sekuler & Blake, 2002)
preferred orientations represented in the pattern of activation. The pattern of activation
to any single orientation allows the visual system to encode orientation with a precision
greater than the 10° to 15° difference between neurons within a hypercolumn.

The bandwidth of V1 neurons is determined in part by lateral-inhibition between
neurons within a hypercolumn. When an orientation sensitive neuron is activated, it
sends signals to inhibit the level of activation of neurons tuned to nearby orientations
(Shapley, Hawken, & Ringach, 2003). This serves to decrease the level of activation of
each neuron to orientations apart from the preferred orientation it is tuned to, thereby
narrowing the tuning curve bandwidth of each neuron.

Of particular interest to the present study is evidence that serotonin may be involved in
the lateral inhibition between orientation sensitive neurons, and thereby affect the tuning
bandwidth of those neurons. This evidence was obtained by Masini et al. (1990) who
studied the effect of serotonin depletion on the tilt aftereffect illusion. Before discussing

\[ \text{Level of activation} \]
\[ \text{The preferred orientation of individual neurons} \]

Figure 7.2 Illustration of the pattern of activation of a population of neurons to a vertical
stimulus. The neuron with a preferred orientation of vertical has the maximum level of
activation. Neurons with nearby preferred orientations have progressively lower levels of
activation in proportion to the difference between their preferred orientation and the
orientation of the stimulus. (Extract from Figure 7.3; adapted from Sekuler & Blake,
2002)
the findings of that study, it is first necessary to be familiar with the tilt aftereffect illusion, and the neural mechanism thought to underlie it, as outlined in the following section.

### 7.1.5 The tilt aftereffect and the neural mechanisms thought to underlie it

The tilt aftereffect is a visual illusion which can be easily observed by staring at a set of parallel lines angled at, say, $15^\circ$ (the ‘adaptation angle’) to the right of vertical for a few minutes (adaptation phase), then looking at a set of vertical lines (test phase). Under these conditions, the vertical lines at test appear to be orientated slightly to the left of vertical. Thus, the tilt aftereffect is observed as a deflection of the orientation of the test stimulus away from the orientation of an adaptation stimulus.

The magnitude of the tilt aftereffect is defined as the difference between the angle perceived as vertical before adaptation, and the angle perceived as vertical after adaptation. Tilt aftereffect studies have tested normal participants over a range of adaptation angles, say between $5^\circ$ and $45^\circ$ from vertical. The maximum effects occur for adaptation angles between $10^\circ$ and $20^\circ$ from vertical (Gibson & Radner, 1937) and can occur with an adaptation time of as little as 90 seconds.

The neural mechanisms underlying the illusion are thought to principally involve changes in the pattern of activation across the orientation-specific V1 neurons (Carpenter & Blakemore, 1973). At the onset of the adapting stimulus, the neurons which are tuned to the orientation of the stimulus will be highly activated. Other neurons that are tuned to nearby orientations will partially activate (see Figure 7.3 column (a)). During the adaptation phase, the prolonged activation of neurons when viewing the adaptation stimulus, the level of activation of all affected neurons decreases by an amount proportional to their initial activation level (see Figure 7.3 column (b)). This lowering of the level of activation persists after the adaptation stimulus is removed, only gradually returning to pre-adaptation levels. As a consequence, when a vertical post-adaptation stimulus is presented, those neurons that have undergone adaptation are unable to activate to the level they would have otherwise achieved. This results in a skewed pattern of activation (see Figure 7.3 column (c)), which is very similar to that which would have been produced by a pre-adaptation stimulus orientated slightly in the opposite direction to that of the adaptation stimulus. The direction of the shift in the perception of vertical is invariably away from the orientation of the adapting stimulus.
This means that a test stimulus has be orientated slightly *towards* the orientation of the adapting stimulus for it to be perceived as vertical.

### 7.1.6 Evidence in literature for an association between serotonin and the magnitude of the tilt aftereffect

Masini et al. (1990) compared the magnitude of the tilt aftereffect before and after participants had been treated with a tryptophan depletion diet. As explained in Chapter 3, tryptophan is critically involved in the regulation of serotonin synthesis in the brain, and the tryptophan depletion technique has been shown to lower plasma tryptophan level by 80% within 5-7 hours of ingestion. This has been shown to result in
a corresponding reduction in serotonin synthesis and release in the central nervous system of animal studies.

Masini et al. (1990) used the tilt aftereffect to produce evidence consistent with serotonin being involved in orientation encoding. Using an adaptation stimulus orientated at 15° from vertical, they measured the magnitude of the tilt aftereffect in 12 male participants before and after administering a tryptophan depletion drink. They found that tryptophan depletion was associated with a statistically significant increase in the magnitude of the tilt aftereffect, from lines at 0.43° being perceived as vertical after adaptation, to lines at 1.07° being perceived as vertical after adaptation. This suggests that serotonin is involved in moderating the magnitude of the tilt aftereffect.

The direction of this finding (i.e., the increase in the tilt aftereffect) is consistent with serotonin being involved in lateral inhibition. If serotonin is involved in lateral inhibition as proposed, then serotonin depletion would result in less lateral inhibition, which in turn would increase the tuning bandwidth of affected neurons (see section 7.1.4). This would increase the range of preferred orientations represented in the pattern of activated neurons, and therefore the number of neurons that would undergo adaptation. The greater number of adapted neurons would in turn increase the size of the distortion in the perceived orientation of the test stimulus, thereby increasing the magnitude of the tilt aftereffect.

7.1.7 Does ecstasy use influence the tilt aftereffect?

The hypothesis tested in the present study was whether or not the long-term disruption to the serotonin system caused by recreational MDMA/ecstasy use results in similar changes to the tilt aftereffect to that found in the Masini et al (1990) study caused by the acute tryptophan depletion of serotonin. To do so, I compared the tilt aftereffect performance of ecstasy users to that of non-drug using controls. In accordance with the Masini et al (1990) results, it was expected that the magnitude of the tilt aftereffect following a 15° adaptation stimulus would be slightly greater in ecstasy users compared to non-drug users.

In addition to the 15° adaptation angle tested by Masini et al (1990), an important addition in the present study was the inclusion of a 40° adaptation condition. The 40° condition was tested to obtain further data regarding whether differences in the tilt
aftereffect of ecstasy users are mediated by decreased lateral inhibition between V1 neurons. As outlined earlier, in non-drug studies, the maximum tilt aftereffect is obtained for adaptation angles of 10-20° away from vertical. For angles greater than 20° and up to 45-55° the magnitude of the tilt aftereffect gradually reduces to zero (see the solid line in Figure 7.4). At a neural level, this is thought to occur because as the adaptation angle is increased, the overlap between the patterns of activation of neurons to the adaptation and test stimuli is decreased, thereby decreasing the size of the effect.

If the tuning-bandwidth of the neurons is increased by ecstasy-related damage to the serotonin system, then the change in the activation of neurons with preferred orientations at large angles away from the stimulus (e.g., 40°) would be large compared to the effect on the activation of neurons with preferred orientations at 15° to the stimulus (see Figure 7.5). Thus, the difference in the magnitude of the tilt aftereffect between ecstasy users and controls should be greater for an adaptation angle of 40° than at 15° (Figure 7.4). This possibility was tested in the present study by comparing the magnitude of the tilt aftereffect for ecstasy users and controls at adaptation angles of 15° and 40°.

Figure 7.4 Illustration of the potential for relatively large increase in the magnitude of the tilt aftereffect to be obtained at larger adaptation angles
7.1.8 Summary and the present study

The aim of the present study was to investigate the impact of recreational ecstasy/MDMA use on behavioural functioning associated with occipital lobe processes. Of the visual functions carried out within the occipital lobe, there is some evidence for the involvement of serotonin in simple orientation perception, possibly in narrowing the tuning bandwidths of orientation sensitive neurons in V1. This has been revealed by Masini et al.’s (1990) finding that the acute depletion of serotonin (achieved using the tryptophan depletion technique) in non-drug participants caused an increase in the magnitude of the tilt aftereffect after adaptation to 15°. It is possible that ecstasy-related disruption of the serotonin system in V1 may cause a similar effect. Moreover, if ecstasy-related serotonergic dysfunction increases the tuning bandwidth of orientation sensitive neurons, a larger difference between ecstasy users and controls might be found for larger adaptation angles (e.g., 40°) than for 15°.

In the present study, the magnitude of the tilt aftereffect was measured using the Method of Constant Stimuli with a two-alternative forced-choice response. This involved the brief presentation (100ms) of the test stimulus over a set of test angles. For
each presentation, participants indicated if the test stimulus appeared to be orientated to the left or the right. The proportion of ‘orientated to the right’ responses at each test angle was calculated for each participant, and a psychometric (sigmoid) curve fitted to the data (Figure 7.6). From this, the point on the psychometric curve at which the proportion of ‘left’ and ‘right’ responses was 0.5 (i.e., 50%) was determined. This point is called the ‘Point of Subjective Equality’ (PSE), because at that test angle the stimulus would appear to the participant to be equally position between left and right (i.e., vertical). This testing procedure was conducted before and after adaptation, and the shift in the PSE (post-adaptation minus pre-adaptation) was taken as the magnitude of the tilt aftereffect for that adaptation angle.

The combination of using brief presentation of stimuli and the Method of Constant Stimuli offered two distinct advantages over the adjust-to-vertical procedure used by Masini et al. (1990). The adjust-to-vertical procedure involves participants’ adjusting the orientation of a continuously presented test stimulus from a random starting angle to where they perceive vertical to be. This procedure tends to return a smaller magnitude of the tilt aftereffect (typically 0.5°-2° following adaptation to 15°. e.g., Gibson & Radner, 1937; Harris, Phillipson, Watkins, & Whelpton, 1983; Masini et al., 1990; Morant & Harris, 1965) compared to the use of briefly presented stimuli (typically greater 3° following adaptation to 15°, especially for high contrast low spatial frequency stimuli. e.g., Harris & Calvert, 1989; Van der Zwan & Wenderoth, 1995). This is possibly due, at least in part, to reduction in the adaptation state of the participants caused by maintaining their gaze on the test stimulus while they adjusted it to vertical.

In the present study, it was important to choose a technique that maximised the size of the tilt aftereffect in order to maximise the chances of detecting a significant tilt aftereffect at 40° where a much smaller aftereffect is expected, and to examine any difference between the control group and ecstasy users at that adaptation angle. Therefore, the Method of Constant Stimuli using briefly presented stimuli was chosen, in preference to the adjust-to-vertical procedure used by Masini et al. (1990).
The second advantage of the method used in the present study was that it allowed the calculation of the slope of the psychometric curve at the PSE of sigmoid function\textsuperscript{18}. While the PSE is the primary measure, the slope of the curve at the PSE may be of interest. A lower slope in ecstasy users compared to controls would suggest that ecstasy users required a greater difference in orientation to be sure a stimulus was orientated to the left, compared to that required for them to be sure it was orientated to the right. Such a decrease in their ability to discriminate just-noticeably-left from just-noticeably-right orientations would be consistent with an increase in the tuning bandwidth of orientation sensitive neurons. Evidence for a relationship between serotonin and discriminability has been found in a study on rats. Asgari et al. (2005) found that interrupting the operation of the serotonin system using a serotonin agonist resulted in both an increase in the average PSE and a decrease in the average slope of the psychometric curves on a temporal discrimination task. It is possible that ecstasy-related disruption to the

\textsuperscript{18} This is also an advantage over the use of the \textit{Staircase} technique, which is a commonly used alternative to the Method of Constant Stimuli procedure in tilt aftereffect studies (e.g., Van der Zwan & Wenderoth, 1995).
serotonin system may result in a similar effect on the slopes for the responses of ecstasy-users engaged in the visual task in the present study.

A final methodological issue was to consider what other variables may influence the difference between ecstasy users and controls on the magnitude of the tilt aftereffect. The Tilt aftereffect has been shown to be affected by menstruation, schizophrenia and changes in dopamine levels (Harris et al., 1983; Symons, Calvert, Snelgar, & Harris, 1990). The potential influence of all of these potential confounds has already been addressed in the criteria designed to maximise the specificity of the results to drug use in general, and to ecstasy use in particular (see Chapter 2), through matching the groups on sex and excluding people with mental illnesses, as well as the statistical control of the potential influence of the use of drugs other than ecstasy, including cannabis and amphetamines (which are known to affect dopamine levels).

7.2 Method

7.2.1 Participants and testing schedule

The present study was conducted in combined testing sessions with the second memory experiment reported in Chapter 5. The participants and the structure of the combined test sessions are described in that chapter. Table 7-1 provides a reminder of the characteristics of the ecstasy users and non-drug using controls.

Importantly, the groups were closely matched on most demographic variables (sex, age and maximum level of education attained), except that ecstasy users had a slightly lower estimated IQ than non-drug using controls. Ecstasy users had also consumed considerably more alcohol in higher maximum doses than non-drug using controls, and had higher scores on some personality variables (the Experience Seeking and Disinhibition indexes of the Sensation Seeking Scale), as well as some mental health measures (the Somatization and Obsessive-Compulsive sub-scales of the Brief Symptom Inventory). The potential influence of these variables on the outcomes of the study were controlled for by statistical means. Some incidental use of cannabis was tolerated in the control group due to the difficulty in finding people who had never tried cannabis (n=11, lifetime dose: \text{mean}=2.9 \text{ times (SD}=2.67) [range 1-9 times]. Last use: \text{mean}=1591 \text{ days prior to testing (SD}=1650) [range 127-6125 days]}. 
Table 7-1 Selected characteristics of ecstasy users and controls in the visual perception study

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=34)</th>
<th>Ecstasy (n=30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>sex (male %)</td>
<td>65%</td>
<td>63%</td>
<td>0.91</td>
</tr>
<tr>
<td>age (years)</td>
<td>23.24 (0.69)</td>
<td>23.23 (0.68)</td>
<td>.ns</td>
</tr>
<tr>
<td>estimated IQ</td>
<td>3.35 (0.09)</td>
<td>3.23 (0.10)</td>
<td>.ns</td>
</tr>
<tr>
<td>highest level of education attained[^a^]</td>
<td>3.35 (0.09)</td>
<td>3.23 (0.10)</td>
<td>.ns</td>
</tr>
<tr>
<td>Ecstasy lifetime dose (tablets)</td>
<td>-</td>
<td>394.54 (123.01)</td>
<td></td>
</tr>
<tr>
<td>abstinence (days)</td>
<td>-</td>
<td>55.81 (15.94)</td>
<td></td>
</tr>
<tr>
<td>Alcohol lifetime dose (standard drinks)</td>
<td>1023 (226)</td>
<td>4846 (771)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>maximum monthly dose</td>
<td>27.0 (5.9)</td>
<td>122.4 (17.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>maximum ever dose</td>
<td>14.2 (1.54)</td>
<td>20.9 (1.40)</td>
<td>0.002</td>
</tr>
<tr>
<td>Sensation Seeking Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>experience seeking</td>
<td>5.53 (0.31)</td>
<td>7.90 (0.23)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>disinhibition</td>
<td>4.74 (0.37)</td>
<td>6.87 (0.35)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Brief Symptom Inventory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>somatization</td>
<td>47.21 (1.10)</td>
<td>51.60 (1.72)</td>
<td>0.04</td>
</tr>
<tr>
<td>obsessive compulsive</td>
<td>56.29 (1.37)</td>
<td>61.03 (1.73)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Note. SEM = Standard Error of the Mean. (.ns indicates p>.05). For more detail see Appendix A: Table A-2.

\[^a^\] 1=Year 10 (middle secondary education); 2=Year 12 (upper secondary education); 3=Bachelor undergraduate degree; 4=post-graduate degree

7.2.2 Design

The effect of ecstasy use on the behavioural sensitivity to orientation was examined by comparing ecstasy users and non-drug using controls on the magnitude of the tilt aftereffect. In a 2x2 mixed factorial design, the within-subjects independent variable was adaptation angle (15°, 40° to the right of vertical), and the between-subjects independent variable was drug cohort (ecstasy users, non-drug using controls). In the memory studies reported in Chapter 6, the testing of a cannabis-control group was an important part of controlling for the effects of cannabis use on memory performance. This was necessary because of significant correlations between cannabis use and memory performance in the results, and also because such an association has been commonly reported in literature. The testing of a cannabis-control group in the current
study was not necessary because there was no indication of an association between cannabis use and the tilt aftereffect in the results.

For each adaptation angle, the experiment included three phases, namely the pre-adaptation test, the adaptation phase, and the post-adaptation test. In each test phase, a Method of Constant Stimuli was used to determine the orientation that the participant perceived to be vertical. The magnitude of the tilt aftereffect (the primary dependant variable) was taken as the difference between the orientations perceived as vertical in the pre-adaptation and post-adaptation tests. The slopes of the psychometric curves at the PSE were also calculated.

After testing was completed for one adaptation angle, there was a filled delay of approximately 10 minutes (during which the participants completed one of the memory tests reported in Chapter 5), before all three phases were repeated for the remaining adaptation angle (the order of the 15° and 40° adaptation angles was counterbalanced across participants). The filled delay was incorporated to minimise the carryover of adaptation between the tests.

### 7.3 Stimuli and equipment

The stimulus consisted of a Gabor, which is a sinusoidal variation of luminance within a Gaussian window (Figure 7.7a; visual angle 9°, standard deviation 1.3, spatial frequency 1 cycle/deg, 100% contrast) displayed on a uniform luminance screen of 100 Cd/m², created using a Cambridge Research Systems VSG 2/5 graphics card (resolution 1312 x 983 pixels at a refresh rate of 80Hz) which was displayed in the centre of a Clinton Monoray monitor. The participants sat with their head on a chin rest approximately 50cm from the screen, such that their eyes where level with the centre of the monitor. An adjustable curved-forehead rest was used to inhibit head tilt. Testing was conducted in a dimly lit room (following several minutes of dim-light adaptation), with featureless black walls and computer equipment shrouded in black cloth.

### 7.4 Procedure

For each pre-adaptation test, a Gabor was displayed for 100ms at an angle randomly selected without replacement from a range of nine possible test angles (-2.8, -2.1, -1.4, -0.7, 0, +0.7, +1.4, +2.1, +2.8 degrees from vertical; where negative angles were to the left of vertical and positive angles were to the right). The participants pressed one key if
they thought the Gabor had been orientated to the left of vertical, or a different key if they thought it had been orientated to the right of vertical. If they failed to respond within three seconds an electronic beep sounded and the trial was reinserted into the remaining set. The next trial commenced following a 500ms delay. This was repeated until the participant had responded to all of the test angles once. The entire set of test angles was then repeated until the participant had responded to each test angle 10 times, making a total of 90 responses.

The participants were then adapted to a Gabor displayed at an adaptation angle of either 15° or 40° for 90 seconds, during which the participants were required to slowly scan the stimulus to avoid generating afterimages. They were specifically instructed to not maintain a fixed gaze on the centre of the stimulus, and to keep the stimulus in focus at all times. The start of the adaptation phase was indicated by the word “Study” flashing on the screen for one second outside the visible perimeter of the adaptation Gabor. The word was positioned perpendicular to the stimulus orientation (as shown in Figure 7.7b) to minimise any effect on adaptation.

Pilot testing revealed that this was necessary because some pilot subjects thought the adaptation stimulus was a pre-adaptation test stimulus that had failed to disappear when they pressed a response key.
Table 7-2 The Mean (Standard Error of the Mean) of the magnitude of the tilt-aftereffect as a function of cohort (controls, ecstasy users)

<table>
<thead>
<tr>
<th>Adaptation angle</th>
<th>Controls (n=34)</th>
<th>Ecstasy Users (n=30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>15°</td>
<td>2.82 (0.58)</td>
<td>2.75 (0.70)</td>
<td>0.66</td>
</tr>
<tr>
<td>40°</td>
<td>1.43 (0.67)</td>
<td>1.58 (0.50)</td>
<td>0.33</td>
</tr>
</tbody>
</table>

The post-adaptation test was the same as the pre-adaptation test, except that a 10 second “top up” adaptation was given after every fifth trial, and additional test angles were used (+3.5, +4.2, +4.9, +5.6, +6.3 and +7.0), in addition to the nine used in the pre-adaptation test, making a total of 15 test angles. Pilot testing revealed that the additional post-adaptation test angles were necessary to ensure adequate data for the fitting of a psychometric curve after the adaptation had shifted the curve to the right (see example in Figure 7.8).

Prior to commencement of the first pre-adaptation test, participants were given between one and three sets of nine practice trials of the post-adaptation test procedure to familiarise them with the display, and to ensure they could correctly use the response keys. For the 10-second top-up adaptation in the practice trials, a vertically orientated Gabor (Figure 7.7a) was used to avoid unwanted adaptation.

7.5 Results

7.5.1 Cohort effects on the magnitude of the tilt aftereffect

The tilt aftereffect data consisted of the proportion of right-hand key responses made by participants for each test angle in the pre- and post-adaptation tests for each adaptation angle (15° pre-adaptation, 15° post-adaptation, 40° pre-adaptation, 40° post-adaptation). A separate psychometric curve was fitted to the data of each participant in each condition (see examples in Figure 7.8), and the PSE of each curve was calculated (as described in section 7.1.8). The magnitude of the tilt aftereffect at each adaptation angle was taken as the PSE of the post-adaptation curve minus the PSE of the associated pre-adaptation curve. The mean for each cohort was then calculated as a function of adaptation angle (see Table 7-2).

A mixed model ANOVA was conducted on the magnitude of the tilt aftereffect as a function of adaptation angle (15°, 40°) and cohort (ecstasy users, non-drug using...
controls). This revealed that the main effect of adaptation angle was statistically significant, $F(1, 62)=308.95$, $\text{MSE}=0.17$, $p<.001$, which indicates that, in accordance with published literature, the magnitude of the tilt aftereffect was larger at an adaptation angle of $15^\circ$ than at $40^\circ$ (as illustrated in Figure 7.4). In terms of ecstasy effects, there was no significant main effect of cohort, $F<1$, $\text{MSE}=0.60$, $p=.78$, and no significant interaction between cohort and adaptation angle, $F(1, 62)=2.28$, $\text{MSE}=0.17$, $p=.14$.

A more detailed investigation of the data, however, revealed a significant effect of ecstasy following adaptation to $40^\circ$, which was disguised by an unanticipated effect of the number of days since the last use of amphetamines. As in the previous studies in this thesis, bivariate correlations between the main variables of interest and the number of days since the last use of ecstasy, alcohol, cannabis, and amphetamines were conducted to determine if any of the observed differences between the cohorts were due to acute or residual effects of those drugs (reported for the present study in section 7.5.3 below). In the present study, the magnitude of the tilt aftereffect at $40^\circ$ was found to be correlated with the number of days since ecstasy users had last used amphetamines, $r(28)=.435$, $p=.02$, such that the more recently they had used the drug the smaller the effect at $40^\circ$. This suggests that a significant difference between the cohorts may be revealed if ecstasy users who had recently used amphetamines had been excluded from the analysis. This was tested by dividing the ecstasy users cohort into two groups, namely ecstasy users who had used amphetamines in the 61 days prior to testing ($n=18$, recent amphetamine users) and ecstasy users who had not used amphetamines for at least 115
days\(^{20}\) (n=12, abstinent amphetamine users). To compare these two groups of ecstasy users to non-drug using controls (n=34), the average magnitude of the tilt aftereffect was calculated for each group (see Figure 7.9). Mann-Whitney Tests\(^{21}\) revealed that ecstasy users who had been abstinent from amphetamines for 115 days or more had a significantly larger tilt aftereffect than both non-drug using controls, U=120, z=2.10, p=.04, and ecstasy users who had recently used amphetamines, U=60, z=2.03, p=.04. Overall these results indicate that the use of ecstasy in the absence of recent amphetamine use was associated with an increase in the magnitude of the tilt aftereffect. Thus, an ecstasy effect in the overall sample was disguised by the recent use of amphetamines which is associated with the opposite effect, i.e., a decrease in the magnitude of the tilt aftereffect at 40\(^{\circ}\).

In accordance with the procedure used in the memory study in the previous chapter, bivariate correlations were used to identify variables other than ecstasy that could account for the statistically significant differences identified in the previous paragraph. For the analysis of ecstasy users who had not used amphetamines for 115 days or more and non-drug using controls, the magnitude of the tilt aftereffect at 40\(^{\circ}\) was not significantly correlated with estimated IQ, or any demographic, mental health, personality or alcohol use variable, all ps\(\geq\).12.

For the analysis of ecstasy users who had recently used amphetamines compared to those who were abstinent from amphetamines, the only potential covariate revealed by the bivariate correlations was a non-significant trend towards a correlation between the magnitude of the tilt aftereffect at 40\(^{\circ}\) and estimated IQ, r(30)=-.330, p=.08. The influence of estimated IQ on the difference between the two groups of ecstasy users was evaluated using regression analysis. This revealed that estimated IQ was a significant covariate, \(\beta=-.35\), t(30)=-2.09, p=.05. Once the influence of estimated IQ was taken into account, the difference between the two groups of ecstasy users on the magnitude of the tilt aftereffect at 40\(^{\circ}\) remained statistically significant, \(\beta=.39\), t(30)=2.36, p=.03. Further

\(^{20}\) These criteria were used because the smallest of the resulting groups was large enough to conduct meaningful statistical tests (n=12), and because there was a convenient gap in the distribution of the last used amphetamines between 62 and 116 days prior to testing.

\(^{21}\) The Mann-Whitney Test was used in these analyses, rather than t-tests, because the sub-groups of ecstasy users had small sample sizes (n<30) with poorly distributed scores (Pagano, 1998).
bivariate correlations within the ecstasy users groups revealed that the magnitude of the tilt aftereffect at 40° was not correlated with any cannabis use measure, all $p$s>.30

The analysis of the recent use of amphetamines on the magnitude of the tilt aftereffect was then applied post-hoc to the 15° adaptation angle data, to see if that measure was also influenced by the recent amphetamine use (see Figure 7.10). The Mann-Whitney Tests indicated that the magnitude of the tilt aftereffect at 15° for ecstasy users who had been abstinent from amphetamines for 115 days or more was not significantly different from either non-drug using controls, $U=195$, $z=.238$, $p=.81$, or ecstasy users who had recently used amphetamines, $U=87$, $z=.889$, $p=.37$.

Overall, the pattern of results for 40° and 15° show that the magnitude of the tilt aftereffect for ecstasy users was greater than non-drug using controls following adaptation to a stimulus orientated at 40° to vertical, at least for ecstasy users who had not recently used amphetamines, but not following adaptation to 15° from vertical. (Unexpectedly, the magnitude of the tilt aftereffect at 40° for ecstasy users who had not recently used amphetamines was also greater than the tilt aftereffect for the ecstasy users who had recently used amphetamines, which remained significant once the effect of estimated IQ was taken into account). This finding of a significant difference between ecstasy users and controls at 40°, and no statistically significant difference
between the cohorts at 15° (i.e., a difference between the groups that is considerably less than that at 40°) is consistent with the proposal that ecstasy-related serotonergic changes in the occipital lobe increases the tuning bandwidths of orientation sensitive neurons.

### 7.5.2 Cohort effects on the slopes of the psychometric curves at the PSE

The slopes at the PSE of the psychometric curves were analysed to see if the serotonergic-related decrease in the slopes of psychometric curves associated behavioural responses in rats also occurs for visual behavioural responses in humans. The slopes in the present study were averaged across participants for the pre-adaptation and post-adaptation test at each adaptation angle (15° pre-adaptation, 15° post-adaptation, 40° pre-adaptation, 40° post-adaptation) and are displayed in Table 7-3.

Table 7-3 indicates that slopes were lower after adaptation than before, indicating reduced discriminability between similar orientations after adaptation. More interestingly, there was also a suggestion that ecstasy users tended to have slightly lower slopes compared to non-drug using controls, for both the pre- and post-adaptation tests. A mixed-model ANOVA analysis of test phase (pre-adaptation, post-adaptation), adaptation angle (15°, 40°), and cohort (ecstasy users, controls) revealed a significant main effect for test phase, $F(1,62)=60.78$, $\text{MSE}=1548.73$, $p<.001$. However, the main
Table 7-3 The Mean (Standard Error of the Mean) of the slope of the psychometric curves at the PSE for the pre-adaptation and post-adaptation tests, as a function of adaptation angle (15° and 40°) and cohort (controls, ecstasy users).

<table>
<thead>
<tr>
<th></th>
<th>Controls (n=34)</th>
<th>Ecstasy Users (n=30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>15°</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-adaptation</td>
<td>94.15 (9.88)</td>
<td>90.43 (10.32)</td>
<td>0.80</td>
</tr>
<tr>
<td>post-adaptation</td>
<td>53.83 (6.03)</td>
<td>42.78 (5.27)</td>
<td>0.18</td>
</tr>
<tr>
<td>40°</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>pre-adaptation</td>
<td>96.68 (10.09)</td>
<td>73.65 (6.68)</td>
<td>0.07a</td>
</tr>
<tr>
<td>post-adaptation</td>
<td>52.69 (4.18)</td>
<td>51.91 (8.39)</td>
<td>0.93</td>
</tr>
</tbody>
</table>

Note.

a It appears that ecstasy users tended to have lower slopes for the 40° pre-adaptation test compared to the controls. A paired samples t-test revealed that there was also a non-significant trend towards a difference between the 15° and 40° pre-adaptation tests for ecstasy users, t(29)=1.79, p=.08. These tendencies are strange, since all of the pre-adaptation tests were identical and were conducted in counterbalanced order across participants within each cohort. One possibility was that Ecstasy Users had different temporal effects for the decay of the TAE for 40° compared to 15°. If this was the case then the order in which they did the tasks would have an effect. To test this possibility mixed-model ANOVA was conducted of the adaptation angle (15°, 40°) and temporal order of the adaptation angles (15° conducted first, 40° conducted first) for ecstasy users only. The main effect for temporal order and the interaction between temporal order and adaptation angle were non-significant, F’s<1. Inspection of histograms of the pre-adaptation slopes by temporal order suggested that the apparent difference was due to the chance distribution of scores rather than any consistent effect.

effect of adaptation angle, F(1,62)<1, MSE=155.68, p=.73, and cohort, F(1,62)=1.64, MSE=3626.53 p=.21, were not significant. Thus, there was no statistically significant support for ecstasy users having lower slopes than non-drug using controls, despite there being slight trends in that direction.

In light of the effect of the recent use of amphetamines on the magnitude of the tilt aftereffect examined in the previous section, analysis of the effect of the recent use of amphetamines on the slopes was also conducted. Mann-Whitney Tests revealed that following adaptation to 40°, the slopes for ecstasy users who had not recently used amphetamines were not significantly different from the remaining ecstasy users, U=99, z= .381, p=.70, or non-drug using controls, U=149, z=1.376, p=.17. Following adaptation to 15°, there was also no significant difference between the slopes for ecstasy users who had not recently used amphetamines and the remainder of the ecstasy users.

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22 This analysis was not conducted on the pre-adaptation slopes due to the anomaly in the data examined in the note attached to Table 7-3.
Table 7-4 Dose dependence and recency of ecstasy and amphetamines: Bivariate correlations between the magnitude of the tilt aftereffect as a function of adaptation angle (15°, 40°) and drug use (number of days since the last, lifetime dose, maximum monthly dose, and the maximum ever dose of ecstasy in a single session) of ecstasy, amphetamines, and cannabis within the ecstasy users group.

<table>
<thead>
<tr>
<th></th>
<th>15°</th>
<th>p</th>
<th>40°</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ecstasy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last use</td>
<td>0.10</td>
<td>0.58</td>
<td>0.05</td>
<td>0.80</td>
</tr>
<tr>
<td>Lifetime dose</td>
<td>0.01</td>
<td>0.97</td>
<td>0.05</td>
<td>0.80</td>
</tr>
<tr>
<td>Maximum monthly dose</td>
<td>0.14</td>
<td>0.46</td>
<td>0.08</td>
<td>0.66</td>
</tr>
<tr>
<td>Maximum ever dose</td>
<td>-0.06</td>
<td>0.77</td>
<td>0.13</td>
<td>0.51</td>
</tr>
<tr>
<td><strong>Amphetamines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last use</td>
<td>0.33</td>
<td>0.08</td>
<td>0.43</td>
<td>0.02</td>
</tr>
<tr>
<td>Lifetime dose a</td>
<td>-0.02</td>
<td>0.93</td>
<td>-0.14</td>
<td>0.46</td>
</tr>
<tr>
<td>Maximum monthly dose</td>
<td>-0.05</td>
<td>0.78</td>
<td>-0.02</td>
<td>0.92</td>
</tr>
<tr>
<td>Maximum ever dose</td>
<td>-0.20</td>
<td>0.31</td>
<td>-0.15</td>
<td>0.44</td>
</tr>
<tr>
<td><strong>Cannabis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Last use</td>
<td>0.15</td>
<td>0.43</td>
<td>0.03</td>
<td>0.89</td>
</tr>
<tr>
<td>Lifetime dose a</td>
<td>0.21</td>
<td>0.27</td>
<td>0.19</td>
<td>0.31</td>
</tr>
<tr>
<td>Maximum monthly dose</td>
<td>0.12</td>
<td>0.52</td>
<td>0.05</td>
<td>0.80</td>
</tr>
<tr>
<td>Maximum ever dose</td>
<td>-0.01</td>
<td>0.95</td>
<td>-0.05</td>
<td>0.78</td>
</tr>
</tbody>
</table>

*a Dose measurements explained in Chapter2, section 2.6.2

U=88, z=.847, p=.42, although there was a non-significant trend towards them having lower slopes than non-drug using controls, U=131, z=1.826, p=.07.

7.5.3 Dose dependence and recency effects for ecstasy, amphetamines, and cannabis: Correlations between the magnitude of the tilt aftereffect and measures of drug use

Earlier it was reported that alcohol use measures were uncorrelated to the magnitude of the tilt aftereffect across the ecstasy users and non-drug using control groups. In this section, the relationship between the magnitude of the tilt aftereffect and the use of amphetamines, cannabis, and ecstasy is analysed using bivariate correlations within the ecstasy users group (see Table 7-4). Apart from the recent use of amphetamine use (analysed in section 7.5.1), there were no other significant correlations between the magnitude of the tilt aftereffect at either adaptation angle, and any measure of ecstasy or amphetamine use.
7.6 Discussion

The aim of the present study was to investigate possible ecstasy-related deficits in visual processes that reflect occipital lobe functioning. Of the various visual processes that are localised in the occipital lobe, orientation perception was selected to be the focus of the present study because there is some evidence in published literature of serotonergic involvement in orientation processing (Masini et al., 1990). Orientation perception was investigated in the present study by comparing ecstasy users and non-drug using controls on the magnitude of the tilt aftereffect illusion after adaptation to a stimulus orientated at 15° and 40° to the right of vertical.

7.6.1 Summary of ecstasy-related findings

The present study provides the first evidence of changes in the behavioural function of the occipital lobe in recreational ecstasy users. In accordance with expectations, ecstasy users had a larger average magnitude of the tilt aftereffect than non-drug using controls following adaptation to 40°. However, an unexpected finding was that this result was only obtained for ecstasy users who had not used amphetamines for 115 days or more. In contrast, there was no significant difference between ecstasy users and non-drug using controls on the magnitude of the tilt aftereffect following adaptation to 15°.

A secondary investigation was conducted regarding the potential impact of ecstasy use on the slopes of the psychometric curves at the PSE. While the average slopes of the psychometric curves of ecstasy users appeared to be slightly shallower on average compared to the non-drug using controls, this difference did not reach statistical significance.

7.6.2 The consistency of the results compared to previous literature

There have been no published investigations of the behavioural function of the occipital lobe in recreational ecstasy users to date to which the results of the present study can be compared. Of interest though, is the study by Masini et al (1990). That study found that the acute disruption to the serotonin system caused by tryptophan depletion resulted in a significant increase in the magnitude to the tilt aftereffect following adaptation to 15°. In contrast to that finding, the present study found that the impact on the serotonin system which is thought to be associated with recreational ecstasy use did not result in a significant increase in the tilt aftereffect at 15°. In the first memory study (Chapter 4),
there was a similar discrepancy between the only evidence of serotonergic involvement in implicit memory in literature from a tryptophan depletion study, and the result obtained in the current thesis from ecstasy users. In the discussion of that result, it was noted that while tryptophan depletion can be a useful tool for identifying cognitive functions that may be sensitive to ecstasy-related changes to the serotonin system, the chronic nature of serotonergic disruptions in ecstasy users may allow time for compensatory neural changes to occur that reduce the size of effects in ecstasy users compared to those seen in participants in tryptophan depletion studies. Therefore, the discrepancies between a significant effect of tryptophan depletion and a non-significant effect in ecstasy users may indicate the action of such compensatory effects in ecstasy users.

7.6.3 Interpretation of findings

7.6.3.1 The tilt aftereffect in amphetamine-abstinent ecstasy users

The pattern results obtained in the present study is consistent with that predicted for ecstasy-related damage to the serotonin system in visual area V1, and that serotonin in V1 is directly involved in lateral inhibition between orientation sensitive V1 neurons. The theoretical consideration in the introduction to this study postulated that if serotonin was directly involved in the lateral inhibition between neurons in visual area V1, as suggested by the Masini et al (1990) tryptophan depletion study, then the disruption to the serotonin system in V1 might result in an increase in the tuning bandwidth of orientation sensitive neurons. For a stimulus at a given orientation, this would increase the range of preferred orientations represented in the population of neurons activated by the stimulus. With regard to the tilt aftereffect, the increased number of activated neurons would all undergo adaptation, which would consequently result in an increase in the distortion of the perceived orientation of the test stimulus, thereby increasing the magnitude of the tilt aftereffect. Importantly, the shape of the tuning curves means that for a given change in lateral inhibition, the expected change in the magnitude of the tilt aftereffect at 15° should be small compared to that at 40° (Figure 7.5). This is the pattern of results obtained in the present study when ecstasy users who had not recently used amphetamines were compared to non-drug using controls. In fact, the difference between the amphetamine-abstinent ecstasy users and controls was so small after adaptation to 15° that it did not approach significance. Thus, the pattern of results
indicated that the amphetamine-abstinent recreational ecstasy users in the present study did have deficits on a behavioural measure which is thought to reflect occipital lobe functioning, and the results were consistent with that effect being mediated by serotonergic changes in lateral inhibition between V1 orientation sensitive neurons.

7.6.3.2 The effect of the recent use of amphetamines

An additional and unexpected finding in the present study was that there was no significant difference on the tilt aftereffect at 40° between ecstasy users who had recently used amphetamines (i.e. within the last 61 days) and the non-drug using controls. Furthermore, the magnitude of the tilt aftereffect at 40° was found to be correlated with the number of days since ecstasy users had last used amphetamines, \( r(28) = .435, p = .02 \), such that the more recently they had used the drug the smaller the effect at 40°. These results indicate that the recent use of amphetamines was associated with the opposite effect of ecstasy use, that is recent amphetamine use was associated with a decrease in the magnitude of the tilt aftereffect. While there have been no reports published in literature of the impact of amphetamines on the tilt aftereffect, other studies have shown an interaction between ecstasy and amphetamines. Daumann et al. (2003) found a reduction in the BOLD signal detected by fMRI in ‘pure’ ecstasy users, who denied regular use of other drugs, but not in ecstasy users who reported regular use of amphetamines and cannabis. The authors suggested that this may have occurred because amphetamines and/or cannabis had a contrary effect to that of ecstasy. This suggestion is supported by the findings in the present study, the significant deficits were only detected for ecstasy users who had not recently used amphetamines. Furthermore, the lack of any effect of cannabis in the present study, suggests that it may be the recent use of amphetamines that is critical to disguising ecstasy-related effects, and not cannabis. This could occur if amphetamines use causes a persistent residual excitation of systems that are inhibited by ecstasy-related damage, or visa-versa. Further research is required to investigate the origin of these apparent amphetamine effects on ecstasy users, including clarification of the circumstances under which they occur.

7.6.4 Summary of discussion

In summary, the present study provides the first evidence of changes in low level visual processing in ecstasy users associated with occipital lobe behavioural functioning. The results were consistent with the proposal that ecstasy-related damage to the serotonin
causes a decrease in the lateral inhibition between orientation sensitive neurons in visual area V1, which increases the tuning bandwidth of these neurons, which in turn results in an increase in the magnitude of the tilt aftereffect, especially following adaptation at 40° compared to 15°.

An unexpected finding was that this result was only obtained for amphetamine-abstinent ecstasy users, and not for ecstasy users who had used amphetamines within the 61 days prior to testing. This result is consistent with at least one fMRI study, which found significant effects in ecstasy users, but only if they reported having never used amphetamines or cannabis. In combination these studies suggest that under certain circumstances amphetamines may produce effects which are opposite to that of ecstasy, thus disguising otherwise significant ecstasy-related effects. More research is required to clarify the circumstances under which this occurs, and the mechanisms underlying the effect.
Chapter 8. General Discussion

8.1 Specificity of the findings in the current thesis to drug use, ecstasy and MDMA

The empirical studies reported in the previous chapters detected significant differences between ecstasy users and non-drug using controls. A key question about those results that will now be addressed is, “To what extent can those differences be attributed to drug use, ecstasy, and MDMA?”

In Chapter 2, I considered each of Hill’s (1965) criteria regarding the derivation of causal inferences from cohort studies, in order to develop a framework within which results from the current series of studies could be attributed to drug use, ecstasy, and MDMA. This included the formulation of inclusion and exclusion criteria, matching the groups on relevant variables where possible, and the measurement and statistical control of potential covariates where group matching was not possible. In the current section, I will consider the specificity of the results obtained to drug use, ecstasy and MDMA.

8.1.1 The specificity of the results to drug use

The degree of confidence with which the results can be attributed to drug use involves the elimination of possible causes of the effects that do not involve drug use. Ideally this would be achieved by having groups of ecstasy users and controls that were identical in every respect apart from their drug use, such that any performance difference between the groups could only be due to drug use. While this is not completely achievable in real life, the groups in the current study were well matched on age and sex, such that we can be confident that the significant differences in memory and orientation processing were not due to those variables.

The samples of ecstasy users and non-drug using controls who participated in the studies in this thesis were different on estimated IQ, as well as some personality (the Experience Seeking and Disinhibition indexes of the Sensation Seeking Scale) and mental health (Brief Symptom Inventory) measures. These differences were potentially important in the memory studies, since all of these variables could cause differences in performance on memory tests. Therefore, a conservative approach was taken to the identification of potential covariates (p<.10) to increase the level of confidence that the observed effects on memory and orientation processing were not due to any of these
covariates. While it is not possible to completely eliminate the potential influence of covariates on the differences detected between ecstasy users and controls, the statistical control of these variables in the present thesis provides reasonable evidence that significant differences between the groups are not due to estimated IQ, mental health or personality differences, and are therefore likely to be due to some aspect of drug use.

The inclusion in Chapter 6 of a second control group, namely the cannabis-controls, increased the confidence with which estimated IQ, mental health and personality variables (as well as alcohol, discussed in the following section) could be rejected as possible causes of the memory and orientation processing effects. This is because the power of a statistical test to detect and control for the influence of a given covariate is influenced by both the number of participants \(n\), and the variability of participants within each group on the covariate \(\text{SEM}\) or \(\text{SD}\). For populations of people, each with a given variability on a covariate, the number of people in the sample who participate in the test has a big influence on the power of the test to detect significant group differences. The inclusion of the cannabis-control group in Chapter 6 substantially increased the number of people in that study, and thereby increased the power of the experiment to detect and control for the influence of variables shared by the cannabis-controls and at least one of the other groups.

### 8.1.2 The specificity of the results to ecstasy use

On the basis that it is likely that the effects are due to some aspect of drug use (above), the degree of confidence with which the results can be attributed to ecstasy involves the elimination of other drugs as possible causes of the effects.

#### 8.1.2.1 Alcohol

Differences between the ecstasy users and non-drug using control group with regard to alcohol consumption were statistically controlled for in the same way as the non-drug use variables in the previous section. Thus, we can have reasonable confidence that the significant effects detected were not due to alcohol use.

#### 8.1.2.2 Cannabis

The influence of cannabis could not be controlled for using covariate analysis of ecstasy users and non-drug using controls, because only incidental use of cannabis by some
participants was tolerated in the non-drug using control group. This was not an issue in the perception study (Chapter 7) because the results were uncorrelated with cannabis use. Neither was it an issue in the first two memory studies (Chapters 4 and 5), because no significant differences between ecstasy users and non-drug using controls were detected. However, in the final memory study in Chapter 6, significant differences were detected between the groups, and the lifetime dose of cannabis was a covariate on at least one of the memory measures used (i.e., immediate recall on the Verbal Paired Associates test, $p=.051$). The influence of cannabis use on memory performance in ecstasy users has been a controversial issue in literature (e.g., Croft et al., 2001; Dafters et al., 2004; Simon & Mattick, 2002). Therefore, the cannabis-control group was tested in order to increase the ability of the experiment to dissociate any effects of cannabis and ecstasy use on the final results. This enabled cannabis use to be statistically controlled for in a covariate analysis of the ecstasy users and cannabis-controls. It also enabled the comparison of the cannabis-controls to the non-drug using controls. In general, the performance of the ecstasy users was different from both cannabis-controls and non-drug using controls, while the control groups were not significantly different from each other. Furthermore, on the Verbal Triplet Associates task, cannabis users had a different pattern of results to both ecstasy users and non-drug using controls. Thus, while cannabis use appeared to influence performance on some memory measures, the final results showed that, at best, cannabis use only accounted for a proportion of the difference between ecstasy users and non-drug using controls, if any.

8.1.2.3 Amphetamines

The influence of amphetamines could not be controlled for using covariate analysis, because none of the non-drug using control group had used amphetamines. Furthermore, it was thought that it would not be possible to find an adequate number of people who had used amphetamines, but who had not used ecstasy, to form an amphetamine-control group. Therefore, the influence of amphetamines was restricted to analyses conducted within the ecstasy users group, and thus involved a smaller number of participants than the analyses for other potential covariates (i.e., lower $n$). This means that the power of the current series of studies to dissociate the potential influence of amphetamines from ecstasy was weaker compared to other potential covariates.
The monthly maximum dose of amphetamines was significantly correlated to many CVLT recall measures, but regression analysis suggested that this association did not significantly influence the performance of ecstasy users once other covariates were taken into account. The recent use of amphetamines was shown to significantly influence the magnitude of the tilt aftereffect recall. In this case, the significant effect of ecstasy compared to controls was only significant for those ecstasy users who had not recently used amphetamines. Thus, while the ability to detect and control for the influence of amphetamines in the current series of studies was lower than that of other potential covariates, the results only support amphetamines as having a restricted influence (in the case of the tilt aftereffect), if any (in the case of all other tests), on the significant differences in memory and orientation processing between ecstasy users and non-drug using controls.

8.1.2.4 Ecstasy: The absence of dose dependent effects

The evidence outlined so far in support of the specificity of the results to ecstasy has all involved the elimination of other likely causes. This has been achieved through group matching and the statistical control of potential covariates. All of this supports Hill’s (1965) specificity criterion for inferring causal relationships in quasi-experimental studies (as outlined in Chapter 2). From such evidence, the attribution of the deficits to ecstasy can be made by inference once all other likely causes have been eliminated.

A more direct form of evidence in support of the attribution of the results to ecstasy is dose dependence, based on Hill’s (1965) biological gradient criterion, in which larger effects are associated with greater exposure to the risk factor of interest. However, in the present study, there was no evidence of such a relationship on any memory or perception measure, in terms of the lifetime dose, maximum monthly dose, or maximum ever dose of ecstasy. These results argue against the attribution of the significant deficits to ecstasy, and is in contrast to the evidence regarding the specificity of the results to ecstasy obtained through the control of other likely causes outlined above.

However, there are a number of plausible reasons why significant dose dependent relationships were not detected in the present study, even if the deficits were caused by recreational ecstasy use. One possible reason is the amount of error variability in the estimation of the dose of ecstasy that recreational users have administered. Despite the evidence outlined in Chapter 2 in support of the validity and reliability of the time-line
interview method, the estimation of the dose of drugs administered over several years incorporates considerable opportunity for error compared to that in controlled administration studies on animals. The accuracy of dose estimates is likely to be further compromised by changes in the composition of tablets overtime, between batches, and between different regions (as outlined in Chapter 1). Any increase in error variability consequently decreases the likelihood of detecting a statistically significant correlation between variables (Howell, 1997), thus reducing the chances of detecting a significant dose dependant effect. Since it is not ethically possible to administer MDMA to humans in precisely recorded neurotoxic doses, as it is in animal studies, the relatively large error variability due to the estimation techniques used in this thesis must be expected. Therefore, while the detection of dose dependent effects is an important form of evidence for the attribution of causal inferences in retrospective cohort studies of drug use, the absence of such an effect cannot be taken as a reliable indication that drug effects do not exist.

Another possible reason that a dose dependent effect of ecstasy was not detected in the present study was the limited range of lifetime ecstasy use amongst the participants. People who had used lower lifetime doses of ecstasy were excluded from the study in order to raise the average lifetime dose of the ecstasy users. This commenced in the second memory study in order to increase the likelihood of detecting significant ecstasy-related deficits. However, excluding these participants meant that the range of ecstasy use in the study was relatively restricted, which reduced the likelihood on detecting significant correlations (Howell, 1997).

A third possible reason for why a dose dependent effect was not detected in the present study is that analysis of dose dependence using bivariate correlations, as defined by the expectation of greater effects for greater doses of ecstasy, assumes that there is a linear relationship between dose and the effects. This is not necessarily the case. There may be a threshold effect, such that the use of ecstasy under a certain dose within a particular drug taking session would not be neurotoxic. If this were the case, then a problem with the use of the lifetime dose as a measure of ecstasy use would be that it includes

23 in the final memory study, this was considered to be less than 75 tablets, although all but 4 participants had used more than 100 tablets.
unknown proportions of both neurotoxic and non-neurotoxic doses. Also, problems with determining the number of neurotoxic doses would include that environmental factors and interactions with other drugs have been shown to influence the neurotoxicity of MDMA and drug taking behaviour in animals (Clemens, Cornish, Li, Hunt, & McGregor, 2005; Clemens et al., 2004; Cornish et al., 2003; Malberg & Seiden, 1998). Consequently the number of neurotoxic doses that a person has administered is likely to be complex and difficult to determine. Therefore, if there is a threshold effect for the neurotoxic effects of MDMA in humans, then dose dependent effects may be difficult to determine. In terms of the current samples, if there were a threshold effect for users, the use of total lifetime dose as the main measure of ecstasy use may have reduced the likelihood of detecting dose dependent effects.

Overall, these arguments indicate that the lack of a dose dependent finding in the present study should be treated with some caution. The evidence in the current study needs to be weighed against the evidence of dose dependant relationships in other cognitive, neuroimaging and neuroendocrine studies in humans, as well as the controlled administration of MDMA in animal studies (as outlined in Chapter 1). In light of this body of evidence it would be unsafe to conclude that ecstasy was not at least a contributory cause of the effects observed in the present study.

8.1.3 The specificity of the results to MDMA

The attribution of results in the current study to MDMA can only be made by inference. In Chapter 1 (sections 1.3.2 and 1.6.2), it was argued that in the local area in which testing for this thesis was conducted, regular recreational ecstasy users typically self-administer doses of MDMA that have been shown to be neurotoxic in animals (once interspecies scaling had been applied), whenever they administer MDMA-based ecstasy tablets. This was based on the results of surveys of local drug users and the analysis of drugs seized in the local area by the Australian Federal Police, as well as the findings of animal research. The average lifetime ecstasy dose for the ecstasy users in the perception and third memory studies was nearly 400 tablets. It would be unreasonable to assume that people could administer that number of ecstasy tablets and not have administered many significant doses of MDMA. In the absence of any significant effects of alcohol, amphetamines, or cannabis, it is at least plausible that the effects on
memory and visual perception observed in ecstasy users are due to MDMA administered through recreational ecstasy use.

8.1.4 Summary of the specificity of findings to drug use, ecstasy and MDMA

In summary, the combination of inclusion and exclusion criteria, group matching, and the use of a cannabis-control group (in the final memory study), as well as the statistical control of differences between the ecstasy users and non-drug using control groups, has provided reasonable grounds to attribute the findings of the current series of studies to ecstasy. Potential causal factors controlled for by these methods included age, sex, estimated IQ, mental health, personality and other drug use, especially alcohol and cannabis. The power of the current study to dissociate the effects of ecstasy from that of amphetamines was weaker compared to other potential covariates. However, where significant effects of amphetamines were detected in the results, they only accounted for a portion of the difference between ecstasy users and controls, at best. The lack of dose dependent effects of ecstasy use fails to meet Hill’s (1965) criteria regarding the attribution of causal inferences in cohort studies. However, it was argued that there are a number of reasons why dose dependent effects were not detected in the current series of studies, even if the effects observed were caused by ecstasy. Given the evidence here against the attribution of the results to any other cause, it would be unwise to conclude that they were not due to ecstasy. Furthermore, given the pattern of local drug use and evidence from drug seizures regarding the composition of tablets containing MDMA, as well as the evidence against attributing the results to alcohol, amphetamines or cannabis, it is both plausible and probable that the observed effects result from the neurotoxic effects of MDMA.

8.2 From the current thesis to future research: Issues regarding the testing of cognitive and perceptual deficits in ecstasy users

8.2.1 Refining the approach to ecstasy research regarding cognitive/perceptual deficits

The broad approach taken in this thesis to the investigation of cognitive and perceptual deficits in ecstasy users was to develop an understanding of the impact of MDMA on the brain, and from that basis to select and design cognitive and perceptual tests that were as specific as possible to particular components and processes of memory and
visual perception affected by MDMA. This was in contrast to much of the literature published in this field of research, which has relied heavily on the application of standard neuropsychological tests. Such tests were designed to detect gross cognitive deficits that reflect the ability – or inability – to function in everyday life, rather than the more subtle deficits to specific components or processes of memory that appear to be associated with ecstasy use. In general, findings from standard neuropsychological tests have been inconsistent across studies. This possibly reflects regional differences in the pattern of drug use, and the various effects of different drugs on the components and processes of memory that the standard neuropsychological tests are sensitive to.

8.2.2 New findings

The approach taken in this thesis of selecting and designing tests which were as specific as possible to particular cognitive/perceptual systems revealed, for the first time, intact implicit memory in ecstasy users, as well as changes in low level visual processes in ecstasy users thought to be associated with occipital lobe functioning. It was also found that ecstasy users had intact performance on tests known to be sensitive specifically to hippocampal functioning, but recall and learning deficits on explicit memory tests on the novel Verbal Triplets Associates test, which involve significant elaborative processing. This was interpreted as indicating that long-term memory deficits in ecstasy users may reflect changes in elaborative processes localised in the frontal lobes, or global functional deficits revealed when many systems are loaded concurrently, rather than to changes in the memory functions localised in the hippocampus and sensory areas of the brain.

8.2.3 Future research

Future research is required in order to determine if these findings can be replicated in other populations of ecstasy users. Importantly, such attempts at replication would confirm whether or not the new tasks introduced in this thesis to this field of research are more reliable in revealing ecstasy-related deficits compared to the standard neuropsychological tests. Future research is also required to clarify mechanisms that underlie some of the effects observed, as noted in the conclusions of the different studies. These include: whether the apparent deficit in elaborative processing in ecstasy users is due to slower processing speed; clarifying the impact of amphetamines on the
tilt aftereffect; and investigating the cause of the faster reaction times in ecstasy users in the first memory study on the digit-monitoring task under divided attention conditions.

Future research can obviously expand on the findings of the present thesis by applying the approach taken in this thesis to other aspects of memory and perception. In particular, with regard to visual perception, orientation is only one of the low-level visual processes localised in the occipital lobe. The apparent involvement of serotonin in determining the tuning bandwidths of orientation sensitive neurons, may signify that serotonin also has a role in the tuning bandwidths of neurons that are sensitive to other rudimentary aspects of visual perception. This may include simple depth perception, and/or the detection of the direction and speed of motion. If the theoretical basis for the significant effects in ecstasy users on the tilt aftereffect in this thesis is correct, then it would seem likely that ecstasy users will also exhibit the effects of broader tuning bandwidths on behavioural tests that are specific to these other low-level visual perception functions.

With regard to cognitive functioning, other functions which could be investigated include: the impact of ecstasy on the allocation of attention; the perception and memory for stimuli which are not attended to; various components of working memory; and specialist areas such as the holistic processing of faces. In particular, testing of elaborative processes in tasks other than long-term memory tasks may clarify if deficits emerge specifically from frontal lobe processes, or instead emerge from any test that requires many brain systems to be loaded concurrently.

The future research outlined above would continue to clarify which cognitive/perceptual functions are affected by recreational ecstasy use. For the purposes of drug policy and public health campaigns, a focus of ecstasy research needs to be the realistic definition of deficits that are actually likely to cause noticeable problems in real life situations, if any, as distinct from small deficits which are only detectable under laboratory conditions. In this thesis, one aspect of the Verbal Triplets Associates task suggests one possible area of research in which such noticeable deficits may be detected. The Verbal Triplets Associates test was the one test for multi-component items for which the significant deficits in ecstasy users were clearly related to task demands rather than possibly to sample differences. It was also the task which tested participants under the highest cognitive load conditions compared to the other tests used. This suggests that
ecstasy users may not notice any cognitive deficits in everyday life situations in which
cognitive demands are low, and in which plenty of time is available for elaborative
processing. However, in situations of high cognitive demands, in which ecstasy users
have to absorb, process and quickly respond to large amounts of new information, they
may experience significant cognitive problems. This could include situations like
driving into a foreign city for the first time, or when being put under pressure in a
business meeting. Such situations may be rare for many people, and in most cases can
be avoided altogether. People can also learn to increase their capacity to cope in such
situations through careful planning, time management, or even by portraying a casual
attitude. However, the results of the Verbal Triplets Associates test suggests that ecstasy
users may suffer from noticeable cognitive deficits in cognitively demanding real-life
situations.

8.2.4 Final summary

In summary, findings of the studies in this thesis indicate intact implicit memory in
ecstasy users, but significant memory deficits that appear to be related to problems in
elaborative processing, as well as significant changes in low level visual processing
though to be associated with the bandwidth of orientation sensitive neurons in the
occipital lobe. The degree of control exercised over potential causes of the effects apart
from ecstasy, including alcohol, cannabis and amphetamines, led to the conclusion that
the results are most likely due to ecstasy, and thereby probably due to MDMA. The
tasks introduced into this field of research for the first time in this thesis may be more
sensitive to ecstasy-related deficits than the standard neuropsychological tests prevalent
in the published literature. Future research can clarify and expand the findings of the
present study by identifying and designing tests which are specific to the components
and processes of other cognitive functions not tested in this thesis, including further
exploration of the possibility that slower processing in ecstasy user may cause
noticeable deficits under high cognitive load conditions, including real life situations.
## Appendix A: Additional sample characteristics

### Table A-1 Additional characteristics of ecstasy users and non-drug using controls in the first memory study (Chapter 4). SEM = Standard Error of the Mean. (.ns indicates p > .05). Additional characteristics are shown in Table 4-3 (p.80)

<table>
<thead>
<tr>
<th>Brief Symptom Inventory</th>
<th>Controls (n=29)</th>
<th>Ecstasy users (n=32)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSI GSI</td>
<td>52.3 (12.3)</td>
<td>53.2 (10.2)</td>
<td>.ns</td>
</tr>
<tr>
<td>BSI PST</td>
<td>54.1 (10.5)</td>
<td>54.6 (8.7)</td>
<td>.ns</td>
</tr>
<tr>
<td>BSI PSTi</td>
<td>49.6 (9.7)</td>
<td>51.9 (7.9)</td>
<td>.ns</td>
</tr>
<tr>
<td>BSI Somatization</td>
<td>48 (7.9)</td>
<td>48.8 (7.1)</td>
<td>.ns</td>
</tr>
<tr>
<td>BSI Obsessive-Compulsive</td>
<td>57.8 (9.7)</td>
<td>57.9 (14.1)</td>
<td>.ns</td>
</tr>
<tr>
<td>BSI Interpersonal Sensitivity</td>
<td>56.8 (14.1)</td>
<td>56.1 (10.6)</td>
<td>.ns</td>
</tr>
<tr>
<td>BSI Depression</td>
<td>56.2 (12.2)</td>
<td>54.1 (9)</td>
<td>.ns</td>
</tr>
<tr>
<td>BSI Anxiety</td>
<td>53.3 (9.2)</td>
<td>55.7 (7.1)</td>
<td>.ns</td>
</tr>
<tr>
<td>BSI Hostility</td>
<td>50.3 (9.4)</td>
<td>53.2 (10.7)</td>
<td>.ns</td>
</tr>
<tr>
<td>BSI Phobic Anxiety</td>
<td>49.9 (8.9)</td>
<td>49.4 (7.1)</td>
<td>.ns</td>
</tr>
<tr>
<td>BSI Paranoid Ideation</td>
<td>50.3 (11.7)</td>
<td>51.5 (10.1)</td>
<td>.ns</td>
</tr>
<tr>
<td>BSI Psychoticism</td>
<td>55.9 (12.2)</td>
<td>55.5 (8.8)</td>
<td>.ns</td>
</tr>
<tr>
<td>BSI Additional items</td>
<td>2.2 (1.7)</td>
<td>2.3 (1.9)</td>
<td>.ns</td>
</tr>
</tbody>
</table>

| Sensation Seeking Scale                      |                  |                      |      |
| Thrill and Adventure                         | 6.9 (2)          | 7.5 (1.6)            | .ns  |
| Experience Seeking                          | 6.2 (1.5)        | 7.8 (1.5)            | <.001|
| Disinhibition                                | 4.3 (2.1)        | 6.7 (2.1)            | <.001|
| Boredom Susceptibility                       | 4.39 (2.35)      | 4.13 (1.93)          | .ns  |

### Ecstasy
- maximum monthly dose: 6.04 (7.05)
- maximum ever dose: 4.06 (2.41)

### Alcohol
- abstinence (days): 9 (10) vs 7 (22); .ns

### Cannabis
- abstinence (days): 1626 (2589) vs 148 (324)
- lifetime administrations\(^a\): 6.8 (7.0) vs 1406.6 (2717.7)
- maximum monthly dose: 0.34 (0.45) vs 50.22 (96.12)
- maximum ever dose: 1.00 (0.00) vs 5.7 (5.44)

### Amphetamines
- abstinence (days): 216 (240)
- lifetime dose (grams\(^a\)): 19.9 (37.7)
- maximum monthly dose: 3.01 (7.71)
- maximum ever dose: 1.04 (1.05)

\(^a\)Dose measurements explained in Chapter 2, section 2.6.2
Table A-2 Additional characteristics of ecstasy users and non-drug using controls in the second memory study (Chapter 5) and the low-level visual perception study (Chapter 7). SEM = Standard Error of the Mean. (.ns indicates p > .05). Additional characteristics are shown in Table 5-3 (p. 109) and repeated in Table 7-1 (p. 192).

<table>
<thead>
<tr>
<th>Brief Symptom Inventory</th>
<th>Controls (n=34)</th>
<th>Ecstasy users (n=30)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSI GSI</td>
<td>53.15 (1.59)</td>
<td>53.93 (1.94)</td>
<td>.ns</td>
</tr>
<tr>
<td>BSI PST</td>
<td>54.88 (1.47)</td>
<td>56.17 (1.80)</td>
<td>.ns</td>
</tr>
<tr>
<td>BSI PSTi</td>
<td>50.06 (1.55)</td>
<td>50.90 (1.41)</td>
<td>.ns</td>
</tr>
<tr>
<td>BSI Somatization</td>
<td>47.21 (1.10)</td>
<td>51.63 (1.72)</td>
<td>.03</td>
</tr>
<tr>
<td>BSI Obsessive-Compulsive</td>
<td>56.29 (1.37)</td>
<td>61.03 (1.73)</td>
<td>.03</td>
</tr>
<tr>
<td>BSI Interpersonal Sensitivity</td>
<td>57.68 (1.77)</td>
<td>56.67 (1.90)</td>
<td>.ns</td>
</tr>
<tr>
<td>BSI Depression</td>
<td>56.91 (1.71)</td>
<td>54.27 (1.75)</td>
<td>.ns</td>
</tr>
<tr>
<td>BSI Anxiety</td>
<td>52.24 (1.45)</td>
<td>51.77 (1.58)</td>
<td>.ns</td>
</tr>
<tr>
<td>BSI Hostility</td>
<td>52.82 (1.48)</td>
<td>54.50 (1.77)</td>
<td>.ns</td>
</tr>
<tr>
<td>BSI Phobic Anxiety</td>
<td>51.24 (1.52)</td>
<td>50.63 (1.42)</td>
<td>.ns</td>
</tr>
<tr>
<td>BSI Paranoid Ideation</td>
<td>51.76 (1.69)</td>
<td>51.80 (1.81)</td>
<td>.ns</td>
</tr>
<tr>
<td>BSI Psychoticism</td>
<td>56.82 (1.67)</td>
<td>57.17 (1.90)</td>
<td>.ns</td>
</tr>
<tr>
<td>BSI Additional items</td>
<td>2.12 (0.31)</td>
<td>1.30 (0.29)</td>
<td>.06</td>
</tr>
</tbody>
</table>

Sensation Seeking Scale

<table>
<thead>
<tr>
<th></th>
<th>Mean (SEM)</th>
<th>Mean (SEM)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrill and Adventure</td>
<td>7.38 (0.32)</td>
<td>7.43 (0.31)</td>
<td>.ns</td>
</tr>
<tr>
<td>Experience Seeking</td>
<td>5.53 (0.31)</td>
<td>7.90 (0.23)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Disinhibition</td>
<td>4.74 (0.37)</td>
<td>6.87 (0.35)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Boredom Susceptibility</td>
<td>3.53 (0.38)</td>
<td>3.90 (0.38)</td>
<td>.ns</td>
</tr>
</tbody>
</table>

Ecstasy

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>maximum monthly dose</td>
<td>18.5 (27.6)</td>
<td></td>
</tr>
<tr>
<td>maximum ever dose</td>
<td>5.7 (4.1)</td>
<td></td>
</tr>
</tbody>
</table>

Cannabis (n=11)

<table>
<thead>
<tr>
<th></th>
<th>Mean (SEM)</th>
<th>Mean (SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>abstinence (days)</td>
<td>1590.5 (1650.1)</td>
<td>119.0 (275.8)</td>
</tr>
<tr>
<td>lifetime administrations</td>
<td>2.9 (2.7)</td>
<td>1656.7 (1993.9)</td>
</tr>
<tr>
<td>maximum monthly dose</td>
<td>0.12 (0.06)</td>
<td>58.5 (74.3)</td>
</tr>
<tr>
<td>maximum ever dose</td>
<td>1.09 (0.3)</td>
<td>6.5 (5.1)</td>
</tr>
</tbody>
</table>

Amphetamines

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>abstinence (days)</td>
<td>230.8 (332.8)</td>
<td></td>
</tr>
<tr>
<td>lifetime dose (grams)</td>
<td>51.3 (80.5)</td>
<td></td>
</tr>
<tr>
<td>maximum monthly dose</td>
<td>4.3 (7.8)</td>
<td></td>
</tr>
<tr>
<td>maximum ever dose</td>
<td>1.5 (1.4)</td>
<td></td>
</tr>
</tbody>
</table>

* Dose measurements explained in Chapter 2, section 2.6.2
Table A-3 Additional characteristics of ecstasy users (n=32), cannabis-controls (n=32) and non-drug using controls (n=33) in the third memory study (Chapter 6). SEM = Standard Error of the Mean. Additional characteristics are shown in Table 6-2 (p.131) and Table 6-3 (p.132).

<table>
<thead>
<tr>
<th>Non-drug using Controls (n=33)</th>
<th>Cannabis-Controls (n=32)</th>
<th>Ecstasy users (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Faces I</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SEM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37.82 (0.71)</td>
<td>37.19 (0.82)</td>
<td>35.94 (0.66)</td>
</tr>
</tbody>
</table>

**Brief Symptom Inventory**

<table>
<thead>
<tr>
<th></th>
<th>Non-drug using Controls (n=33)</th>
<th>Cannabis-Controls (n=32)</th>
<th>Ecstasy users (n=32)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BSI GSI</strong></td>
<td>50.03 (1.84)</td>
<td>54.75 (2.04)</td>
<td>55.94 (2.04)</td>
</tr>
<tr>
<td><strong>BSI PST</strong></td>
<td>51.94 (1.72)</td>
<td>55.75 (2.01)</td>
<td>57.00 (1.53)</td>
</tr>
<tr>
<td><strong>BSI PSTi</strong></td>
<td>49.82 (1.50)</td>
<td>52.13 (1.55)</td>
<td>53.28 (1.54)</td>
</tr>
<tr>
<td><strong>BSI Somatization</strong></td>
<td>48.91 (1.36)</td>
<td>51.56 (2.11)</td>
<td>52.84 (2.06)</td>
</tr>
<tr>
<td><strong>BSI Obsessive-Compulsive</strong></td>
<td>57.21 (1.65)</td>
<td>60.34 (1.83)</td>
<td>61.13 (1.71)</td>
</tr>
<tr>
<td><strong>BSI Interpersonal Sensitivity</strong></td>
<td>53.61 (1.79)</td>
<td>56.03 (1.91)</td>
<td>57.00 (1.94)</td>
</tr>
<tr>
<td><strong>BSI Depression</strong></td>
<td>52.55 (1.52)</td>
<td>54.78 (2.04)</td>
<td>56.69 (1.86)</td>
</tr>
<tr>
<td><strong>BSI Anxiety</strong></td>
<td>49.52 (1.68)</td>
<td>53.34 (2.03)</td>
<td>55.25 (1.82)</td>
</tr>
<tr>
<td><strong>BSI Hostility</strong></td>
<td>52.36 (1.26)</td>
<td>54.13 (1.98)</td>
<td>54.16 (1.68)</td>
</tr>
<tr>
<td><strong>BSI Phobic Anxiety</strong></td>
<td>49.06 (1.20)</td>
<td>48.97 (1.50)</td>
<td>51.75 (1.59)</td>
</tr>
<tr>
<td><strong>BSI Paranoid Ideation</strong></td>
<td>48.24 (1.53)</td>
<td>50.91 (2.08)</td>
<td>53.81 (1.76)</td>
</tr>
<tr>
<td><strong>BSI Psychoticism</strong></td>
<td>53.15 (1.47)</td>
<td>55.81 (2.02)</td>
<td>56.69 (1.64)</td>
</tr>
<tr>
<td><strong>BSI Additional items</strong></td>
<td>1.61 (0.33)</td>
<td>2.78 (0.42)</td>
<td>2.38 (0.51)</td>
</tr>
</tbody>
</table>

**Ecstasy**

|                      |                          |                      |
| Maximum monthly dose | 0.38 (0.15)              | 19.82 (4.70)         |
| Maximum ever dose    | 1.22 (0.17)              | 6.50 (0.65)          |

**Alcohol**

|                      |                          |                      |
| Abstinence (days)     | 170.5 (103.9)            | 25.5 (16.3)          |
|                      | 29.2 (18.1)              |                      |

**Cannabis**

|                      |                          |                      |
| Abstinence (days)     | 1427.0 (449.3)           | 36.47 (18.3)         |
|                      | 186.95 (85.5)            |                      |

**Amphetamines**

|                      |                          |                      |
| Abstinence (days)     | 1316.1 (445.4)           | 292.2 (99.1)         |

\(^{a}\) grams of “Speed” (methamphetamine power cut with a filler) or the roughly equivalent amounts of other forms of amphetamines thought to give a similar effect. See Chapter 2.

\(^{c}\) p<.05 compared to non-drug using controls; \(^{b}\) p<.05 compared to ecstasy users

\(^{c}\) p<.10 compared to non-drug using controls; \(^{b}\) p<.10 compared to cannabis-controls; \(^{b}\) p<.10 compared to ecstasy users
Appendix B: Participant information sheet and consent forms

THE AUSTRALIAN NATIONAL UNIVERSITY

Ecstasy research participant information sheet

My name is John Brown and I am conducting a research program into the possible consequences on brain functioning of “Ecstasy” use. The study you are being invited to participate in is one of a series of studies in that research program.

As part of this study I will be asking your information about your use of illicit drugs, if any, as well as your psychiatric and medical history. You will then be given a number of un-intrusive psychological tests, which will be pen-and-paper, verbal, or computer implemented tasks. Data from all of these components of the study will be stored such that there is no written record that can be used to connect your name and contact details to other information (except if you indicate that you would like to be involved in future studies – see below). All information will be stored in a locked filing cabinet in a secure office in the ANU Psychology building.

The results of this research will be presented in summary form only, that is, individual scores will not be used, and you will not be identified in any way. Data in aggregate form only will be used for the purpose of my PhD thesis and any subsequent publications. Apart from this, information from the research will not be released to any third party unless I am legally compelled to do so, which is very unlikely.

I am obliged to inform you that with any research regarding illicit drug use, there can be a possibility of incriminating yourself when providing information about illicit drug use.

If you agree to participate in the research you will be asked to initial the first part of the consent form. If you wish to participate in future studies then you may initial the second part of the consent form as well. If you initial the second part of the consent form, information which can be used to link your name and contact details to other data collected during this study, including records of your illicit drug use, will be kept in a locked filing cabinet in a separate office in the psychology building in order to facilitate your participation in future studies. This information will be destroyed at any time if you request it, or at the end of the research program.

Thank you for your interest and participation.

John Brown

If you have any further concerns regarding your participation in this study, please feel free to contact any of the following people:

Mr John Brown (School of Psychology) 
Email: john.brown@anu.edu.au 
Ph. (02) 6125-3827

Dr. Jeff Ward (School of Psychology)
Email: Jeff.Ward@anu.edu.au
Ph. (02) 6125 4208

Mrs Sylvia Deutsch (Human Ethics Officer, Research Services Office)
Email: Human.Ethics.Officer@anu.edu.au
Ph. (02) 6125 2900
THE AUSTRALIAN NATIONAL UNIVERSITY  
School of Psychology

Dear Participant,

This research is part of a postgraduate student research project in psychology at the Australian National University regarding possible consequences on brain functioning of “Ecstasy” use. The protocol has received approval from the ANU Human Research Ethics Committee (protocol no. 2002/3).

Could you please read the attached participant information sheet, and then complete Part 1 of the consent form below to acknowledge that you agree to participate in the study.

Participant Consent Form: Part 1

I, the undersigned, have read the participant information sheet and willingly consent to participate in a study investigating possible consequences of “Ecstasy” use on brain functioning. I understand that this will include questions regarding my current and past illicit drug use, if any, and that there is the possibility of incriminating myself when providing such information. I agree to allow my data to be used in an aggregate form for the purpose of John Brown’s PhD thesis and any subsequent publications. I understand that I can withdraw from the study at any time, and that I will receive a full explanation of the details and purpose of the research at the end of the study.

Initial: ___________________________ Date: __________________________

If you wish to participate in future studies associated with this research project then you are invited to read an initial Part 2 of the consent form.

Participant Consent Form: Part 2

I, the undersigned, wish to participate in future studies as part of the John Brown’s research project. I understand that initialising this part of the consent form means that I have granted permission for a record to be kept of my name and contact information, as well as a separate record of information (which will be stored in a separate secure office) that can be used to link me to other data collected about me during this study.

Initial: ___________________________ Date: __________________________

If you have any further concerns regarding your participation in this study, please feel free to contact any of the following people:

Mr John Brown (School of Psychology)  Dr. Jeff Ward (School of Psychology)  
Email: john.brown@anu.edu.au  Email: Jeff.Ward@anu.edu.au  
Ph. (02) 6125-3827  Ph. (02) 6125 4208

Mrs Sylvia Deutsch (Human Ethics Officer, Research Services Office)  
Email: Human.Ethics.Officer@anu.edu.au  
Ph. (02) 6125 2900
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