THE DIFFERENTIAL EFFECTS OF MDMA (ECSTASY) USE ON EXECUTIVE AND MEMORY PROCESSES.

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Abstract

The purpose of this thesis was to examine the nature of executive function deficits in ecstasy users, and the contribution of these executive functions to performance on other cognitive tasks. Using recent theoretical models of executive functioning recreational ecstasy-polydrug users were tested in laboratory settings on measures of mental set switching, response inhibition, memory updating and access to semantic memory. It was found that ecstasy users performed significantly worse than nonusers on measures of updating and access, although cocaine also emerged as an important factor in deficits in access. The contribution of access and updating to performance on more complex executive function tasks was then assessed. It was found that while associative learning is relatively independent of access and updating, the same was not true for everyday memory and syllogistic reasoning. Ecstasy group related deficits in syllogistic reasoning were slightly attenuated following control for access and substantially following control for updating. It emerged that everyday memory deficits were more related to the use of cannabis than the use of ecstasy. The results of this thesis have serious implications for those who use ecstasy and should be used in educating such individuals. Outside the area of Psychopharmacology this thesis provides further support for the nature of executive functions and their relationship with syllogistic reasoning and everyday memory. Future research should assess executive functions along the same paradigm and seek to recruit polydrug control groups.

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Chapter 1: Overview of Thesis

This Chapter provides a brief overview of each Chapter of this thesis. Chapter 2 provides a brief introduction to the study of executive functions in ecstasy users and gives an overview of the theoretical models of working memory and executive functioning upon which this thesis is based. The chapter provides a rationale for studying executive functions as separable in ecstasy users.

Chapters 3, 4, and 5 are literature review chapters. Chapter 3 is a review of studies of aspects of cognition in ecstasy users. This chapter outlines areas that are in need of more research and further clarification, and thus provides a basis for the areas of intended study in this thesis. It is proposed that the use of ecstasy affects cognitive functioning via degradation of the serotonin system, thus Chapter 4 reviews studies in human ecstasy users that use objective measures of serotonergic functioning. This includes functional and structural brain imaging studies and measures of serotonin and glucose metabolism. The final literature review chapter is related to the use of cannabis and cocaine. Chapter 5 reviews some studies that have assessed cognitive functioning in cannabis and cocaine users, as it is possible that the use of these drugs may also contribute to cognitive deficits in ecstasy users.

Chapters 6, 7, 8, 9, 10 and 11are the empirical chapters of this thesis with the first three assessing the four postulated executive functions. Chapter 6 assesses memory updating performance in ecstasy users via a running memory task. Chapter 7 assesses performance of ecstasy users and nonusers on measures of mental set switching and response inhibition. Chapter 8 assesses performance of ecstasy users and nonusers on a task of access to semantic memory.

The results from these three Chapters revealed that ecstasy users are impaired in measures of memory updating and access, although switching and inhibition appear to be relatively unaffected. The final three empirical chapters assessed the

contribution of executive processes to performance on higher-level cognitive tasks and everyday memory tasks. Chapter 9 assesses the contribution of updating and access to syllogistic reasoning performance. Chapter 10 assessed the contribution of executive processes to associative learning performance. In Chapter 10 the underlying processes involved in associative learning performance are also investigated. Chapter 11 examines the contribution of updating and access to everyday memory processes.

The final chapter is a general discussion of the results. Chapter 12 evaluates the results in terms of the implications for drug users and the implications for the structure of executive functions and cognitive processes in general.

Chapter 2: The structure of Working Memory and Executive processes

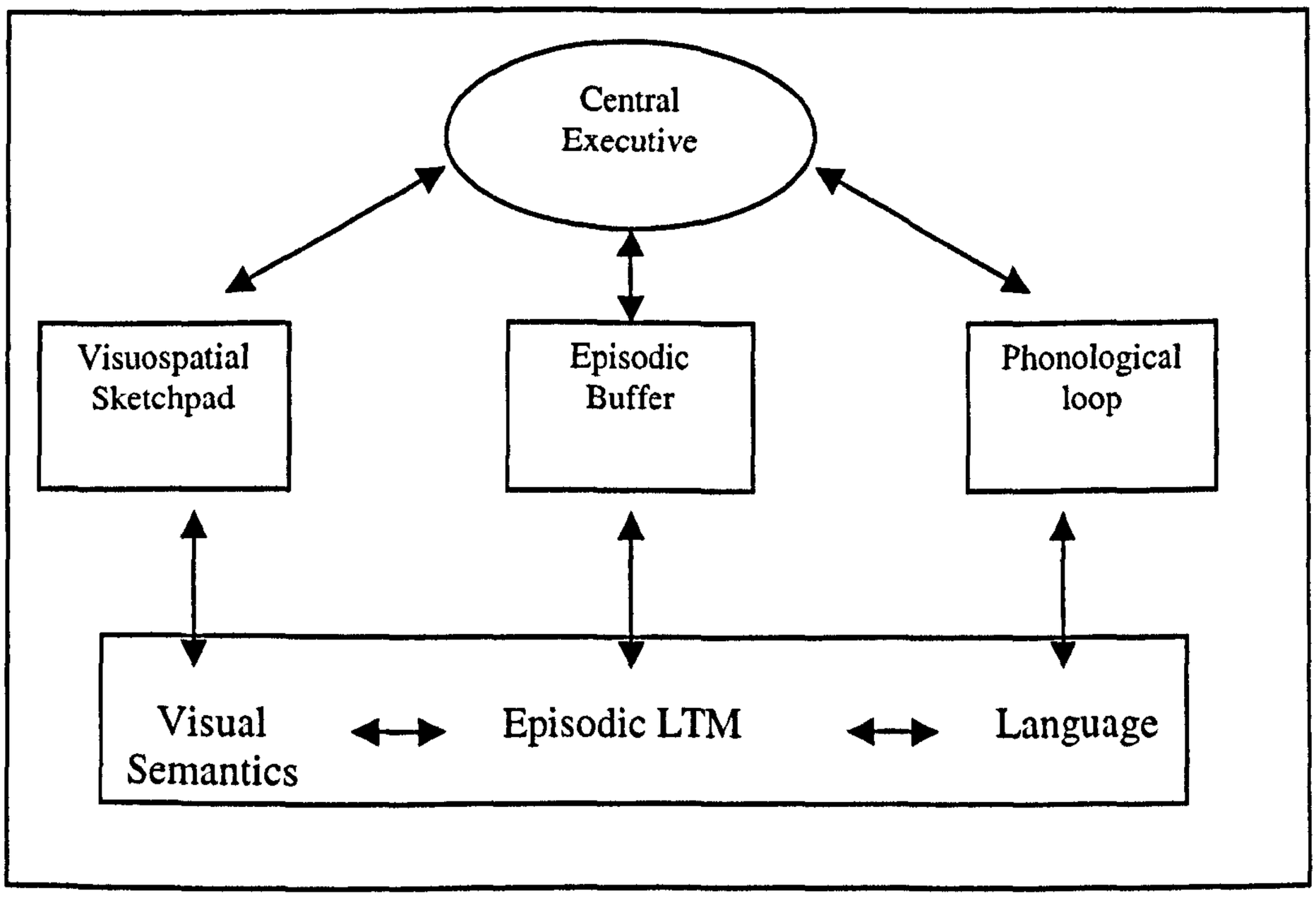
2.1 Chapter Overview

This chapter briefly provides a theoretical basis for studying the executive components that are explored in more depth in Chapter 3. Baddeley's model of working memory is referred to followed by recent advances of research in to executive processes and the fractionation of the central executive.

Theory of working memory and executive functions in relation to ecstasy studies

A key construct in cognitive psychology is Baddeley's (1986) model of working memory. The model consists of two "slave" systems, one that is involved in the processing of verbal sequences (the phonological loop) and one that is involved in the processing of visuo-spatial sequences (the visuospatial sketchpad) and a modality free central executive. Recent research from the same laboratory (Baddeley, 2000) proposes a new component of the working memory model: the episodic buffer. Baddeley assumes that the episodic buffer is a modality-free short-term store, under the control of the central executive. Baddeley proposes that the episodic buffer plays an important role in both transfer into- and retrieval from- long-term episodic memory. In light of this it is unclear how the episodic buffer component may be related to this thesis (indeed the concept was not as well-received in the literature as the previous model) and it is thus not discussed further. Figure 1 below shows a diagram of Baddeley's most recent conceptualisation of working memory.

Figure 1: Working Memory Model (reproduced from Baddeley, 2000).



There is a growing body of research suggesting that the central executive may not be a unified structure, with different tasks tapping different processes that are to some extent independent. Most studies in ecstasy users to date refer to executive functions as a unitary concept, using archaic clinical models of executive functioning, and until now there has been no systematic investigation of the nature of executive process deficits in ecstasy users. Indeed, it was unclear why ecstasy users exhibited deficits on some "executive function" tasks, but not others. For example, Fox, Parrott and Turner (2001) assessed the performance of a group of ecstasy users who reported experiencing cognitive deficits, and those who did not report such problems. Paradoxically, non-problem users were found to have significantly longer Tower of London (TOL) planning times than the problem users and the control group. Both ecstasy groups made significantly more errors than controls on a spatial working memory task, while higher use of ecstasy was associated with longer TOL planning times. Testing executive function and spatial working memory, Fox, McLean, Turner,

Parrott et al. (2002) found that ecstasy users performed worse than controls on verbal fluency, spatial working memory, attention shifting and pattern recognition. Moving on to verbal working memory, Wareing, Fisk, Murphy and Montgomery (2004b) found that previous and current users of ecstasy were impaired on a computation span task, requiring the concurrent processing and updating of information in working memory. The main effect of ecstasy remained significant after control for the use of other drugs. However, no ecstasy related deficits were observed on the reading span task, which supposedly uses the same mechanism. Wareing, Fisk and Murphy (2000) also found ecstasy users to be impaired in a random letter generation task, but no such effect was found in a subsequent study (Fisk, Montgomery, Wareing and Murphy 2004). While the results of such studies suggest global executive function deficits in ecstasy users, some studies fail to find ecstasy related cognitive deficits. Turner, Godolphin and Parrott (1999) found that ecstasy users were unimpaired on the Wisconsin Card Sort Task (WCST) (replicated by Fox et al. 2001), while Morgan, McFie, Fleetwood and Robinson (2002) found ecstasy users to be unimpaired in word fluency, Stroop, and Subtracting Serial Sevens among other tests. Alting von Geusau, Stalenhoef, Huizinga, Snel et al. (2004) also found that ecstasy users were unimpaired on the stop signal reaction time task (believed to measures response inhibition). One possible reason for such disparate results is that the central executive of working memory is not a unified structure, and ecstasy use differentially impairs its components. The next section of this Chapter discusses the separability of executive processes.

Recent theoretical models of executive functioning postulate that the central executive is fractionated, with its different components performing separate tasks with varying degrees of competence. Lehto (1996) found that while more complex memory

span tasks (involving concurrent processing and storage of information) were correlated with memory updating tasks, the correlations between these tasks and other executive function tasks such as the Tower of Hanoi and the Wisconsin Card Sort Task were not significant. Lehto (1996) argued that this demonstrates the fractionated nature of the central executive. In a more recent study, Miyake et al. (2000) studied the separability of three supposed executive functions: mental set shifting ("shifting"), information updating and monitoring ("updating"), and inhibition of pre-potent responses ("inhibition"), and how they contributed to executive tasks. Structural equation modelling revealed that the three executive functions were moderately correlated with each other, but clearly separate, and they contribute differently to performance on various executive prefrontal tasks. For example, the Wisconsin Card Sort Task (WCST) was linked to the shifting component, the Tower of Hanoi to the inhibition component, random number generation to both the inhibition and updating components, and operation span to the updating component. That is not to say that these three are the only executive functions, and it is possible that Miyake et al only found these as this is all they aimed to find. Thus one aim of the present study was to assess these three target functions in ecstasy users. However, in a study of age-related differences in executive functioning, Fisk and Sharp (2004) administered a number of executive tasks to assess the target functions of updating, shifting, inhibition, and another executive function: the temporary activation of long-term memory/access to long-term memory (Baddeley, 1996). Fisk and Sharp (2004) found that the three target functions proposed by Miyake et al. (2000) loaded on to distinct factors, but there was a clear separable factor which word fluency and "redundancy" (the extent to which each letter is said with the same overall frequency in the random letter generation task) mapped on to.

To date there has been no systematic investigation of whether or not ecstasy users are impaired in the different aspects of executive functioning identified by Miyake et al (2000). Existing research findings are piecemeal and have not always made use of the traditional measures of the different executive subcomponents identified by Miyake et al (2000). Therefore, one aim of this thesis is to ascertain the nature of executive function deficits in a sample of recreational ecstasy users. We aimed to use "pure" measures of each of the four postulated executive functions (updating, shifting, inhibition and access), and provide further clarification of the nature of executive deficits in ecstasy users.

The next Chapter reviews studies of cognitive deficits in ecstasy users. Although previous studies have assessed the central executive as a unified structure, in the following Chapter studies targeting the same executive functions have been grouped under sub-headings to enable the literature review to follow the same structure as the thesis.

Chapter 3: Review of Scientific Literature on Cognitive Deficits in ecstasy Users

MDMA, or "ecstasy" is a ring substituted monoaminergic agonist producing both the release and inhibiting the reuptake of Serotonin-5HT (Schmidt, 1987), and Dopamine (Yamamoto & Spanos, 1988). The ever-increasing recreational use of ecstasy is of great concern, with an estimated 2,097,000 adult users in the UK alone (British Crime Survey, 2004-05). Ecstasy has been associated with memory/cognitive deficits, and problems with psychological affect, which are thought to be due to the drug's neurotoxic effects on the serotonin system. However, research into the long-term effects of ecstasy does not yet yield conclusive results.

In addition to evidence of ecstasy-related memory deficits in rats and non-human primates, a growing number of studies are reporting persistent deficits in human working memory, compared to drug-naïve controls. The present chapter will summarise the research evidence in a number of specific aspects of cognition, including intelligence, recall, verbal learning, non-verbal learning, switching, inhibition, updating, access to long-term memory, visuo-spatial functioning, and recognition. Table 1 which is found at the end of the chapter contains summaries of the ecstasy use variables from the studies reviewed. [1]

3.1 Intelligence:

A number of studies have assessed intelligence in ecstasy users, rarely as a between groups factor but as a control method to match the groups in the study. Some studies have used measures of crystallised intelligence (e.g. the National Adult Reading Test) while some studies have assessed fluid intelligence (e.g. the Wechsler Abbreviated Scale of Intelligence, Raven's Progressive Matrices). Both Fluid and Crystallised Intelligence scores are correlated with higher cognitive capabilities, so it

[1] Specific dosages have not been referred to throughout the Chapter; this would involve much repetition.

is important that studies adequately match their groups on Intelligence scores, otherwise apparent ecstasy-related effects might in fact be attributable to group differences in intelligence.

Croft, Mackay, Mills and Gruzelier (2001a) used the National Adult Reading Test (NART), a list of 50 words that are of decreasing frequency in the English language, and of atypical phonology, meaning that pronunciations cannot be derived from standard grammatical rules. Estimated IQ was not significantly different between the groups (ecstasy users 116.2, cannabis users 115.2 and non-users 115.2). In Curran and Verheyden's (2003) study, NART IQ scores were not significantly different between current ecstasy users (111.38), previous users (111.27) and controls (113.54). In a correlational study with no control group, Dafters, Duffy, O'Donnell and Bouquet (1999) found that NART scores were not significantly associated with extent of ecstasy use (number of tablets used in a year), and a further study by Dafters, Hoshi and Talbot (2004) found that NART scores were not significantly different between the groups (as did Morgan et al. 2002 and Fox et al. 2002). Morgan (1998) also matched IQ via the NART; in Study 1 IQ was not significantly different between the groups (ecstasy users 114.9, polydrug users 112.3 and nonusers 113.5); but in study 2, estimated IQ was lower for ecstasy users than polydrug and nonusers (113.1, 116.1, and 115.1 respectively). Morgan (1999) also found that NART scores were significantly different between the three groups tested: 35.9 for ecstasy users, 39.1 for polydrug users and 37.5 for drug naïve controls. Although the groups were not matched for IQ in this study, the NART scores did not correlate with either immediate or delayed recall scores, where the performance differences lay between the groups. Semple et al. (1999) also matched their two groups using the NART. Groups did not differ significantly on this test (ecstasy user average IQ: 107.6;

nonuser: 109.7). Gouzoulis-Mayfrank, Daumann, Tuchtenhagen, Pelz et al. (2000) used the German language version of the WAIS-R Mosaic test to assess fluid intelligence (participants have to reproduce patterns using cubes: measuring fluid intelligence and assessing visuomotor performance and problem solving ability), the Wechsler Adult Intelligence Scale- Revised (WAIS-R) general knowledge test (to measure crystallised intelligence) and the LPS-4 abstract logical thinking test (in which participants are required to discover the rule for a series of letters or digits and indicate the incorrect element, testing fluid intelligence). On the LPS-4, mosaic and general knowledge test cannabis users and controls performed better than ecstasy users, indicating that ecstasy users in this study had a lower IQ. Krystal, Price, Opsahl, Ricaurte et al. (1992) also used the general intelligence scale of the WAIS-R. Estimated IQ was within the normal range (115), as were performance and verbal IQ. Zakzanis and Young (2001a) used the WAIS-R vocabulary (to measure verbal IQ) and block design (to measure performance IQ) subtests. Participants were tested on two occasions a year apart, while self-administering ecstasy in the year between testing sessions. Although there were no differences between performance at baseline and follow up for either test, there was a significant negative correlation between the vocabulary change score (score at second session subtracted from score at first session) and the frequency of use indicating that vocabulary performance declined with increasing use of ecstasy. Gouzoulis-Mayfrank, Thimm, Rezk, Hensen et al. (2003) again used the WAIS-R general knowledge (crystallised intelligence) task. Intelligence was significantly different between the groups, with moderate ecstasy users and controls performing better than heavy users. Moreover, control for differences in intelligence reduced some of the memory deficits to below statistical significance (see later sections).

Simon and Mattick (2002) again used the vocabulary subtest of the WAIS-R and the Kaufman Brief Intelligence Test (K-BIT), which consists of both verbal and nonverbal elements to form a composite IQ score. No differences were apparent on the K-BIT task, but ecstasy users did score significantly lower on the vocabulary test of the WAIS-R (which was a significant contributor to most of the memory deficits observed in this sample). Zakzanis, Young and Radkhoshnoud (2002) used the Wechsler Abbreviated Scale of Intelligence (WASI) performance and verbal IQ subtests. The performance IQ subtest involved matrix reasoning (participants have to conceptualise spatial, design and numerical relationships of varying difficulty) while the vocabulary subtest involved providing definitions of words in an incremental order of difficulty. Intelligence was not significantly different between the groups and correlations with dosage and usage (occasions) were non-significant. Wareing, Fisk, Murphy and Montgomery (2004a; 2004b) used sets D and E of Raven's Progressive Matrices, a test of fluid intelligence which requires participants to identify the next element in a sequence and indicate the correct answer from a choice of 8 possible answers (matrix reasoning). Scores were not significantly different between the groups in either study. Using the quick test Bhattachary and Powell (2001) assessed both fluid and crystallised Intelligence. Participants were required to examine line drawings and decide which was the most appropriate referent for a particular word. The words are of increasing abstractness and it is believed the test taps both crystallised (knowing the meaning of the words) and fluid (abstracting and comparing meanings of pictures) intelligence. Neither cannabis use nor ecstasy use was related to performance. In addition, neither recency of ecstasy use nor lifetime consumption predicted IQ scores in either the combined group of ecstasy users (novice, regular, currently abstaining), or the current users (novice, regular). Thomasius, Petersen,

Buchert, Andresen et al. (2003) assessed premorbid IQ via a German multiple choice test of vocabulary knowledge, while current IQ was assessed via performance on the "observation" and "calculation" subtests of the German Wilde Intelligence Test, and the reverse digit recall component of the Hamburg-Wechsler Intelligence Scale. No ecstasy-group related differences were observed on any of the IQ tests and all groups had similar premorbid IQ (current users: 102.5; ex-users: 106.48; polydrug: 104.28; drug-naïve: 104.97).

In summary, most studies have attempted to control for differences in IQ, and the majority of studies have found no between group differences in IQ scores, and little relationship between IQ scores and performance. In the four studies that did find between group differences in IQ scores (Gouzoulis-Mayfrank et al. 2000; Gouzoulis-Mayfrank et al. 2003; Morgan 1999; Simon & Mattick. 2002), three found that the effects of ecstasy on some other cognitive domains were reduced to below statistical significance following control for IQ. One study (Zakzanis et al. 2002) also found that IQ change over a year was negatively correlated with indices of ecstasy use, which raises the possibility that ecstasy may adversely affect IQ (although this area needs further clarification). In light of this evidence, every study that is researched in this thesis will adequately control for both premorbid and fluid intelligence.

3.2 Speed of Processing

Speed of processing is a much-researched area in ecstasy users. Tasks used include simple and choice reaction time tasks, the Trail Making Test-A (TMT-A), the Digit Symbol Substitution Task (DSST), Stroop-A, and some novel measures. On the whole, it appears that ecstasy users are not impaired on tasks that assess speed of processing, although some studies report increased incidence of errors.

Parrott, Lees, Garnham, Jones et al. (1998) assessed processing speed via simple and choice reaction time tasks. In the simple reaction time task, participants were required to press a key as soon as the target word ("YES") appeared on the screen, while choice reaction time involved pressing either the "yes" key when "yes" appeared on the screen or the "no" key when "no" appeared on the screen. Response latency was recorded. Regular and novice ecstasy users did not differ significantly from controls on these tasks. Fox, Parrott and Turner (2001) used a similar task in which fifty crosses appeared on a computer screen at random intervals and participants had to respond to them. Reaction times were not significantly different between controls and the three dosage groups (low, medium, high) but those who complained of ecstasy-related problems were significantly slower than those not complaining of problems (both groups had similar lifetime doses 372:357 tablets respectively, although the abstinence period for problem users was slightly longer, 7.8:2.5 months respectively) and controls. To assess processing speed, Thomasius et al. (2003) used the Trail Making Test-A (TMT-A) which consists of the numbers 1-25 encircled and spread randomly across a sheet of paper. The object of the task is to connect the numbers in order, beginning at 1 and ending at 25 in as little time as possible. The task requires visual scanning, numeric sequencing and psychomotor speed. No significant group differences were observed in psychomotor speed in this sample. This finding was replicated by McCardle, Luebbers, Carter, Croft et al. (2004) using the TMT-A test, in a sample of 17 recreational ecstasy users compared to 15 nonusers, and Morgan, McFie, Fleetwood and Robinson (2002) with a sample of 18 current heavy ecstasy users, 15 former heavy users, 16 polydrug controls, and 15 drug-naïve participants. Two of the nine participants tested by Krystal et al. (1992) showed mild impairment on the TMT test, but these results should be treated with

some caution as the sample size was so small. Semple et al. (1999) also used the TMT-A task and the CANTAB simple reaction time tasks. Again, no differences were observed between the groups regarding reaction time, but again sample sizes were relatively small and comprised of males only.

Wareing et al. (2000) measured information processing speed via a visual search match to sample task in which participants were required to indicate whether two sets of letters were the same or different, at three list lengths of three-, six-, or nine-letters. Participants were scored on number of targets classified and number correct at each list length. While nonusers had a higher percentage correct than previous and current users at the longest list length, there were no group differences in total number completed or numbers correct at the three and six item lengths. The sample size in this study is however rather small (N=10 per group), so the findings should be treated with some caution. In a conference paper Wareing, Fisk, Murphy and Montgomery (2003) reported that there were no ecstasy-related deficits on a pattern recognition match-to-sample processing speed task. On the letter comparison task (as used by Wareing et al. 2000) ecstasy users performed marginally worse than nonusers (which just attained statistical significance), although there was no interaction between complexity and user group. After controlling for differences in years of education the effect was reduced to below statistical significance.

Rodgers (2000) measured visual and auditory reaction time via a computerised task in which participants had to press spacebar after seeing/hearing a target (which was a white circle for visual reaction time, and a simple tone for auditory reaction time), and complex reaction time in which participants had to press the number that corresponds to the number presented on the computer screen (1-9). Ecstasy users, cannabis users and nonusers performed similarly on all tests of reaction time

(however ecstasy users had used on an average of 20 times over 5 years, which is perhaps a little low compared to other studies: see Table 1). Verkes, Gijsman, Pieters, Schoemaker et al. (2001) assessed reaction time to simple auditory and visual stimuli, and a binary choice task. Reaction time was longest in heavy users and shortest in nonusers (with moderate users performing between the two). After control for group differences in education level and Beck Depression Inventory (BDI) scores, group differences in reaction time were no longer significant. In a clinical study (Cami, Farre, Mas, Mas et al. 2000), simple visual reaction time was not affected after administration of 75/125mg of MDMA.

A number of studies have used the Matching Familiar Figures-20 (MFF-20) task in which participants view a sample geometric shape and attempt to identify a matching choice figure from a displayed selection as quickly as possible: 20 trials are implemented. In Dafters et al's (2004) study time and errors were not significantly different between the four groups (heavy ecstasy and cannabis, light ecstasy and cannabis, cannabis only and nonuser). Morgan et al (2002) also used the MFF-20, and a digit cancellation task (in which participants were required to mark every occurrence of the number "5", which was distributed randomly among 400 two-digit numbers in a 20x20 layout) to assess speed of processing. Performance between current ecstasy users, previous ecstasy users, polydrug users and nonuser controls was not significantly different on the digit cancellation task. There were however significant ecstasy-related group differences on the latency to first response, total number of errors and composite I score (calculated by subtracting the standardised score of the mean latency from the standardised score of the number of errors committed) on the MFF-20 task. The number of errors on the MFF-20 task was positively correlated with the reported average dose of ecstasy consumed by all

ecstasy users, and stepwise regression analyses revealed that MFF-20 errors, mean latencies to first response, and I scores were only significantly predicted by the average dose of ecstasy. This was interpreted as an ecstasy-related deficit in impulsivity (with ecstasy users being more impulsive and thus having faster response latencies and more errors). Using the Digit Symbol Substitution Task (DSST) a sample of 22 ecstasy users had similar digit symbol scores to a group of nonusers (Back-Madruga, Boone, Chang, Grob et al. 2004). Likewise, Thomasius et al. (2003) failed to find differences in DSST performance between 30 current users and 31 former users, compared to 29 polydrug users and 30 controls. McCardle et al. (2004) also failed to detect any differences using this test with 17 ecstasy users and 16 cannabis users. Similarly, Halpern, Pope, Sherwood, Barry et al. (2004) found no ecstasy group related difference between 23 users compared to a light polydrug control group (N=16). In a clinical study Cami et al. (2000) found that administration of either placebo, 40mg of amphetamine, 75 mg of MDMA or 125mg of MDMA did not impair reaction time on the DSST (although 125mg of MDMA was associated with slightly increased errors and reduced number of correct responses) at any of the testing periods (over 30 minutes to an hour for the 24 hours after administration).

Halpern et al. (2004) also used the Stroop task to measure information-processing speed. In Stroop A, colour words (e.g. RED) are all printed in black ink, and participants are required to read them aloud. In Stroop B, colour words are printed in same and different coloured ink, and participants have to name the colour ink. While Stroop A measures speed of processing, Stroop B measures speed of processing under interference. Although Halpern et al. failed to find group related differences on the Stroop task in this sample, when the ecstasy group was split into 12 moderate users (fewer than 50 occasions) and 11 heavy users (50+ occasions), it was

found that greater lifetime ecstasy use was associated with poorer performance on the Stroop interference task. However, Back-Madruga et al. (2004) failed to find any differences in Stroop performance between ecstasy users and nonusers. Croft et al. (2001a) used the Stroop task A and B (interference). Stroop B performance was not significantly different between drug users and nonusers. Conversely, a combined ecstasy and cannabis user and cannabis only user group performed worse than nonusers on Stroop A, and performance was correlated with total ecstasy use (at .31) and frequency of ecstasy use (at .24). McCardle et al. (2004) also failed to find any ecstasy related differences on the Speed of Comprehension Test (SCT). Verbaten (2003) published a Meta analysis examining ten studies of ecstasy users that had abstained for at least a week prior to the studies, and concluded that ecstasy use was not associated with impaired information processing speed.

The majority of studies have failed to detect ecstasy-related differences in information processing speed, although a small number of studies that did find differences were not limited to one type of test (most of the types of test reported had one study finding an effect). While Fox et al. (2001) found that problem ecstasy users (lifetime dose of 372.3 tablets) were slower than non-problem users (356.9 tablets), another study that did find a significant effect found that it was dose related: Morgan et al. (2002) found that current and former users of ecstasy (with a lifetime dose for men and women of 513/93 and 336/577 respectively) performed worse than polydrug users and controls; Verkes et al. (2001) found that heavy users (lifetime dose of 741 tablets) took longer than light users (although this was reduced to below statistical significance after control for education and BDI scores). One study also found that performance was more related to ecstasy-polydrug use or cannabis use (Croft et al. 2001a) rather than ecstasy use. This area has been much researched in ecstasy users

with studies generally yielding few between group differences; it is likely that deficits in higher level cognitive functions are separable from deficits in information processing (e.g. Wareing, Fisk, Murphy, Montgomery & Chandler, 2005), and this area will thus not be investigated further in this thesis.

3.3 Executive Tasks

3.3.1 Switching

"Switching" or "shifting" refers to a participant's ability to switch their attention between different tasks or different elements of the same task. It therefore requires greater temporal cost than a task in which no switching is required. Some studies in ecstasy users utilised the Trail Making Test-B, a novel Go/No-Go task and classification tasks (e.g. Wisconsin Card Sort Task). Again, most results in this area are equivocal.

To measure mental set switching, Krystal et al. (1992) used the Trail Making Test-B (TMT-B). This is more complex than TMT-A as it requires the participant to connect numbers and letters in an alternating pattern (e.g. 1-A-2-B-3-C etc.) in as little time as possible. As TMT-B requires attentional switching between the letters and numbers, it is more cognitively demanding and thus requires more time. In Krystal et al.'s study, only 1 participant showed mild impairment, and one moderate impairment on the TMT-B test. However, the sample size in this study was very small, so the results should not be generalised to the population (N=9). Semple et al. (1999) also failed to find any ecstasy-related differences between 10 regular ecstasy users and 10 polydrug users matched for age, education and IQ using this task. Again comparing a sample of 30 current heavy ecstasy users, 31 former ecstasy users, 29 polydrug controls (with significantly higher lifetime exposure to cannabis, psilocybin

mushrooms and amphetamine, and having used significantly more cannabis and amphetamine in the last year) and 30 drug naïve controls who were matched for age and IQ, Thomasius et al. (2003) observed no significant differences using the TMT-B task. This was supported by McCardle et al. (2004) who found no ecstasy-related group differences on the TMT-B in a sample of 17 ecstasy users compared to 15 non-ecstasy user controls. Morgan et al. (2002) used the TMT-B task to assess executive function in four groups: 18 current ecstasy users, 15 former ecstasy users, 16 polydrug controls (with similar drug use histories to the ecstasy groups) and 15 drug naïve controls who were matched for age and IQ. Although completion times for TMT-B did not differ significantly between the groups, ecstasy users did commit significantly more errors on this task (current users committed slightly more than previous users although this was non-significant). Performance on TMT-B was not significantly correlated with observed differences in General Health Questionnaire (GHQ) scores, Impulsiveness Venturesomeness Empathy (IVE) scores or any of the Symptom Check List-90 (SCL-90) scores. However, regression analysis using measures of previous ecstasy and other drug use revealed that TMT-B errors were only predicted by the number of LSD trips and the number of psilocybin mushrooms consumed in the year prior to testing. Following control for these other drugs via ANCOVA, the group differences in TMT-B errors were reduced to below statistical significance.

McCann et al. (1999) used the Serial Add and Subtract Task from the Walter Reed Army Institute of Research Performance Assessment Battery (WRAIR-PAB). This is a computer based mental arithmetic task requiring sustained attention. Two random digits and a "plus" or "minus" sign flash rapidly on a computer screen. The participant has to perform the addition or subtraction and enter the least significant

digit of the result. If the answer is negative, the participant has to add 10 to obtain the correct response. The 22 ecstasy users were matched for age, gender, education level and use of other drugs with 23 nonusers (although no values of amounts are reported for the use of other drugs, ecstasy users reported using other drugs more frequently, and greater numbers reported trying other drugs), and both groups reported being abstinent from psychoactive drugs for three weeks prior to testing. There were no differences between the groups at baseline (day 1), but ecstasy users were slower than nonusers on days 2 and 3 although errors were similar between the groups. Furthermore performance was not related to decreased 5HIAA in the cerebrospinal fluid of ecstasy users.

Fox, McLean, Turner, Parrott et al. (2002) compared 20 ecstasy users with 20 controls matched for age (27.3:27.5 years), and intelligence (estimated PMI 100.3:103). One measure of switching used was a go/no go task consisting of 10 separate blocks, each of which involved 18 symbols appearing rapidly at the centre of a computer screen. Half of the symbols were "targets" and half were "non-targets" and comprised either letters (A-G) or numbers (2-9). Participants were told to tap the space bar as quickly as possible only when they saw the target for that block. The target was switched from letters to numbers (or vice versa) following every two blocks. The initial two blocks were practise blocks where the target was counterbalanced across participants. All participants were scored for mean number of errors made across trials (i.e. failure to tap the spacebar), mean number of "distractors" (i.e. the number of times they had responded to a non-target) and mean reaction time. No between group differences were observed in distractor errors or latencies, and as both groups scored predominantly zero on the omission errors, these were not included in the analysis. Fox et al. (2002) also used the 3-D IDED

attentional shift task, based on the CANTAB battery task, which assesses ability to form, maintain, and shift attentional set. Participants were requested to learn a series of two alternative forced choice discriminations and their reversals. The stimuli used varied along three possible dimensions (one relevant, and two irrelevant). In the simple visual discrimination stage, the stimuli differed on only one of the possible three dimensions, and in the following reversal stage, the previously incorrect stimulus became the correct one. In the compound visual stage, the contingencies from the previous stage remained the same (i.e. colour); however, the stimuli differed along all 3 possible dimensions. In the "intra-dimensional shift" stage, the relevant dimension (i.e. colour) still remained unchanged despite the introduction of two novel stimuli. In the final "extra-dimensional shift" stage, participants were required to "shift" response set to a previously irrelevant dimension (i.e. shape). Each of the four stages also preceded a reversal stage where the previously non-reinforced stimulus became the reinforced target. In order to proceed along each stage, participants were expected to achieve six correct successive discriminations in a row. If these were not achieved following 50 attempts, the task was terminated. Errors and response latencies for each stage were recorded. There were no significant between group differences in the number of errors committed (although for the reversal trials, the group x difficulty interaction approached significance, with ecstasy users making more errors on the simple and compound reversal trials, but slightly fewer on the extra-dimension reversal). Ecstasy users also performed worse than controls on the reversal latencies at all levels.

One study that did find ecstasy-related deficits in task switching (in male users only) used a novel task to assess switching performance. Alting von Geusau, Stalenhoef, Huizinga, Snel et al. (2004) used the "dots-triangles" task involving the

maintenance and switching of response set. In a 4x4 grid on a screen, varying numbers of either dots or triangles appear. In the first block, dots appear and participants have to decide whether there are more dots in the left or right part of the screen; in the second block, triangles appear and participants have to indicate if there are more in the top or bottom part of the screen. In the third block, participants had to alternate between blocks of dots and triangles. The local-global task was also used requiring participants to respond to randomly presented rectangles or squares by pressing a left or right response button respectively. Larger (global) rectangles/squares consist of smaller (local) rectangles/squares. In blocks one and two, participants respond only to the local or global elements. In the third block, the participants had to switch between local/global responses. Switch costs were calculated as the time taken to complete block three, minus the average times of blocks one and two for both tasks. Male ecstasy users showed greater temporal switch costs, but were actually more accurate than male nonusers on the dots triangles task. Male ecstasy users were slower than nonusers in the local/global task, but did not differ in their accuracy.

Fox et al. (2001) used a computerised version of the Wisconsin Card Sorting Task (WCST) in which participants must earn a rule in order to establish which one of three dimensions a pack of 128 cards are being sorted under (i.e. colour, shape and number). Once 10 consecutive cards were placed successfully into the correct pile, the rule was changed. Six trials were implemented whereby relevant dimensions were changed from colour to shape to number and then repeated. The task was terminated if a trial was not complete within 50 attempts. Participants were scored for number of trials taken to complete the first category, percentage number of perseverative and non-perseverative errors and failure to maintain set. There were no significant

differences between dosage groups (control, low, medium, high) or problem versus non-problem users. Thomasius et al. (2003) also used the WCST task in a sample of 30 current ecstasy users, 31 former ecstasy users, 29 polydrug controls with illegal drug use similar to that of the ecstasy users (with the exception of ecstasy), and 30 drug-naïve controls. Only the measure of perseverative errors (i.e. giving the same incorrect response twice) was significant, with polydrug controls scoring significantly higher than either ecstasy group. Although failing to find an overall ecstasy-related effect, Alting von Geusau et al. (2004) found that when the groups were split by gender, 17 male ecstasy users performed less well on the WCST (by making more perseverative errors, making more errors on ambiguous trials, and having an impaired conceptual level response) than 12 male non-ecstasy users. Female users were not significantly impaired on this task (possibly because of the smaller lifetime dose). Halpern et al. (2004) also reported that a group of 23 ecstasy users did not perform significantly worse on the WCST than a group of 16 light drug-using controls. When the ecstasy group was further divided into moderate (fewer than 50 occasions of use) and heavy (more than 50 occasions of use) users, the heavy users performed less well on the "categories" score of the WCST. As both samples were infrequent users of other drugs, it is suggested that this relates to some parameter of ecstasy use. Back-Madruga et al. (2004) also failed to find ecstasy related differences in a sample of 22 ecstasy users compared to 28 nonuser controls (no differences in perseverative responses, which are believed to be an index of switching ability). Two research groups also used tasks similar to the WCST to assess mental set shifting. Dafters et al. (1999) used the Behavioural Assessment of Dysexecutive Syndrome (BADS) Card Sort Task also involving a sudden change in the rules of card sorting. Twenty-three ecstasy users were split into 12 low users (less than 20 tablets across their lifetime)

and 11 high users (20+ tablets across their lifetime). Although no control group was incorporated in this study, correlations indicated that extent of ecstasy use was associated with a decrease in performance on the BADS card sort task. In a further study Dafters et al. (2004) found no significant ecstasy-related differences on this task when comparing non-ecstasy users (18), cannabis users (n=15; lifetime cannabis dose of 1023 joints), cannabis and light ecstasy users (n=19; lifetime cannabis dose of 1252 joints) and cannabis and heavy ecstasy users (n=16; lifetime cannabis dose of 1680 joints). Another study (Zakzanis and Young 2001b) also failed to find any ecstasy related differences on this task in 24 ecstasy users compared to 24 controls. Finally, Verkes et al. (2001) used the classification task, a derivative of the WCST where participants have to identify the sorting criteria for four stimuli cards through a trial error process through feedback with a computer. Heavy users and moderate users did not differ from nonuser controls on this task.

Six of the reviewed studies have found a difference between the groups in switching. Two of these studies found that either ecstasy related deficits were more related to use of hallucinogens (Morgan et al. 2002) or that polydrug users performed worse than the ecstasy user group (Thomasius et al. 2003). Another study found that ecstasy users only performed worse relative to controls on days 2 and 3 of a controlled study, although performance between the groups on days 4 and 5 was not reported (McCann et al. 1999). One study found ecstasy-related effects in male ecstasy users only on two tasks of switching, and male ecstasy users also gave more perseverative responses on the WCST (Alting von Geusau et al. 2004). To further support a deficit in task switching, Dafters et al. (1999) found that decreases in scores over a year of ecstasy self-administration were related to extent of ecstasy use. It is surprising that the studies which have found the deficits to be related to ecstasy

(Alting von Geusau et al. 2004; Dafters et al. 1999; McCann et al. 1999) have much smaller total lifetime doses than those studies not reporting ecstasy related deficits. So it appears that any observed ecstasy-related deficits in task switching may not be related to dosage. Moreover, the paradoxical evidence of the presence of deficits in light users, but not heavy users, casts doubt on the robustness of the positive findings. Nevertheless, as one aim of this thesis is to assess the impact of ecstasy (and polydrug) use on executive functions, measures of task switching will form one chapter combined with measures of response inhibition (see section 3.3.4).

3.3.2 Word Fluency

Word fluency recruits executive resources to access semantic memory and retrieve task-relevant information; thus the more correct words an individual can retrieve from a particular category, the more efficient the central executive is at this task (Ruff, Light, Parker & Levin, 1997). The most commonly used tasks in ecstasy users involve participants being given one minute to recall as many words as possible beginning with a certain letter (usually F, A, S), or from a particular category (e.g. animals). This appears to be one task in which between groups effects are apparent in half of the studies (although most studies have used the same task so it may be something in the nature of the task).

Using an unspecified word fluency task Klugman, Hardy, Baldeweg and Gruzelier (1999) compared 36 ecstasy users with 19 controls. Ecstasy users did not perform worse than controls. Also using an unspecified task, Wareing et al. (2000) found that current ecstasy users, former users and nonusers performed similarly. Using the Controlled Oral Word Association (COWA) task where participants have to generate as many words as possible beginning with the letter "F", "A" or "S" in 60

seconds, Semple et al. (1999) found that there were no significant differences in the performance of 10 regular ecstasy users and 10 polydrug controls. Fox et al. (2002) also used the COWA task with letter and semantic categories. In the letter category, participants had to generate as many words as possible beginning with a specified letter (F, A, S) in one minute. In the semantic category, participants were asked to produce as many different members of a semantic category (animals) as possible in one minute. Mean word generation was calculated for both conditions, and in the letter category, participants were also given scores for semantically linked words and phonemically linked words (e.g. flash, flake). Twenty ecstasy users were compared with 20 controls, matched for age (27.3:27.5 years), and intelligence (estimated PMI 100.3:103). Ecstasy users generated significantly fewer words than the polydrug control in the letter condition, but not the semantic condition. In the letter category, regression analysis revealed that effective use of phonemic strategy accounted for the majority of the variance, while semantic strategy approached significance. Heffernan, Jarvis, Rodgers, Scholey et al. (2001a) used a similar task in which participants had one minute for each of 3 categories: verbal fluency (words beginning with "C"), semantic fluency (animals) and a combined verbal/semantic category (household items beginning with "T"). The 30 ecstasy users performed significantly worse than the 37 non-ecstasy users on all three tasks. The results remained significant after control for alcohol, cannabis and tobacco. The age range for both groups was atypically high for samples in this area (upper limit 40 for ecstasy users and 50 for nonusers), so it is possible (although perhaps unlikely) that the results reflect some aspect of ecstasy use combined with cognitive ageing.

Bhattachary and Powell (2001) used the COWA test comparing 20 nonusers, 18 novice users, 26 regular users, and 16 currently abstinent users. Nonusers

performed significantly better than regular users and currently abstinent users on a total score for the 3 categories (F, A, S), although novice users did not differ from controls, and regular and currently abstinent users did not differ from each other. In the ecstasy user group (novice, regular, abstinent) there was a strong correlation with lifetime consumption of ecstasy, but not recency of use, which was replicated when the abstinent users were excluded (correlations with cannabis used in the last 30 days were also non-significant). In addition, word fluency scores of those reporting 31-50 doses of ecstasy scored significantly lower than those reporting 1-30 doses (although differences between the 31-50 and 51+ groups were non-significant). Hanson and Luciana (2004) reported that 26 ecstasy users made more errors on the COWA task than 26 non drug-user controls, although they generated just as many words. When the ecstasy group was split into those diagnosed with a substance abuse disorder (N=14; lifetime consumption 95.4 tablets) and those without (N=12; lifetime consumption 29.3 tablets), those diagnosed with a disorder had a lower total word score than those without (although error scores, inappropriate words and perseverations were non-significant). The relationship between substance use and word fluency is unclear from the paper. Croft et al. (2001a) used the COWA and an "animal" category fluency test in a sample of 11 ecstasy/cannabis users (mean lifetime cannabis consumption of 10964 joints), 18 cannabis only users (mean lifetime cannabis consumption of 7762.4 joints), and 31 drug-naïve controls. There were no significant differences between the ecstasy/cannabis and cannabis only groups. A combined drug-using group (ecstasy/cannabis and cannabis only) performed significantly worse than controls on the "animals" category, although test scores were correlated with frequency of cannabis use rather than frequency of ecstasy use, or total ecstasy use. Croft and co-workers concluded that the observed deficits in word

fluency were more related to cannabis than ecstasy. In another study Morgan et al. (2002) used the COWA test, and a category fluency task in which participants were given 90 seconds to name as many fruits as they could, then a further 90 seconds to name as many vegetables as they could. Eighteen current heavy recreational ecstasy users, who had used ecstasy on 20+ occasions and also used other drugs, 15 heavy ecstasy users who had been abstinent for at least 6 months but still used other drugs, 16 poly-drug users and 15 drug-naïve controls were recruited. No significant differences were observed between the groups, although there was a trend towards significance in the category fluency task, as ecstasy users tended to generate significantly fewer items for both categories. Back-Madruga et al. (2004) also used the COWA task, and found that 22 ecstasy users did not perform worse than 28 nonusers on a total score for the "FAS" categories, and no indices of ecstasy use were correlated with task performance.

Using a variation of the COWA task in which the three categories were letter, semantic and alternating criteria (phonological/phonological, semantic/semantic, phonological/semantic), Gouzoulis-Mayfrank et al. (2000) found no significant differences between 28 ecstasy users, cannabis users (matched for cannabis use with the ecstasy users) and nonuser controls in terms of number of words produced. Likewise, Halpern et al. (2004) found that ecstasy users did not differ from controls on this task, and there were no significant differences between dosage groups (moderate= fewer than 50 occasions, high= more than 50 occasions). Curran and Verheyden (2003) also failed to detect differences on category (letters "H" and "L" for 90 seconds) and semantic (fruit/vegetables for 90 seconds) fluency tasks between 32 current ecstasy users, 32 former users and 32 nonuser controls. In a clinical controlled study, Lamers, Ramaekers, Muntjewerff, Sikkema et al. (2003)

administered either 75 mg of MDMA or 0.5 g/kg of pure ethanol to 12 recreational ecstasy users (mean use 9 times a year; total average use 39 times). The word fluency task required participants to name as many four-letter words as possible beginning with a particular letter (B, H, R, L, P, or M) within one minute. Order of the six versions was balanced over test days, and number of correctly produced words was recorded. No significant differences were observed between baseline and treatment, although no control group was included, so it is possible that as the sample were already recreational ecstasy users, they were impaired at the start of testing.

Four of the studies that assessed word fluency in ecstasy users found an ecstasy-related effect, with a further one study finding a trend towards an ecstasy-related effect (Morgan et al. 2002). Another study found that performance on a category fluency task (animals) was more related to cannabis use than ecstasy use (Croft et al. 2001a). Of those studies finding an ecstasy-related effect, one found that this was due to the ineffective use of a phonemic strategy by ecstasy users (Fox et al. 2002), while another study found that ecstasy users generated similar numbers of words to nonusers, but gave more incorrect words (Hanson & Luciana 2004). Only one study related performance on the word fluency task to lifetime dose of ecstasy use: in Bhattachary & Powell's (2001) study regular and currently abstinent users were worse than controls and novice users, with lifetime consumption of ecstasy use being strongly correlated with performance. In the other studies which did find ecstasy related effects, lifetime dose of ecstasy was not atypically high, so this is in need of further clarification.

Most studies reviewed have used short versions of a word fluency task. It may be that in a task that only requires the generation of words for a minute, ecstasy users perform comparatively with nonusers as this is a relatively short amount of time.

Access to semantic memory has recently been elucidated as a separable executive function (Fisk & Sharp 2004; see also Chapter 2 on the structure of working memory). Chapter 8 of this thesis will therefore assess word fluency performance in ecstasy users using a longer version of a word fluency task, to give a complete assessment of the nature of executive function deficits. The Chicago Word Fluency Test also imposes constraints on words like Heffernan et al. (2001a) who found ecstasy-related deficits. On another supposedly harder version, Gouzoulis-Mayfrank et al. required ppts to switch between phonological and semantic aspects without obtaining ecstasy-related deficits, so it is unclear whether ecstasy-related deficits will be observed on this task. The CWFT is also very useful at discriminating between brain damaged and non-brain damaged individuals (Cohen and Stanczak, 2000) and may thus provide further support for the supposition that ecstasy damages the brain.

3.3.3 Reasoning/Decision Making

Reasoning is an area that is under investigated in users of ecstasy. This section incorporates studies that have looked at planning ability (usually time taken to plan a specific action), logical reasoning, and analogical reasoning.

A number of studies have investigated decision-making and planning in ecstasy users using the Tower of London (TOL) task. The task requires participants to move three different coloured balls across three different sized pegs in order to duplicate the goal configuration. The smallest peg can only hold one ball, the middle sized can hold two, and the largest peg can hold three. Only the highest ball on a peg can be moved, only one ball at a time, and a larger ball cannot be placed on a smaller one. The number of trials to be completed varies from two upwards. Trials are scored for planning and solution times. Fox et al. (2001) compared TOL performance

between polydrug controls and ecstasy users over 12 trials (two 2-move trials, two 3-move trials, four 4-move trials, and four 5-move trials). The ecstasy users who reported cognitive problems (average lifetime dose of 372.3) had significantly longer planning times than the non-problem users (average lifetime dose 356.9 tablets) and controls. Of the three dosage groups (low, medium, high), the high users also exhibited significantly longer planning times than the low and medium users. The groups did not differ in solution times, number of errors or number of trials completed. Schifano, Di Furia, Forza, Minicuci et al. (1998) compared the performance of 10 ecstasy users presenting for treatment at a clinic with 20 healthy controls. Ecstasy users performed significantly worse than controls on the TOL task (specific dimensions not specified), but as the sample is relatively small, and the users were presenting for treatment, it is possible that the results reflect some non-ecstasy related psychological deficit. Alting von Geusau et al. (2004) found that 17 male ecstasy users performed significantly worse than 12 non-ecstasy using men on two dimensions of the TOL (number of extra moves and hence total number of moves), but needed significantly less planning time, and completed the task is less time overall (although this was non significant). Female users were not significantly impaired on this task compared to female nonusers.

Again using the TOL, Morgan (1998) compared 16 ecstasy users, 12 polydrug users, and 16 non-drug users. There were no group differences in number of excess moves, initial thinking time, proportion of perfect solutions or thinking time per move, meaning that all three groups performed similarly. In the second study of this paper, Morgan (1998) reported that ecstasy users, polydrug users (using tobacco, cannabis, cocaine, amphetamine, alcohol and "mushrooms"), and controls performed similarly on the TOL task; there was a trend towards longer initial thinking times for

the nonuser controls on the first trial (although not statistically significant), but no differences in the number of excess moves, proportion of perfect solutions, or thinking time per move for the 1st or 2nd administrations. After analysing the pooled data for studies 1 and 2, there were no group differences in TOL performance. Lamers et al. (2003) also used the TOL task in a sample of 12 recreational ecstasy users. All participants were tested on 3 occasions at least 2 weeks apart. On each occasion, they were administered either 75mg MDMA, 0.5g/kg of pure ethanol, or placebo (participants were unaware of which condition they were in). There were no significant effects of MDMA on reaction time or number of errors made, although the alcohol condition did produce fewer errors than the placebo group. Fox et al. (2002) used a slight variation of this task in which participants were shown two arrangements of balls hanging in stockings, one at the top of the screen, and one at the bottom. They were asked to touch a numbered box at the bottom of the screen (numbered 1-6) which corresponded to the minimum number of moves it would take to match the bottom arrangement to the top arrangement, without actually moving the balls. Each participant was given 24 trials comprising of four of each kind of trial (1-move through to 6-move). Trials were collapsed into 2 categories: easy (1-3 moves) and difficult (4-6 moves). Percentage correct, mean number of attempts taken to completion of trial, and mean latency to first response were recorded. The performance of twenty ecstasy users and 20 non-ecstasy user controls was compared. No between group differences were observed on the three test measures (percentage correct, mean attempts to completion, mean latency to first response), and although there was a within groups effect of difficulty of trial, there was no interaction between difficulty and group.

In the same sample, Fox et al. (2002) also assessed decision-making. An array of ten red and blue boxes was displayed at the top of the screen, and participants were informed that a yellow counter was hidden inside one of the boxes. The task was to decide whether it was more likely for the counter to be found in a red or blue box; ratios of red and blue boxes were changed from trial to trial. Participants started with 100 points, and if incorrect, points were deducted, but added if their bet was correct. Participants had to select the appropriate response from a selection at the side of the screen. Mean percentage of total points bet, mean deliberation time, and mean probability of choosing the correct outcome were recorded. Both groups bet fewer points in the higher risk condition, although there was no group by ratio interaction. No significant group differences were observed regarding probability of choosing the most likely outcome, or deliberation time.

Moving on to logical reasoning, Gouzoulis-Mayfrank et al. (2000) compared 28 ecstasy users, 28 cannabis users (matched with the ecstasy group for cannabis use) and 28 non drug-users. Participants were assessed on the LPS-4 abstract logical thinking task (a problem solving task in which subjects have to find out the rule in a series of digits and letters and indicate the "wrong" element which is violating the rule) and the Mosaic test from the WAIS-R (which is a fluid intelligence test that also assesses visuomotor performance, planning and problem solving. Participants are required to reproduce complex visual patterns with cubes). Post-hoc analysis revealed that ecstasy users performed worse than both cannabis users and nonusers on these tasks. In Gouzoulis-Mayfrank et al.'s (2003) study, 60 ecstasy users and 30 nonuser controls (reporting only moderate cannabis use) were recruited. The ecstasy users were split into 2 groups, heavy users and moderate users. The Plan-a Day (PAD) task was used to assess planning ability; it requires participants to plan a working day and

try to solve as many tasks as possible within a given time period. In order to achieve this, they have to "go" to different locations, and consider the distances between locations, and prioritise their goals. A demanding version, with a large number of tasks was used. There were no performance differences on any of PAD measures (peak score, end score, single deletions of actions, sequences of deletions) or on the test overall. McCann et al. (1999) measured logical reasoning in 22 ecstasy users compared to 23 non-ecstasy user controls over a 5 day study. The logical reasoning task, taken from the WRAIR-PAB is a self-paced task of semantic recognition and transformational grammar. The letter pair "AB" or "BA" is presented with an active, passive, positive or negative statement, that correctly or incorrectly describes the order of the letters within the pair (e.g. "A is not preceded by B"). The participant was required to press a key indicating whether the statement was correct or incorrect. There was a main effect of ecstasy use on logical reasoning, although no group by time taken interactions were observed, and indices of ecstasy use were not significant predictors of performance in the regression equation. In addition, performance was not significantly correlated with decreased metabolite levels in CSF.

In a study of polydrug users, Verdejo-Garcia et al. (2005) used the "similarities" scale of the WAIS-R to assess analogical reasoning, which requires participants to state a word that is similar to a given word[2]. Although the difference between ecstasy users and nonusers was not directly assessed, in the regression equation the use of ecstasy among the polydrug users was a significant predictor of performance on the similarities task. Halpern et al. (2004) tested 23 ecstasy users and 16 nonusers using the Revised Strategy Application Task (R-SAT), an unstructured pencil and paper task requiring participants to work towards an overall goal of

[2] The authors state that this is a test of analogical reasoning; It is possible that the test is a vocabulary measure.

achieving points by identifying targets with high payoff among readily available lesser-value targets. To maximise efficiency, participants must gradually shift strategy as the test progresses (i.e. become more selective in which items they choose to complete), thus inhibiting the response pattern reinforced at the beginning of the test. Ecstasy users did not perform significantly worse than nonusers, but when the ecstasy user group was split into moderate vs. heavy users, heavy users completed significantly fewer total items (counting both high and low payoff items) in the 10-minute period allowed, suggesting that they were less successful at developing efficient strategies for quickly identifying high payoff items. Zakzanis and Young (2001b) assessed 24 ecstasy users and 24 nonusers on The Action Program Task (involving novel problem solving where participants have to devise a plan of action in order to solve the problem at hand. Number of steps completed on their own was recorded), The Key Search Task (designed to examine a participants ability to plan an effective and efficient course of action), The Zoo Map Test (participants have to plan in advance how they would visit a series of designated locations on a map of a zoo, without breaking a number of rules; correct locations, and number of rules broken were scored), and the Revised Six Elements Task (requiring participants to organise themselves according to certain rules and restrictions in order to complete at least some of the 6 subtasks at hand. Participants were scored on the number of tasks attempted, the number of rules broken, and time taken on any one subtask). Significant group differences were only observed on the overall score for the six elements task, and as no break down is given for the 3 separate scores on this task, it is difficult to ascertain the contribution of logical thinking to the decrement in overall performance.

Finally, in a clinical study, 21 MDMA experienced participants (aged between 20 and 58) were allowed to self-administer doses of MDMA ranging from 0.8mg/lb to 1.9mg/lb (mean of 1.14 mg/lb) and were then tested on a decision-making gambling task. Although no statistical analyses were performed, baseline and post-drug scores were compared with on-drug scores, and it was reported than 4/10 participants gave idiosyncratic responses during the task, which implies impaired judgement while on-drug. These effects were not however observed post-drug (Downing, 1986).

It appears that one of the studies assessing planning ability using the TOL found that ecstasy users exhibited slower planning times than nonusers (Fox et al. 2001), finding both a dose related effect (heavy users slower than moderate and nonusers) and that problem users were slower than those not reporting problems. One study also reported that ecstasy users performed worse on the overall measure of TOL performance (Schifano et al. 1999). However, one study found that although male ecstasy users made more moves, they actually required less planning time (Alting von Geusau et al. 2004). Logical reasoning and analogical reasoning seem to be susceptible to the effects of ecstasy, with three out of six studies finding that ecstasy users were impaired on tasks that assess this. One of these also found that ecstasy users performed worse than cannabis users and controls (Gouzoulis-Mayfrank et al. 2000). Most studies report using tests that rely more on planning abilities (recorded in times), and it would be interesting to see if ecstasy users exhibit deficits "pure" reasoning tasks, which rely solely on one's reasoning ability. As syllogistic reasoning has been described as the basis for rational thought and impairments in this may be quite detrimental to the lives of users of ecstasy, Chapter 9 will focus on assessing syllogistic reasoning performance. It is also possible that performance on reasoning tasks may be related to deficits in executive functioning. Thus one aim of this thesis is

to ascertain the contribution that executive deficits may have on performance in reasoning tasks.

3.3.4 Response Inhibition

Inhibition is an executive process that refers to an individual's ability to inhibit automatic responses when they are no longer appropriate. A classic test used to assess inhibition is the Stroop test. In the test, colour words (e.g. blue, red) are printed in the ink of another colour, and participants are required to report the colour of the ink rather than the word. Thus they have to inhibit the normal response of reading the word. Gouzoulis-Mayfrank et al. (2000) used this task, and found no significant differences between ecstasy users, cannabis users and nonusers on the interference factor (it is not stated how this was calculated). In Morgan et al.'s (2002) study, the Stroop task was used, and dependent measures were the time taken to complete the task (longer time indicating impaired response inhibition), and number of errors made. Again, no statistically significant differences were observed between ex-ecstasy users, current users, polydrug users and nonusers. Back-Madruga et al. (2004) also found that ecstasy users and nonusers did not perform significantly different on this test, although ecstasy users did take slightly longer to complete the task (114 seconds to 110.6 seconds). Again, Semple et al. (1999) failed to detect a significant difference between ecstasy users and polydrug users (N=10 in each group- which is perhaps too small for adequate statistical power) using the Stroop task. In a clinical within-participants study, Vollenweider et al. (1998) tested 13 MDMA naïve participants on the Stroop task, at two different sessions: 1 placebo, and 1 receiving 1.7 mg/kg of MDMA. Participants completed both the congruent (colour words printed in correct colour) and incongruent (colour words printed in different colour),

and dependent measures were "facilitation" (percentage of time reduction in congruent condition compared to control condition), "interference" (percentage of increase in time in incongruent condition compared with control word condition), time taken, and errors. In all cases, the main effect of MDMA was non-significant, and the MDMA by condition interaction was non-significant, suggesting that a single dose of recreational ecstasy does not affect response inhibition while on-drug.

Alting von Geusau et al. (2004) used the Eriksen Flankers task and Stop Signal task to measure response inhibition. In the arrow version of the Eriksen Flankers task, participants are required to respond to a left vs. right pointing arrow in the centre of the screen by pressing a left or right response key. The central arrow is flanked by four arrows pointing in the same direction (congruent condition). Occasionally and unpredictably, the flanking arrows point in the opposite direction (incongruent condition), thereby activating the competing response. A rectangle appears on the screen, and the stimulus appears in the rectangle 500ms later. There were 50 practise trials and 100 experimental trials. In the Stop Signal task, participants have to respond as fast as possible to a left vs. right pointing arrow, by pressing a button on the right or left. On 25% of the trials, the colour of the arrow changes randomly from green to red indicating that the response should be inhibited. The time interval between arrow presentation and arrow colour change ranges from 200 to 1250 ms: the longer it takes the arrow to change colour, the more difficult it is to inhibit the pre-potent response. There were 50 practise trials and two blocks of 100 experimental trials. On the Eriksen Flankers task, although there was a within groups effect of interference on reaction time, there was no between groups difference; with reference to accuracy, male ecstasy users did not perform worse than male controls, but there was a main effect of ecstasy use in the female group, and the group by

interference interaction was significant for females, indicating that female ecstasy users performed worse on the incongruent condition. There were no group differences in either reaction time on the stop signal task, either in males or females.

Using the Random Letter Generation task, Wareing et al. (2000) assessed response inhibition in current, previous and non-ecstasy users. In the version used, participants are required to generate random sequences of consonants only, and are asked to avoid repeating the same letter sequence, avoid alphabetical sequences, and try and speak each letter with the same overall frequency. Three sets of letters were generated, one at a rate of 1 letter every 4-seconds, one every 2-seconds and one every 1-second. Redundancy (the extent to which each letter is said with the same overall frequency), number of letters produced, and number of vowel intrusions were recorded. Both ecstasy user groups were impaired relative to controls on the task (mainly due to more vowel intrusions at all 3 rates, and also a higher degree of redundancy, and fewer letters at the 1-s rate), and the deficit remained significant after control for the use of other drugs. This suggests that the effects of ecstasy persist for at least 6 months after abstinence. However, the estimated average lifetime dose of ecstasy was atypically high (about 1000 tablets) and the sample sizes are relatively small. In a subsequent follow up study, where participants were allowed to generate consonants and vowels (not the consonants only version used in the first study), the results were not replicated (although the average lifetime dose was also somewhat smaller at 583 tablets- Wareing, Fisk and Murphy 2002). More recently, Fisk et al. (2004) also found that ecstasy users were unimpaired on the random letter generation task. There was no overall group effect and interactions between task difficulty and user group were non-significant.

None of the published studies that used the Stroop inhibition task found that ecstasy users were impaired to compared to nonusers. One study using the random letter generation task (Wareing et al. 2000) found that ecstasy users performed worse than nonusers, however this result has not been replicated by two subsequent follow up studies from the same laboratory (Fisk et al. 2004; Wareing, Fisk, Murphy and Montgomery 2003), and should be treated with caution, especially as the lifetime dose of ecstasy users in the original paper may be atypically high. In only one paper using a novel test of inhibition, female users performed worse than female nonusers (Alting von Geusau et al. 2004). Consequently it appears that recreational use of ecstasy does not appear to impair response inhibition. Nonetheless, one aim of this thesis is to provide a complete assessment of executive functions in ecstasy users, and as mentioned earlier one chapter will focus on deficits in task switching and response inhibition.

3.3.5 Working Memory and Updating

Updating the contents of working memory refers to an individual's ability to monitor incoming information and update the contents of working memory, deleting material that is no longer relevant. The updating executive component process also appears to be affected by ecstasy use.

One popular task which uses the updating component of working memory is the backward digit span task. In this task participants are required to repeat sequences of digits presented orally by the experimenter, backwards. The length of the sequences increases with the participants' success, and points are gained for each sequence repeated in the correct order. Results on this task suggest that ecstasy users are unimpaired. Gouzoulis-Mayfrank et al. (2003) found no differences between

heavy ecstasy user, moderate users and nonusers on this task. Thomasius et al. (2003) also failed to detect a difference between current ecstasy users, former users, polydrug users and controls. It is also noteworthy that the male current ecstasy users had a mean maximum exposure per session of 12 tablets, and the male former users of 9 tablets. It has been suggested that a single neurotoxic dose of ecstasy is all that is required for serotonergic neurotoxicity, which in turn would supposedly manifest itself in cognitive deficits. Assuming that self-reports of ecstasy use in this study are accurate, it is especially surprising that no between group differences were observed, and also that indices of ecstasy use were not significant predictors of performance. Similarly, McCardle et al. (2004) failed to find ecstasy-related differences on this task. Likewise, Bhattachary and Powell (2001) found no differences between nonusers, novice users, regular users and currently abstaining users on this task, neither did recency of ecstasy use, lifetime ecstasy consumption, or cannabis use in the last 30 days correlate with performance on the task. By way of contrast, Gouzoulis-Mayfrank et al. (2000) found that ecstasy users performed worse on the backward digit span task (with a score of 7 compared to 9 for nonusers), but differences between cannabis users and ecstasy users, and cannabis users and nonusers were non-significant. Finally, Croft et al. (2001a) found that while a combined ecstasy/cannabis group did not perform significantly worse than cannabis only users and controls on the task, a combined drug user group (incorporating ecstasy/cannabis and cannabis only users) did perform worse than non-drug users. This suggests the possible mediating effects of other drugs on memory, and highlights the possibility that cognitive deficits in ecstasy users may be in part related to cannabis use.

The Subtracting Serial Sevens (SSS) task has also been used to tap working memory updating in ecstasy users. The task requires participants to subtract 7 from a given 3-digit number and then continue to count backwards in 7s. The number of correct subtractions and errors made in 90-seconds are usually the dependent measures. Curran and Verheyden (2003) found that prior to a tryptophan drink, previous ecstasy users carried out fewer correct subtractions (22.8) than current users (28.5), or controls (27.7). After controlling for pre-tryptophan supplementation scores, there were no significant group or treatment effects on post supplementation scores. Frequency of ecstasy use was also correlated with baseline scores on the task. A previous study from the same laboratory (Curran & Travill 1997) also found that ecstasy users carried out significantly fewer subtractions than nonusers on days 1, 2, and 5 after ecstasy use, although there as no difference in terms of errors committed. In a study comparing former and current ecstasy users with polydrug users and nonusers (Morgan et al. 2002), it was found that while there was no ecstasy-related deficits in terms of number of correct subtractions made in 90s (number not reported), both groups of ecstasy users produced significantly more errors than controls and polydrug users (again numbers not reported).

Wareing et al. (2004b) used the computation and reading span tasks which both contain a serial recall component and the simultaneous processing of information (the former numerical, the latter verbal). Both current and former users of ecstasy performed worse on the computation span task. This remained significant after control for the use of other drugs. This was replicated by Fisk et al. (2004), where ecstasy users again performed worse than controls on the computation span task (which also remained significant after control for indices of other drug use). A similar task was used by Dafters et al. (1999), which required the recall of words following distraction

with a mathematical problem, in which participants were presented with a series of cards that contained either a word or a mathematical problem to solve. Recall of the words was tested at appropriate points throughout the task. As this was a correlational study (which did not incorporate a control group), statistical analysis for between group differences was not performed, although correlations between ecstasy use and performance on this task were non significant.

The final task in this section which is used to tap working memory updating is the "N-back" task. This task consists of the sequential visual presentation of single digits or simple figures. Participants have to press a button when the presented digit or figure is the same as the one presented a specified number of trials earlier. Gouzoulis-Mayfrank et al. (2003) used the 2-back version (i.e. having to remember the stimulus that was presented 2 trials earlier). No significant differences were observed between the heavy users, moderate users and controls either for errors or correct responses for figures or digits. In Daumann et al.'s (2003) study, participants performed three N-back tests, consisting of the visual presentation of single letters (B, C, D, G, P, T, F, N, L), and had to press a button when the target stimulus appeared. For the 0-back condition, participants responded when a stimulus within a sequence matched a target stimulus specified at the beginning of the trial (specified letter was "D"). In the 1-back condition, targets were defined as stimuli within the sequence that were identical to the immediately preceding one, and in the 2-back, if the target was identical to one that was presented two trials before. Thus the 2-back is the hardest of the three, placing the most demand on updating resources. Although there was a within-participants effect of memory load, pure ecstasy users (using solely ecstasy), polyvalent ecstasy users (also using amphetamine/cannabis), and controls did not differ significantly in terms of reaction times or errors. Pure ecstasy users did however

present lower levels of activation during the 1-back task in the inferior temporal and angular region. Again in the 2-back condition, pure ecstasy users showed lower activations, mainly in the angular gyrus compared to polyvalent users and controls. Jacobsen et al. (2004) used this task, and although they did not perform statistical analysis for between group differences, ecstasy users did fail to activate certain brain areas relative to nonusers on the 1- and 2-back conditions.

In attempting to separate the effects of ecstasy on various executive functions, Alting von Geusau et al. (2004) used the Tic-Tac-Toe and mental counters tasks. In the Tic-Tac-Toe task, participants are required to keep visual information active in working memory about the orientation of patterns and figures. In a 3x3 grid, Xs and Os are presented briefly during the memorising phase. In the recognition phase, Xs and Os are presented one after another in the grid. The task is to press a button as soon as soon as the pattern of Xs and Os matches the pre-specified pattern. Memory load is varied using patterns consisting of three or four stimuli. The number of trials per block was 15, and the series length of the stimulus presentation until the pre-specified pattern was reached varied from 4-9 presentations. The mental counters task requires participants to keep numerical information active in working memory, by keeping track of the values of two or three (blocked) independent "counters" which change rapidly and in random order. The counter consists of a horizontal line above or below which squares appear. Participants add one to the value of the counter if above the line, and subtract one if below the line. When any counter reaches a given criteria value, participants have to press a button. Length of the series of stimuli was 5 or 7. On the Tic-Tac-Toe task, there were no significant between groups differences in terms of accuracy, but in male ecstasy users, there was an interaction between working memory load and reaction time (as the male ecstasy users were slower in the

high load condition). Male ecstasy users were also slower than controls on the mental counters task, although females were not impaired. It is noteworthy that these tasks appear to be relatively simple compared to other tasks used to assess memory updating, and may thus not be true indices of performance on this function.

Only two of the six studies using backwards digit span to assess memory updating found group differences, one finding that ecstasy users were worse than controls but not cannabis users (Gouzoulis-Mayfrank et al. 2000), and one finding that a drug-using group (ecstasy/cannabis and cannabis only) performed worse than a non drug-using control group (Croft et al. 2001a). It is therefore possible that deficits on the backwards digit span task may relate to cannabis use more than ecstasy use, or the concomitant use of cannabis and ecstasy. Three studies using the Subtracting Serial Sevens task found that current and former users of ecstasy performed worse than nonusers, one through making more errors on the task (Morgan et al. 2002) and two through fewer correct subtractions in the allotted time (Curran & Travill 1997; Curran & Verheyden 2003). The latter study also found that frequency of ecstasy use was correlated with baseline scores. Using the computation span task two studies have found that ecstasy users performed worse than nonusers (Fisk et al. 2005; Wareing et al. 2004b). Two studies that did not incorporate a control group (Daumann et al. 2003; Jacobsen et al. 2004) found that ecstasy users failed to activate certain brain areas while performing the 1- and 2-back conditions of the n-back task. So it appears that ecstasy users do not consistently show impairments on simple tasks of memory updating (e.g. digit span and SSS). It has been suggested that poor performance on the SSS task (through giving more errors) is related to heightened impulsivity so it is possible that ecstasy users exhibit heightened impulsivity leading to shorter response latencies and so more errors on this task, rather than being unable to perform the

subtractions correctly). Both studies that used a more complex memory updating task (Fisk et al. 2004; Wareing et al. 2004b) found that ecstasy users performed worse than nonusers supporting the view that memory updating is relatively preserved after ecstasy use under less demanding task conditions. The two studies finding that ecstasy users failed to activate certain brain areas during the 1- and 2- back test did not make between group comparisons in performance measures, so this should be treated with caution as another study using the task and comparing heavy users, moderate users and controls found that ecstasy users were did not perform worse (Gouzoulis-Mayfrank et al. 2003).

Chapter 6 of this thesis will seek to investigate ecstasy-related differences in memory updating. The more complex tasks mentioned above that did find between group differences may also rely heavily on arithmetic ability (the SSS through being able to subtract, and the computation span task through being able to add).

Accordingly a purer memory-updating task will be used to assess working memory updating. The task used will be a running memory task in which participants are presented with strings of letters (of varying length), and are required to remember the last six letters of each string (unaware of how long each will be). According to Morris and Jones (1990) and Kusak, Grune, Hagendorf and Metz (2000) updating from the fourth letter onwards is believed to require executive control processes. Consonant updating was chosen to tap this aspect of executive function as it is relatively complex. Whereas the n-back task is only generally used with a maximum memory load of three, the task used in this thesis will require participants to recall six letters from strings of varying length. It is therefore expected that under this higher memory load, ecstasy-related updating deficits may be elucidated.

3.4 Attention

It is possible that while ecstasy users are exhibiting deficits in higher level cognitive processes, this may be due to lower level functions such as poorer attentional skills (i.e. ecstasy users find it harder to concentrate their attention for example on a memory updating task, but are not impaired on the task per se). Most studies in this area have assessed focused and divided attention, although some papers have reported findings on more complex tasks (e.g. Object Movement Estimation under Divided Attention).

Parrott et al. (1998) used a number vigilance task to assess attention. A single target was displayed on the right of the screen and when it matched a pre-specified target (from a changing series), participants were required to press the yes response key. Dependent measures were number of target selections and response time. All three groups (nonusers, novice users, and regular users) had similar reaction times and a similar percentage correct indicating that they were not impaired compared to controls in this task. Gouzoulis-Mayfrank et al. (2000) used a number of subtests from the Test for Attentional Performance (TAP) test battery. Test 1, for tonic and phasic alertness required participants to respond to a simple visual target appearing on a computer screen, preceded or not preceded by a warning acoustic signal (reaction time measured). The selective visual attention subtest required participants to identify two critical pre-specified targets (from five similar complex figures), and react by pressing a computer key (and ignoring non-critical targets). The divided attention subtest is a demanding dual RT task, requiring attention to simultaneously presented visual and acoustic cues. Participants have to respond to the appearance of a square composed of small crosses among other irregular shapes on the screen, and to any irregularity occurring in an alternate sequence of high and low tones. In the

intermodal integration subtest, participants view upward or downward directed arrows on the screen, and simultaneously listen to high or low tones. They have to react by pressing a computer key whenever a match is detected (e.g. simultaneous appearance of a high tone and upward arrow). Finally, the visual scanning task requires participants to scan a 5x5 matrix of similar graphic elements for a target, which is presented before the onset of the trial. In the test of selective visual attention, the ecstasy users had longer reaction times than the nonusers, and cannabis users. In the divided attention and intermodal integration tasks, ecstasy users had significantly longer reaction times than cannabis users. Longer reaction times in the ecstasy users in the divided attention task were also associated with a longer period of ecstasy use. In their 2003 study, Gouzoulis-Mayfrank et al. used the visual scanning sub-test of the TAP and found that there were no group differences between heavy, moderate and non-ecstasy users. To further support this Thomasius et al. (2003) also used the divided attention and selective visual attention subtests of the TAP test battery, but no significant differences were observed between previous ecstasy users, current users, polydrug users, and nonuser controls.

Using the Test of Everyday Attention (TEA) battery Zakzanis et al. (2002) assessed attentional processes in ecstasy users and nonusers. The first subtest is a map search task, requiring participants to circle as many symbols (restaurants, garages, and petrol stations) as they can on a map of Philadelphia, USA. They are given one minute to circle as many symbols as they can in red pen (map search 1), then an additional minute to circle more symbols in blue pen (map search 2). In both cases, total number of symbols correctly circled in the time span is recorded. In the Elevator Counting subtest, participants have to count a series of single tones which each symbolise a floor on the elevator. The floor count obtained at the end of counting is

compared with the correct count. This task is used as a baseline for the elevator counting with distraction task, which is essentially the same, except participants are required to ignore a high pitched distracter tone. The visual elevator task requires participants to count a series of elevator icons and to change direction on the basis of the arrows within each series (either up or down). The floor count, and time taken to complete each series are recorded. The elevator counting with reversal task requires participants to listen to three different tones; the middle tone represents a floor, while high-pitched tones represent upward arrows, and low-pitched tones downwards arrows (thus participants change direction of counting when they hear a high or low tone). The telephone search test requires participants to search through a phone directory and circle services with double symbols (two squares, stars, circles, crosses) by the company name. Total number correctly circled and time taken to complete were recorded. The Telephone search while counting task was the last subtest, and combined elevator counting with the telephone search. Dependent measures were the floor count for each series, the total number correctly circled, and time taken to complete the tasks. Although the only significant ecstasy-related effect was on the map search 2 task, correlations between ecstasy dosage and map search 1, visual elevator 2, and elevator counting with reversal were significant. A significant correlation was also observed between the number of ecstasy tablets used and the telephone search while counting. In the same test battery Dafters et al. (2004) used the visual elevator to assess attentional processes, although in this study differences between heavy ecstasy/cannabis users, light ecstasy/cannabis users, cannabis only and drug-naïve participants were non-significant.

In Curran and Verheyden's (2003) study participants were administered a tryptophan drink, and the digit cancellation task (cross out target digits in a random

sequence of 400 digits) was used to assess focussed attention, and the Rapid Visual Information Processing (RVIP) test was used to assess sustained attention. In the first part (10 minutes) of the RVIP, digits are presented on a computer at a rate of 100 digits/minute, and participants have to press a key when either 3 consecutive odd, or 3 consecutive even digits appear. In the second part (5 minutes), participants performed the task again while listening to high and low tone through headphones, and were required to count the number of low tones. On single digit cancellation, there were no group or treatment effects. On double-digit cancellation, groups did not differ pre treatment, but there was a group by time interaction: current ecstasy users were slower post than pre drink, and previous users were slower than other groups, but took about the same time pre and post drink. On the 10-minute RVIP task, previous users made fewer correct responses than current users or controls pre-drink. After covarying for pre-drink scores, these differences were non-significant post-drink. Ex-users also performed slower than current users and controls. In the 5-minute RVIP, there was a trend for pre-drink differences. After covarying for these, ex-users made fewer correct responses than the other two groups, although errors and reaction times were not significantly different. One possible implication of this study is consequently that discontinuing ecstasy use may adversely affect attentional processes more so than continuing use, as both user groups had similar average doses (although ex-users reported using the drug more frequently. See Table 3.1), and current users had used for a longer period of time overall and had a shorter abstinence period.

Jacobsen et al. (2004) assessed sustained attention using Conners Continuous Performance Test (CPT), and selective and divided attention were assessed using a computerised word recognition task. Auditory selective attention was assessed by comparing an auditory simple attention condition (press one button if verbal stimulus

is a real word and another if not; simultaneously presented with 4 diagonal lines on the screen) with an auditory selective attention condition (same judgement, with visual word or non-word distractors on the screen). Visual selective attention was assessed by comparing a visual simple attention condition (participants viewed a letter string and pressed one button if the stimulus was a real word, and another button if not; with simultaneous presentation of a tone) with a visual selective attention condition (same judgements, but instead of tones auditory word or non-word distracters were played through the headphones) condition. In the divided attention condition, word or non-word stimuli were presented simultaneously in both auditory and visual modalities. A visual cue was then presented to indicate which word/non-word combination was correct, and participants then pressed the corresponding button. So, unlike selective attention, divided attention in this case required participants to fully process both auditory and visual stimuli before making a judgement. There were no significant between group differences in terms of accuracy, although there was an ecstasy-related trend towards less accuracy. Ecstasy users did have significantly longer reaction times across simple, select, and divided attention conditions (this remained significant after removal of those with THC metabolites in their urine). There was also an ecstasy-related trend towards longer reaction times on the CPT. Significant correlations were observed between the number of ecstasy episodes reported and accuracy on the visual simple and divided attention tasks.

Gamma, Buck, Berthold and Vollenweider (2001) also used a computerised CPT in which participants have to click a mouse button with the right index finger whenever they view the target sequence of letters (A followed by X), but ecstasy users did not give more omission (missed targets) or commission (false alarms) errors on this task.

Similar results were obtained by Gamma, Buck, Berthold, Hell and Vollenweider (2000) in a clinical study after administration of 1.7mg/kg of MDMA.

Lamers et al. (2003) used three tasks to assess attentional processes in 12 regular ecstasy users, who were administered either 75mg MDMA, 0.5 g/kg of pure ethanol, or placebo. The Divided Attention Task (DAT) assesses a participant's ability to divide attention between tracking (trying to keep a cursor on a computer screen central using a joystick) and monitoring (participants have to monitor 24 peripheral LED displays fixed to the four sides of the screen; these display the numbers 0-9, and change every 5-s; participants have to remove their foot from a pedal when they detect the target numeral-"2") tasks performed simultaneously. The Object Movement Estimation under Divided Attention (OMEDA) task requires participants to estimate the Time To Contact (TTC) of a moving object to a fixed point (in this case, the time taken for a red dot to travel to the centre of the screen, disappearing under a yellow circle before it gets there), while in the divided attention condition, participants also have to press a key if a geometric shape at the top of the screen, and the centre match. The Signal Detection Task (SDT) was also used, which is a visual search task requiring participants to press a key when a target configuration of squares is achieved on the screen (400 squares are presented altogether, with 56 target configurations). There was a main effect of treatment on tracking performance in the DAT, and separate comparisons showed that MDMA administration actually improved performance by lowering errors, compared to placebo. In the OMEDA task, MDMA elevated TTC error (both over and under estimation), but no treatment effects were observed on the OMEDA divided attention condition. There were no group differences on the SDT task. There thus appears to be an unanticipated ecstasy-related improvement in some aspects of attention (tracking performance) although ecstasy

users were neither impaired nor improved by a dose of ecstasy on the SDT task or the divided attention aspect of the OMEDA (although there was an increased incidence of errors on this task.

Semple et al. (1999) also assessed attention using the Wechsler Memory Scale-Revised (WMS-R) digit span task, but no differences were observed between the groups, and performance was not related to observed reduced serotonin binding in ecstasy users. Hanson and Luciana (2004) assessed attention using a letter cancellation task, and found that 26 ecstasy users made more errors (failing to cancel a letter) than 26 nonusers, although there were no differences in reaction time or commission errors. These participants had a relatively low lifetime dose, and those who were diagnosed with mental health problems performed worse than those without, lending further support to the importance of predisposing factors in drug use research. Using a visual search task requiring participants to pick a target letter ("L") out of a 2x2 or 4x4 array of distractor letters in different orientations, Parrott and Lasky (1998) found that there were few differences in scanning ability between the novice, regular, and non-ecstasy users off-drug, but the regular users were impaired compared to controls while on-drug, as were the novice users (to a lesser extent).

To summarise, of the studies assessing selective visual attention two found that ecstasy users had longer reaction times than nonusers (Gouzoulis-Mayfrank et al. 2000; Jacobsen et al. 2004), with two studies also finding significant correlations between performance and ecstasy dosage (Zakzanis et al. 2002) and ecstasy use and accuracy (Jacobsen et al. 2004). Of the studies assessing divided attention, one found that ecstasy use exhibited longer reaction times than nonusers (Jacobsen et al. 2004), and one found that previous ecstasy users gave fewer correct responses (Curran & Verheyden 2003). Three studies also found correlations between reaction times and

length of ecstasy use (Gouzoulis-Mayfrank et al. 2000), DAT performance and ecstasy dosage (Zakzanis et al. 2002), and accuracy and dosage (Jacobsen et al. 2004). Of the studies assessing simple attention, one found that ecstasy users were slower after tryptophan supplementation (Curran & Verheyden 2003); one found that ecstasy users made more errors than nonusers (Hanson & Luciana 2004); and one found that performance was associated with lifetime dose of ecstasy (Zakzanis et al. 2002). Assessing on-drug performance, one study found that a dose of ecstasy improved tracking performance (Lamers et al. 2003); conversely one study found that ecstasy users made more errors on a visual search task while on-drug (Parrott & Lasky 1998). Clearly there is much evidence for ecstasy-related deficits in attentional processes. Given that executive processes have been viewed from the perspective of an attentional control system (Norman and Shallice, 1986), while this thesis will not directly assess attention per se, a key focus will be on higher level executive functioning. Clearly it is possible that deficits in lower-level attentional processes might result in executive function deficits. A key purpose of this thesis is to establish whether ecstasy-related executive deficits do actually exist.

3.5 Immediate and Delayed Recall

Immediate and delayed recall are areas that most consistently appear to be susceptible to the effects of ecstasy use. Most studies in this area have used word recall tasks such as the Rey Auditory Verbal Learning Test, or prose recall tasks such as the Rivermead Behavioural Memory Test. Twenty out of the twenty-five reviewed studies found a relationship between ecstasy use and performance on recall tasks.

Parrott et al. (1998) used immediate (15 words appear on a screen, then participant has to write down as many as they can remember) and delayed (required to

again recall the words from the original list after a number of other tasks) recall tasks. On both of these tasks, novice and regular ecstasy users performed worse than controls. The immediate word recall task (using 16 words) also revealed ecstasy-related differences in Parrott & Lasky's (1998) study, in which recreational ecstasy users (both novice and regular) recalled fewer words than controls at all testing sessions (at baseline when ecstasy free for 7 days, on-drug, 2-days post-drug, and 4-days post drug).

Gouzoulis-Mayfrank et al. (2000) used a German version of the Rey Auditory Verbal Learning Task (RAVLT) which consists of the presentation 15 words, and a number of learning and recall trials, with trial 1 being the immediate recall condition. Ecstasy users recalled fewer words than nonusers, and furthermore poorer performance was associated with heavier ecstasy use (estimated cumulative lifetime dose). Thomasius et al. (2003) found that ex-ecstasy users recalled fewer words on trial one than drug naive participants (no significant differences between current users and controls or polydrug users), and performance was best predicted by the typical number of exposures to ecstasy. Again using word recall, Reneman, Lavalaye, Schmand, de Wolff et al. (2001a) found that both former and current ecstasy users recalled significantly fewer words than controls on both the immediate and delayed recall RAVLT tests, although extent of ecstasy use was only associated with immediate recall performance, and in addition, recall performance was not related to observed decreases in serotonin transporter density. In a further study from the same laboratory (Reneman, Majoie, Schmand, van den Brink et al. 2001b) ecstasy users (N=8) recalled significantly fewer words than 7 controls on the delayed condition only, and decrements in delayed recall were strongly associated with decreases in N-acetylaspartate creatine (a measure of neuronal function) in the prefrontal cortex. In

another study, monthly dose of ecstasy (not duration of use, number of exposures, or cumulative lifetime dose) was the only significant predictor of impaired immediate verbal memory, and the interaction between vocabulary score and dose on immediate verbal memory approached significance, with those with higher doses and lower vocabulary scores performing worst (Bolla et al. 1998).

Ecstasy users also performed worse at baseline (day 1 of a 5-day inpatient study) on the delayed recall of digit and symbol pairs (McCann et al. 1998). Not all studies however report differences in immediate recall: on trial 1 of the Rey Auditory Verbal Learning Test (participants hear a list of words, and in trial 1 have to recall as many as possible after initial presentation) there were no significant differences in recall between ecstasy users and nonusers (McCardle et al. 2004). Using a similar test, Halpern et al. (2004) found that list learning performance of ecstasy users and polydrug-using controls was not significantly different, and no dosage effects were observed (moderate <50 occasions vs. heavy >50 occasions). A study employing the California Verbal Learning Test (participants are presented orally with "Monday's shopping list" containing 16 items in 4 groups e.g. fruit, herbs, and have to recall as many as possible on successive repetition trials, and after a delay) used sample sizes of limited statistical power (N=10), and although larger doses of ecstasy were associated with decreased overall verbal memory performance, this was reduced to below statistical significance after control for pre-morbid IQ (Semple et al. 1999).

Moving onto prose recall, using a task adapted from the WMS participants were required to listen to a short story, and then recall as much of it as they could remember (immediate condition), and then recall it again after 90 minutes (delayed condition). One point was given for each correct idea (maximum of 40). Neither users reporting problems, nor those not reporting problems were impaired on the prose

recall task, and no dosage effects were observed (control vs. low, medium, and high users) between the groups on either condition (Fox et al. 2001). Using the same test, an early study found that compared to published norms, 5 out of 9 ecstasy users exhibited deficits on the immediate recall condition, with four also exhibiting deficits on the delayed recall condition (Krystal et al. 1992), although performance was not correlated with cumulative lifetime dose of ecstasy. Bhattachary and Powell (2001) also used a prose recall task containing 24 ideas, with immediate (immediately after oral presentation of story) and delayed (after 30 minutes) recall. There was a main effect of group, with non-users showing significantly better memory than novice, regular and abstaining ecstasy users (although regular and abstaining users did not differ). For delayed recall, there was also a main effect of group, with nonusers recalling more than regular and abstinent users (although differences between nonusers and novice users were non-significant). Immediate and delayed recall were both correlated with lifetime consumption of ecstasy (higher consumption predicting lower scores). In the novice and regular users, there was also a positive correlation between recall and days since last ecstasy use (although when the currently abstaining users were included, this was reduced to below statistical significance. Bhattachary and Powell (2001) also controlled for cannabis and IQ in the regression equation, and both came out as non-significant predictors).

Zakzanis and Young (2001a) used the immediate and delayed prose recall subtests of the Rivermead Behavioural Memory Test (RBMT), again requiring participants to listen to a short news story and recall as many ideas as possible (maximum of 21) immediately, then after a delay. The 15 ecstasy-users were tested twice over a period of 12 months, and performance on both the immediate and delayed recall tests had declined. Morgan (1999) also used the immediate and delayed

recall subtests of the RBMT. Ecstasy users recalled significantly fewer ideas than polydrug users and controls in both the immediate and delayed recall conditions. Cannabis consumption was significantly correlated with immediate recall performance in the ecstasy group, and across the ecstasy and polydrug group, although cannabis consumption was not a significant covariate. There were also trends towards significant correlations between immediate recall and average dose of ecstasy and duration of use. Further analysis also revealed that those ecstasy users who had used ecstasy within the last 1-6 months recalled significantly fewer ideas than those who had not used ecstasy for over 6 months. A further study using the same test found that current and ex-ecstasy users performed significantly worse than controls on both the immediate and delayed recall tasks, and ex-users also performed worse than polydrug users (although current users and polydrug users were not significantly different). There were also significant negative correlations between the lifetime consumption of current ecstasy users and immediate and delayed recall performance, and lifetime ecstasy consumption was the only significant predictor of recall in the regression equation (Morgan et al. 2002). In another study, former ecstasy users performed worse than drug-naïve controls on both immediate and delayed recall subtests of the RBMT, although amount of cannabis smoked in the last year was found to be the most significant predictor of performance (Thomasius et al. 2003). Curran and Verheyden (2003) found that only former users of ecstasy were impaired on the delayed recall condition, with current users showing no impairment, although duration of use was associated with lower scores in both groups.

By way of contrast, in Dafters et al's (2004) study, there were no immediate or delayed recall differences between heavy ecstasy/cannabis users, light ecstasy/cannabis users, cannabis only users and controls. When the drug-users were

collapsed into one group, there was a main effect of drug use, with the combined drug user group performing significantly worse than the drug-naïve. The combined drug using group also performed significantly worse than the controls on a free recall task, where participants were presented orally with 30 words, and immediately required to recall them. In a correlational study, performance on the RBMT news story was not significantly correlated with indices of drug use (Dafters et al. 1999). In a sample of ecstasy users reporting for treatment (Schifano et al. 1998), 150 ecstasy users were significantly impaired compared to 20 nonuser controls on the overall RBMT battery measure (separate subtest scores not reported). Ecstasy users were also found to have lower age-corrected percentile scores in a study assessing immediate and delayed prose recall, although no control group was incorporated. Those ecstasy users who also reported substance use disorders (N=14) scored lower on both tests than those not diagnosed with substance use disorders (N=12) (Hanson & Luciana 2004). There was a trend for poorer performance in former, not current users of ecstasy in Curran and Verheyden's (2003) study, and Halpern et al. (2004) noted that 23 ecstasy users performed worse than polydrug controls on a similar prose recall task; when the group was split into 2 dosage groups: <50 occasions, >50 occasions, no such deficits were seen (although once again, small sample sizes may have given limited statistical power). Gouzoulis-Mayfrank et al. (2003) used the "construction of a library" subtest of a German test battery (LGT-3), in which participants are given a text consisting of 10 sentences about the construction of a library (e.g. name of the architect, address etc.), and in the retrieval phase they have to answer a list of 21 questions on these items. There was a main effect of group, and post-hoc analyses revealed that this was due to the heavy users performing worse than the moderate users, but not controls. This was reduced to below statistical significance following control for general

knowledge scores. Frequency of ecstasy use was also significantly associated with immediate recall.

To recapitulate, eight studies found that ecstasy users were impaired in some aspect of word recall with seven (Bolla et al. 1998; Gouzoulis-Mayfrank et al. 2000; McCann et al. 1999; Parrott et al. 1998; Parrott & Lasky 1998; Reneman et al. 2001a; Thomasius et al. 2003) finding deficits in both immediate and delayed recall, and a further one (Reneman et al. 2001b) in delayed word recall only. Of these, three studies found that indices of ecstasy use were related to performance: in one study recall was correlated with estimated lifetime dose of ecstasy (Gouzoulis-Mayfrank et al. 2000); in one performance was predicted by typical number of ecstasy exposures; and in another monthly dose predicted immediate recall score (Bolla et al. 1998). Referring to Prose recall, six studies found that ecstasy users performed worse than nonusers (Bhattachary & Powell, 2001; Halpern et al. 2004; Krystal et al. 1992; Morgan 1999; Morgan et al. 2002; Schifano et al. 1998), with a further two finding deficits in former users only (Curran & Verheyden 2003; Thomasius et al. 2003). One study found deficits on a novel prose recall task to be dose related with heavy users recalling fewer items than moderate users (Gouzoulis-Mayfrank et al. 2003). Finally, one study found that deficits in prose recall were more related to polydrug use than solely to ecstasy use (Dafters et al. 2004). Consequently this seems to be an area of ecstasy research that yields significant results in the majority of studies, and it is therefore likely that the use of ecstasy does impair word and prose recall; thus immediate and delayed recall will not be researched further in this thesis.

3.6 Recognition

Tasks used to assess recognition in ecstasy users used either visual (e.g. face or figure recognition) or verbal (e.g. word recognition) tasks. Tasks took the format of

matching-to-sample requiring participants to recognise a pre-specified target from a number of choices. Recognition tasks in ecstasy users did not generally yield significant differences, perhaps due to the relative simplicity of the tasks.

An auditory recognition task was used by Fox et al. (2001) in which participants were required to recognise 24 pre-specified target words from a list of 40 unrelated words. No significant differences were observed in the number of words recognised with respect to those reporting problems/not reporting problems or dosage. Using a verbal and face recognition task (The Warrington Recognition Task, requiring participants to identify the face/word that was previously presented from a pair of faces/words) Croft et al. (2001a) found that a combined drug using group performed worse (recognised fewer correct items) than a drug-naïve group on the face recognition task only, although there were no group differences between cannabis only users and cannabis/ecstasy users; it was concluded that deficits were more related to cannabis use than ecstasy use. Using a similar task, Klugman et al. (1999) also found that ecstasy users exhibited poorer facial recognition than nonusers. Verkes et al. (2001) used word and figure recognition tasks (requiring the recognition of a previously presented word/figure from 6 items; 24 trials in total), and found that performance was related to dosage and difficulty: serially presented words were recognised less well by heavy users than nonusers, but simultaneously presented words were recognised less well by both heavy and moderate users. In the serial and simultaneous presentation of figures, heavy users recognised fewer items than moderate users, who recognised fewer items than nonusers. Using the delayed figure and face recognition tasks from the RBMT, Zakzanis and Young (2001a) found that over a one-year period, performance remained static. Using the Sternberg task (participants are required to identify a target digit from lists of presented digits),

Parrott et al. (1998) found no dosage effects (comparing nonusers, novice users and regular users). No group differences were observed between ecstasy users and nonusers on a matching to sample task requiring the identification of a target configuration of red and yellow squares on a 6 x 6 matrix, from two possible stimuli (McCann et al. 1999). On a delayed matching to sample task (CANTAB) ecstasy users and nonusers performed similarly, and performance on the task was not related to indices of ecstasy use (Semple et al. 1999). Rodgers (2000) also used the matching to sample subtest of the Wechsler Memory scale, and found no significant differences between ecstasy users, cannabis users and nonusers.

To sum up, one study found that ecstasy users performed worse than nonusers on face recognition (Klugman et al. 1999) and a further one study finding a dose related effect with heavy users exhibiting worse figure and word recognition than nonusers (Verkes et al. 2001). One study also found that word and figure recall was impaired in a combined drug-using group (ecstasy/cannabis and cannabis only) compared to drug-naive controls (Croft et al. 2001a). It appears that recognition of visual and verbal material is relatively preserved after ecstasy use, with only 2 out of the nine studies that assessed it finding a relationship with ecstasy use, and one of these (Verkes et al. 2001) having an especially high estimated lifetime dose compared to the other studies (see Table 3.1). As not many studies assessing recognition in ecstasy users found group differences, this will not be investigated further in this thesis.

3.7 Everyday Memory

A number of laboratory studies have assessed self-reports of cognitive failures and prospective memory in ecstasy users.

3.7.1 Prospective Memory

Prospective memory refers to one's efficiency at remembering to do something in the future (for example keeping an appointment, remembering someone's birthday). Five studies have reported findings of prospective memory deficits in drug users, with different subscales being related to the use of different drugs. Heffernan et al. (2001a) assessed prospective memory in recreational drug users. Ecstasy users reported more prospective memory errors on the subscales of short-term habitual prospective memory (e.g. "I forgot to turn my alarm clock off when I got up this morning"), long-term episodic prospective memory (e.g. "I forgot to pass a message on to someone") and internally cued prospective memory (e.g. "I forgot what I wanted to say in the middle of a sentence") than non-users in study one, although there were no group differences in strategies used to aid remembering. This was replicated for short-term habitual and long-term episodic prospective memory in study two, where ecstasy users also performed worse on an executive function task (word fluency- see earlier). It was concluded that prospective memory and executive function are linked, although the possible link was not investigated. The findings of study one were replicated by Heffernan et al. (2001b), where ecstasy users reported more errors in short-term habitual, long-term episodic, and internally cued prospective memory (although the mean occasions of ecstasy use for this study was at least 10 times per month, which is atypically high). There were no group differences in strategies used to remember. Using the belonging (a possession belonging to the participant is borrowed, hidden, and participants have to ask for it and remember where it is at the end of the testing) and appointment (an alarm is set for 20 minutes, and participants have to ask a particular question when it sounds) subtests of the

RBMT, no ecstasy-related decline was observed after a one-year follow up, during which ecstasy users had been self-administering ecstasy (Zakzanis & Young 2001a).

In a study on the World Wide Web, Rodgers et al. (2001) assessed everyday memory and prospective memory in drug users. It was found that while cannabis use was associated with recent memory deficits in short-term habitual and internally-cued prospective memory, ecstasy use was associated with long-term memory problems, that were more related to storage and retrieval problems. In a second World Wide Web study, Rodgers et al. (2003) found that long-term prospective memory deficits were associated with ecstasy use. Thus it is possible that different recreational drugs affect human memory in distinct ways.

Although the World Wide Web is an effective way of collecting large amounts of data, and Rodgers et al (2001, 2003) have managed to attribute specific deficits in everyday memory to specific drugs, it is possible that individuals visiting drug websites may already believe that they have a memory problem, and thus are not representative of the drug-using population as a whole.

3.7.2 Cognitive Failures

Cognitive failures refer to everyday memory slips, and three studies have collected data on self-reports of cognitive failures in ecstasy users. This is an area that is under investigated in ecstasy users, and research in this area is relatively new.

Although in one study, ecstasy users reported a higher incidence of cognitive slips (e.g. failing to notice signposts on the road) than nonusers (Fox et al, 2001), this was not replicated by Rodgers (2000). Furthermore, Heffernan et al. (2001a) reported no differences on the cognitive failures questionnaire between ecstasy users, cannabis users, and nonusers.

3.7.3 Everyday Memory

Only one study has assessed everyday memory via a separate questionnaire (Rodgers et al. 2003), but increases in self-reported everyday memory slips were more related to cannabis than ecstasy use.

3.7.4 Objective Measures of Prospective Memory

The lack of evidence on self-reported cognitive failures and the inconsistent results with reference to the three subscales of the prospective memory questionnaire could reflect a metacognitive deficit in ecstasy users, whereby they do not realise their cognitive slips. Heffernan, Jardine and Betney (2005) attempted to control for this by using a self-report and objective measure (video-based) prospective memory task. Ecstasy users reported significantly more forgetting on the long-term prospective memory scale, and also recalled significantly fewer items on the video-based prospective memory task.

To summarise, ecstasy users report more prospective memory slips on Long-Term PM, although self-reports of slips in other areas of PM may be related to the use of cannabis. Everyday memory slips also appear to be related to cannabis use, while only one of three studies assessing cognitive failures has found that ecstasy users report more failures. In addition, it is possible that ecstasy users do realise their prospective memory slips as one study found that objective and subjective measures of PM were similar.

This area of research is relatively new, and is in need of further clarification. The reliance on the World Wide Web to collect data may perhaps lessen the extent to which the findings of such research can be generalised. A link has also been suggested between prospective memory slips and executive function deficits (Heffernan et al. 2001a) although the existence of such a link has not been investigated. Therefore Chapter 11 of this thesis will systematically investigate

aspects of everyday memory, and investigate a possible link with executive functioning, and the knowledge of one's own slips will be assessed using an objective measure. As it is clear from the literature that the use of other drugs, cannabis in particular, is related to self-reports of slips, the potential effects of cannabis as a mediator or sole contributor will also be investigated.

3.8 Simple Span

A number of studies (Back-Madruga et al. 2004; Dafters et al. 2004; Gouzoulis-Mayfrank et al. 2000; Klugman et al. 1999; Rodgers 2000; Semple et al. 1999; Wareing et al. 2004b) have assessed simple span via the digit span task, which requires participants to recall strings of digits increasing in length. However, only two studies have found drug related differences: McCardle et al. (2004) found that ecstasy users performed worse than controls, while Croft et al. (2001a) found that a drug-using group performed worse than controls.

3.9 Verbal Learning

Most studies with ecstasy users have used associative learning tasks (learning links between previously unrelated concepts) or word list learning (where a list of words is read out over a number trials and recall measured at each trial) tasks to assess verbal learning. A number of studies have used the RAVLT to measure verbal learning: a list of 15 words is read out loud, after which a participant has to recall as many of the words as possible. The same list is then read out 4 more times after which a new list is read out and recall again requested. The new list serves as an interference task, and following it, the original list is read out and recall again requested. Thus list 1 measures immediate recall and trial 6 (after 30 minutes delay) delayed recall

(reported earlier in section 2.6), while trials in between provide an index of list learning. Gouzoulis-Mayfrank et al. (2000) used a German version of this task, and found that ecstasy users exhibited poorer learning performance over 5 trials than nonusers, and required more trials to learn the associations than cannabis users and nonusers. The ecstasy users also forgot more words than controls after presentation of the second word list. Poor performance in the test overall was associated with heavier ecstasy use; interference of the second word list with frequency of ecstasy use, and number of repetitions required with average nightly ecstasy dose and frequency of cannabis use. Croft et al. (2001a) found that ecstasy/cannabis users did not perform worse than cannabis only users or controls, although a combined drug-user group performed worse than controls on a composite measure of lists 1-5. Using a slightly longer version of the test in which trial 7 is recall after interference and trial 8 is delayed recall, former ecstasy users performed worse than drug-naïve controls on a composite score of trials 1-5, and on the interference list (trial 6), although within the whole sample the latter was associated with the amount of cannabis smoked in the year prior to testing (Thomasius et al. 2003). In another study, controls recalled more words than ecstasy users on trials 4 and 5 of the RAVLT (McCardle et al. 2004) although performance was not significantly correlated with indices of drug use.

Some studies have also used paired associates learning tasks requiring participants to learn associations between previously unrelated concepts (usually words or spatial locations). Croft et al. (2001a) used a task requiring participants to learn associations between 6 colour pairs, primarily through guessing, then through feedback with the experimenter ("yes" or "no"). The task finishes when the participant correctly reports 18 consecutive associations, and the number of guesses it takes to get to this point is the score. Again, only after the ecstasy/cannabis and

cannabis only groups were merged to form a drug-user group were there any group differences, with the drug users performing worse than controls. Rodgers (2000) used the verbal paired associates sub-test of the Wechsler Memory Scale-Revised (WMS-R), requiring participants to learn eight word pairs, four reflecting common associations and four reflecting non-common associations, however, the performance of ecstasy users, cannabis users and controls did not differ significantly. There were also no significant performance differences between heavy ecstasy users, moderate users and nonusers on a task requiring the learning of associations between German-Turkish word pairs (Gouzoulis-Mayfrank et al. 2003).

By way of summary, of the studies measuring verbal learning through word list learning, all four found some group differences, although in one of these the combined drug-using group performed worse than the nonuser control group (Croft et al. 2001a). One of these found that ecstasy users learned fewer words by trials 4 & 5 (McCardle et al. 2004) and one that former ecstasy users performed worse than a drug-naïve control group (Thomasius et al. 2003). The fourth found that ecstasy users performed worse over the five trials than nonusers, required more trials to learn all words than cannabis users and nonusers, forgot more after the second list presentation, and there was also a significant correlation between performance and heavier ecstasy use (Gouzoulis-Mayfrank et al 2000). Consequently, there is a degree of consensus that deficits in verbal learning appear to be related to the use of ecstasy and are thus not the focus of this thesis. Research on associative learning is not as well documented, with one study using a word-pair learning task finding that ecstasy users, cannabis users and nonusers did not differ (Rodgers 2000), and another (Gouzoulis-Mayfrank et al. 2003) also finding that ecstasy users were not impaired on a word-pair learning task. One study that used a colour-pair learning task found that a

combined drug user group performed worse than non-users (Croft et al. 2001a). To summarise, in ecstasy users only two studies have assessed word pair learning as an index of associative learning, and one of these required the learning of a Turkish word (non-native) paired with a German word (native). As it was not stated that all participants were bilingual, it is possible that the task was too difficult for everyone, and so masked the ecstasy-related deficits. In light of the evidence set out above, there seems a dearth of evidence on associative learning deficits so Chapter 10 of this thesis will focus on associative learning deficits in ecstasy users, assessed using a word-pair learning task. In addition to the measures assessed in previous studies (trials taken to learn all associations, total number learned), new measures will be introduced so as to better understand the processes underlying any potential ecstasy-related deficits: number of pairs recalled correctly at each trial, number of pairs forgotten at each level (with level one forgetting being forgetting after one correct recall of the pair), trials to completion (the number of trials it takes participants to learn all associations) and the number of perseverative errors (i.e. giving the same incorrect response on successive trials).

3.10 Visual Processing

A number of visual attention task results have been reported in section 3.4, and are not repeated here, so this section focuses on spatial span, spatial working memory and spatial learning.

3.10.1 Spatial Span

Studies that assess spatial span usually use it as a simple span measure, to covary for if deficits in higher level visuospatial processing are apparent. Like the reports on digit span performance (section 3.8), group differences are not usually

significant in this task. Verkes et al. (2001) used a computerised version of the Corsi Block Tapping Test consisting of nine grey buttons on the screen. It starts with three buttons flashing in serial order. The task of the participant is to tap out the same order. If all responses are correct, the number of flashing buttons is increased in increments of 1 until the participant fails on two consecutive trials- the maximum is defined as span, and subsequently, superspan is defined as span-plus-one for 24 trials. Corsi Block span and Span plus one was significantly less in both moderate and heavy ecstasy users than in nonusers. Using the original wooden block version of the Corsi Block task, ecstasy users, cannabis users and nonusers did not differ significantly (Gouzoulis-Mayfrank et al. 2000). In a study utilising a similar task from the CANTAB battery (requiring participants to replicate the sequence of highlighted squares from a computer screen, starting with 2 locations to a maximum of 9), nonusers, polydrug users and ecstasy users did not differ significantly (Morgan, 1998). Using a similar task, Wareing et al. (2004a) found that former and current ecstasy users performed similarly to nonusers. Again using a similar task from the Wechsler Memory Scale-Revised (WMS-R) Rodgers (2000) found that cannabis users, ecstasy users and nonusers performed similarly. It is noteworthy that the only study that found a deficit in spatial span had a noticeably larger lifetime dose than all of the other studies where no differences were evident (see Table 3.1). Although unlikely, the possibility that very high lifetime doses of ecstasy impair spatial span performance cannot be ruled out.

3.10.2 Visual Memory

The visual recognition tests used in the studies reviewed require participants to reproduce or recognise complex visual figures.

Rodgers (2000) used the WMS-R Figural Memory (participants have to identify pre-specified abstract design from array of designs), and visual reproduction (participants have to draw from memory simple geometric shapes that they are exposed to for 10-seconds) subtests, but again, ecstasy users, cannabis users and nonusers performed similarly. Back-Madruga et al. (2004) also found that ecstasy users and controls performed similarly on this task, and no dosage effects were observed. Bhattachary and Powell (2001) used the Rey-Osterrieth task in which participants are requested, without warning, to reproduce a complex geometric figure that they had previously copied, but there were no performance differences between nonusers, novice users, regular users and currently abstaining users. Another study using the Rey-Osterrieth test found that after ecstasy users were divided into 11 light users and 11 heavy users, those reporting higher lifetime ecstasy consumption had lower visual recall scores on the Rey-Osterrieth, and also an increased rate of false-alarm errors on the Continuous Visual Memory Test (CVMT), although no between group differences were observed between ecstasy users and nonusers in the initial analysis. Lifetime ecstasy consumption was however associated with lower scores on the CVMT, for both false alarms and recognition (Back-Madruga et al. 2004). In another study, Rey-Osterrieth scores were not significantly different between ecstasy users and light polydrug using controls (Halpern et al. 2004). Gouzoulis-Mayfrank et al. (2003) used the LGT-3 Logos (participants have to remember and identify 20 logo-like figures) and city-map (participants have to memorise and reproduce a line drawn through a map-like display of geometric shapes) subtests. Recall on both tasks was significantly impaired in heavy users compared to controls and moderate users, although moderate users did not differ significantly from controls. Recall in this study was correlated with frequency of ecstasy use. Finally, Thomasius et al. (2003) used

the "company signs" test of visual memory, requiring the retention of learned information over a period of 30 minutes, but no group differences were observed between current ecstasy users, former ecstasy users, polydrug users and drug-naïve controls.

For visual memory, it appears that ecstasy users are not generally impaired on the tasks that have been administered. Only one of the reviewed studies reports differences between ecstasy users and nonusers (Gouzoulis-Mayfrank et al. 2003), and this was only the case for heavy users of the drug (503 tablets average lifetime dose). One other study also found that heavy ecstasy users performed worse than light users but not controls, and also had increased errors on a visual memory test (Back-Madruga et al. 2004). While it remains a possibility that visual memory is comparatively preserved until a certain threshold of ecstasy use is reached (most of the studies finding no ecstasy related deficits have lower lifetime doses than Gouzoulis-Mayfrank et al. 2003), this is unlikely as the study reporting the highest estimated lifetime doses in abstinent and current ecstasy users (Thomasius et al. 2003) found that there were no differences in performance. Hence it is possible that the test used (LGT-3 Logos) by Gouzoulis-Mayfrank and colleagues is supersensitive to cognitive deficits in ecstasy users, or does not actually measure the target function. As the majority of studies have not found ecstasy-related deficits in visual memory, this aspect of cognitive functioning will not be investigated further in this thesis.

3.10.3 Spatial Working Memory

Some tasks of visual working memory have been reported previously in this chapter as they belong to another cognitive domain also (Alting von Geusau et al. 2004, section 3.3.5). The studies reviewed in this section refer specifically to spatial

working memory tasks and include visuospatial rotation tasks, backwards spatial span tasks, and "dual-task" span measures.

In a study performed by Hanson and Luciana (2004) ecstasy users were more accurate overall on a visual working memory task but had lower scores than controls when they had to delay their responses. Using a visual version of the two-back task in which participants had to press a key when the figure presented is the same as that presented two trials earlier, heavy ecstasy users, moderate users and controls performed similarly (Gouzoulis-Mayfrank et al. 2003). McCann et al. (1999) used the Manikin test, a visuospatial rotation task testing the ability to mentally manipulate objects and determine the orientation of a stimulus (an object in the hand of a model). There were no differences between ecstasy users and controls on days one, two or three of testing in this inpatient study. Using the spatial span backwards test from the WMS-III battery no group differences were observed between ecstasy users and controls, and when the groups were further divided into heavy and moderate users, the differences failed to achieve statistical significance (Halpern et al. 2004). Semple et al. (1999) used the CANTAB spatial working memory task (similar to that used by Fox et al. 2002) but again, no group differences were observed between ecstasy users and nonusers, although in the ecstasy user group larger lifetime doses of ecstasy were associated with lower scores indicating that higher ecstasy use is associated with deficits in spatial working memory. As the study also found decreased serotonin transporter binding in certain brain areas, but not dopamine, this was interpreted to be directly related to reduced serotonin binding as a result of ecstasy use.

Fox et al. (2002) used a task requiring participants to search through a display of boxes in order to find a certain number of hidden blue tokens. Only one box was filled at a time and only once over the task, so participants were scored for errors in

going back to an empty box, or one that had previously held a token. Ecstasy users performed significantly more of both types of error than nonusers, and in both cases there was also a significant group by trial size interaction indicating that ecstasy users performed more errors on the most difficult trials. No differences were observed in terms of search strategy. Lastly, Wareing et al. (2004a) used a spatial working memory task in which participants have to remember a spatial sequence on a 4x4 matrix while at the same time performing a concurrent visual judgement. Both current and former ecstasy users performed worse than nonusers, and this remained significant after control for the use of other drugs in the last three months, and was not related to decreased visual memory capacity (spatial span).

Two studies assessing spatial working memory found that ecstasy users performed worse than nonusers, one that current and former users were worse than nonusers (Wareing et al. 2004a) and one than ecstasy users committed more errors, especially on the more difficult trials (Fox et al. 2002). Ecstasy users also performed worse in the delayed recall of material on one task, but were actually more accurate overall (Hanson & Luciana 2004), and in one task increased lifetime doses were associated with lower scores on a spatial working memory test. Thus there is a broad consensus that spatial working memory is impaired in ecstasy users and this aspect of cognitive functioning will not be explored further in this thesis. In addition, since the role of executive processes in maintenance and maintenance plus visuo-spatial processing tasks remains unclear, spatial working memory will not be assessed. The focus will instead be on executive measures that are well defined in the existing research literature (e.g. Miyake et al. 2000).

3.10.4 Spatial (Associative) Learning

Spatial learning appears to be an element of cognitive function that is particularly neglected in ecstasy use research, with only the design learning task (similar to the AVLT) yielding drug-related deficits. In this task, participants have to redraw 15 designs that they were shown previously instead of a list of 15 words (with a reminder being given after each trial- 5 trials in total). Thus the task also yields scores for each trial. Cannabis users performed worse (recalled fewer figures) than ecstasy users, although when the drug using groups were combined, the drug users did not perform significantly worse than controls (Croft et al. 2001a). Using a similar task (VIG) Gouzoulis-Mayfrank et al. (2000) found that found that ecstasy users performed worse than both cannabis users and nonusers on the immediate recall component, although there were no between group differences in terms of number of trials required for learning and learning score over 5 trials.

Fox et al. (2002) used a paired associates learning task in which participants are presented with a set of six white boxes around the screen, and are required to remember the location of a number of abstract patterns that appear inside these boxes. The task increased in difficulty as participants were required to remember more patterns in each subsequent trial. No group differences were observed with respect to number of presentations required, number of errors, or memory score, although the group by difficulty interaction for errors approached significance indicating that ecstasy users made more errors on the 8-box trials. In Croft's (2001a) study, participants were required to learn the associations between six spatial (unspecified as to the nature of these) pairs, beginning by guessing, then being prompted by feedback from the experimenter. No differences were observed between ecstasy users, cannabis users and nonusers, and when the ecstasy users and cannabis users were combined

into a drug-user group, the results remained non-significant. Using the WMS-R visual paired associates task, requiring participants to learn the colours associated with six abstract line drawings, ecstasy users, cannabis users, and nonusers performed similarly on a composite measure of the first three trials of the first presentation, however, when the task was repeated (measuring delayed recall of the material), the ecstasy users were found to be performing at a significantly lower level than the cannabis users and controls (Rodgers 2000).

Therefore both studies that have assessed spatial learning by AVLT-type tasks have found that ecstasy users performed worse than nonusers. The results with respect to spatial associative learning do not appear to be as clear. Only one study found that ecstasy users performed worse than nonusers, and this was only on the delayed recall of the material, so may reflect some deficit in delayed recall, and not learning performance in itself (Rodgers 2000). This area is perhaps in need of more research to clarify the precise nature of deficits in spatial associative learning (recall or learning deficits) but is outside the aims and scope of this thesis.

Summary

This thesis utilises recent theoretical models of executive functioning (see Chapter 2). The present chapter has presented a rationale for studying the four specific executive functions updating, switching, inhibition and access in ecstasy users, to establish whether these deficits exist. The first three empirical Chapters (6, 7, 8) will examine the nature of ecstasy-related deficits in executive processes. More specifically, Chapter 6 will assess memory updating (via a running memory test), Chapter 7 will assess Switching (via the plus-minus and number-letter tasks) and Inhibition (via random letter generation), and Chapter 8 will assess access to long-

term memory (via the Chicago Word Fluency Test). The pattern of results obtained in these Chapters will form the basis for the next three empirical Chapters (9, 10, 11). If executive deficits are observed, then Chapter 9 will assess their contribution to reasoning performance (via a syllogistic reasoning task), Chapter 10 their contribution to associative learning (via a verbal paired associates task) and Chapter 11 their contribution to lapses in everyday memory (via prospective memory, cognitive failures, everyday memory and cognitive-failures-for-others questionnaires). The executive functions under investigation in this thesis are of vital importance in everyday life, and thus the results of thesis could have very serious implications for individuals concerning using the drug.

Before investigating whether or not executive deficits might be found in ecstasy users, brief reference will be made to serotonergic neurotoxicity and its role in ecstasy-related deficits. There is still much debate about whether ecstasy is actually a neurotoxin in humans, and the amount required for a neurotoxic dose in humans. The next Chapter will briefly review studies that have assessed alterations in brain function in ecstasy users and possible corollaries of these alterations in terms of function.

Table 3.1.

Summary of Participants' ecstasy use in reviewed studies

Authors	Groups (N)	Total Lifetime Use (tablets unless specified)	Frequency (days/month unless specified)	Average Dose (Tablets)	Duration of use	Time since last use (weeks)
Alting von Geusau et al. (2004)	26 E 33 NU	M 53.82 F 38.78	1.96; 1.44 tabs/mth		2.28; 2.24 Years	~2
Back-Madruga et al. (2003)	22 E 28 NU	74.6 times			6.3 years	25.56 *
Bhattachary & Powell (2001)	26 E 18 EN 16 Abs 20 NU	16+ times 1-5 times 16+ times				1.06 * 1.22 * 6.61 *
Curran & Verheyden (2003)	32 E 32 Abs 32 PD		3.48 6.95	2.58 2.43	4.33 years 3.49 years	5.57 * 120.19 *
Dafters et al. (1999)	23 E	14.04 in previous year				~1 *
Dafters et al. (2004)	16 EH+C 19 EL+C 15 C 19 NU	363.8 20.21				~1 *
Daumann et al. (2003)	8 E 8 E PD	74.5 56.25	1.44 3.65	1.66 1.44	34.29 18.43 months	3.29 * 8.91 *
Fox et al. (2001)	20 E Pr 20 E NPr 20 NU	372.3 356.9		1.9 2.9	62.6 65.2	33.8 * 10.83 *
Fox et al. (2002)	20 E 20 NU	172			51.9 months	~2
Fisk et al. (2005)	44 E 59 NU	343	0.44	2.14	183 weeks	10.90
Gamma et al. (1999)	16 E 17 NU	270				
Gouzoulis-Mayfrank et al. (2000)	28 E 28 C 28 NU	93.4	2.4	1.4	27 months	5.86 *

Authors	Groups (N)	Total Lifetime Use	Frequency (days/month unless specified)	Average Dose (tablets)	Length of Use	Time Since Last Use (Weeks)
Gouzoulis-Mayfrank et al. (2003) Hanson & Luciana (2004)	30 EH 30 EM 30 NU	503.2 39.5	4.5 1.8	2.6 1.4	40.9 16.0 months	27.83 * 36.61 *
Halpern et al. (2004)	20 E 20 NU	60 occasions				
Heffernan et al. (2001a) Study 1	46 E 46 NU		10	1.0		0.14 *
Heffernan et al. (2001a) Study 2	30 E 37 NU		5.6 tablets/ month			0.14 *
Heffernan et al. (2001a) Study 3	15 E 15 C 15 D-Na		20 times/ year	1.0		8.66 *
Heffernan et al. (2001b)	30 E 31 NU		13.1			Not under influence at time of study
Jacobsen et al. (2004)	6 E 6 NU	10 times				
Lamers et al. (2003)	14 E	39 times	9 times/year			Urine screen performed. Time unspecified
McCann et al. (1999)	22 E 23 NU	215 times	5.72	2.72*	4.52 years	13.91
McCardle et al. (2004)	17 E 15 NU	4-9 times (median)		1.65	2.2 years	18.57 *
Morgan (1998) Study 1	16 E 12 PD 16 D-Na	35.6	2.94	1.12	2.12 years	2.91 *
Morgan (1998) Study 2	25 E 20 PD 19 D-Na	49.6	4.36	1.47	4.12 years	9.3 *
Morgan (1999)	25 E 22 PD 19 D-NA	50				~9.3 *

Authors	Groups (N)	Total Lifetime Use	Frequency (days/month unless specified)	Average Dose (tablets)	Length of Use	Time Since Last Use (weeks)
Morgan et al. (2002)	18 EH 15 Abs 16 PD 15 D-Na	513; 93 336; 577 M:F		2.6; 1.8 1.6; 1.8	6.4; 2.4 years 3.5; 4.3 years	5.1; 3.0 110; 113
Parrott & Lasky (1998)	15 E 15 EN 15 NU	10+ times 1-9 times		1.8 1.45		Pre-, on-, and post- drug
Parrott et al. (1998)	10 E 10 Nov 10 NU	10+ times 1-9 times				Not taken "recently"
Parrott et al. (2000)	12 EH 16 EL 22 NU	371 times 6.8 times				Drug-free on day of testing
Parrott et al. (2002)	109 EN 136 EM 37 EH	1-9 times 10-99 times 100+ times		1-2 (mode)		
Reneman et al. (2000) altered 5-HT trans	5 E 9 NU	218				19.93 *
Rodgers (2000)	15 E 15 C 15 D-Na		20 times over 5 years			8.67 *
Rodgers et al. (2001)	69 EN 66 EM 20 EH 333 NU	1-9 times 10-99 times 100+ times				
Rodgers et al. (2003)	EN EM EH	38:51% 50:35% 12:14%		1-2 (mode)		
Schifano et al. (1998)	79 Prob 71 N-Prob	47 3	1/week 0.4/week tablets		52 14	
Semple et al. (1999)	10 E 10 NU	672 tablets				2.57 *
Simon & Mattick (2002)	47 E 37 C	258	2.4		45.9 months	2.63 *

Authors	Groups (N)	Total Lifetime Use	Frequency (days/month unless specified)	Average Dose (tablets)	Length of Use	Time Since Last Use (weeks)
Thomasius et al. (2003)	30 E 30 Abs 29 PD 30 D-Na	1033:600 987:534 M:F		5:3 6:2	46:61 56:52 months	3.14:3.57 * 69.377.86 *
Verkes et al. (2001)	21 EM 21 EH 20 NU	169 741		2 3.1	4.4 years 4.5 years	2.24 * 1.29 *
Wareing et al. (2000)	10 E 10 Abs 10 NU		101 100 days/ year	3.25 3.40	4.1 years 3.9 years	1.17 * 46.14 *
Wareing et al. (2004a)	36 E 12 Abs 31 NU	591 433			221 weeks 177 weeks	3.3 weeks 93 weeks
Wareing et al. (2004b)	42 E 17 Abs 31 NU	552 385			212 weeks 197 weeks	3 weeks 112 weeks
Zakzanis & Young (2001a)	15 E Baseline Follow-up	19 times 55 times	2.4 2.4	1.17* 1.75*	18.4 months 30.4 months	6 weeks 4 weeks
Zakzanis & Young (2001b)	24 E 24 NU	31 times	1.91	1.21	1.99 years	17 weeks
Zakzanis et al. (2002)	24 E 30 NU	22.3 times	1.7	1.3	14.7 years	26 weeks

* Denotes number converted (if dose then from milligrams assuming 100 mg per tablet; if abstinence period then from months or days to weeks)

NU = Nonuser of ecstasy
E = Regular Ecstasy User
Abs = Currently abstinent ecstasy user
EH = Heavy ecstasy user
EM = Moderate user of ecstasy
EN = Novice user of ecstasy
EL = Light user of ecstasy
PD = Polydrug user
C = Cannabis user
D-Na = Drug-Naïve

Chapter 4: Review of Literature on ecstasy Neurotoxicity

Chapter 3 reviewed evidence for cognitive deficits in users of ecstasy. The use of ecstasy may cause such deficits by degrading/damaging the serotonin system. This chapter will focus on evidence in humans for the neurotoxicity of ecstasy. It is believed that ecstasy is neurotoxic to the serotonin system, and the most likely cause of this is oxidative stress from serotonin or dopamine metabolites, or a down-regulation of serotonin neurons (see Sprague, Everman & Nichols 1998). Due to ethical constraints most studies are retrospective. There are a number of indices that can be used to assess the integrity of the serotonin system, and each is discussed at the beginning of the sub-section. It is possible that any in deficits in human memory and cognition observed in this thesis, might be related to deficiencies in serotonergic functioning. Thus possible memory deficits resulting from deficiencies in certain areas are discussed.

4.1 Single Photon Emission Computer Tomography (SPECT)

A number of studies have assessed the densities of serotonin receptors (SERT) in different brain areas via means of SPECT. This involves labelling receptors with radioactive markers that can then be "tracked" in the brain enabling researchers to assess the densities of the receptors. While high density of serotonin receptors may reflect a functional serotonin system, lower density may reflect some ecstasy-related damage to serotonergic functioning. Indeed the serotonin transporter is a structural element of the serotonin neuron and is believed to reflect the integrity of serotonin neurons (see e.g. Scheffel & Ricaurte 1990; Zhou et al. 1998).

Reneman, Booij, Schmand, van den Brink et al. (2000) sought to investigate neurotoxic damage in post-synaptic receptors. Post-synaptic 5HT-2a receptors are associated with cognitive abilities such as learning (See Buhot, Martin & Segu 2000

for review), so if deficits in learning are observed in this thesis, it is possible that they may be due to serotonergic neurotoxicity. Reneman et al. used Single Photon Emission Computed Tomography (SPECT) in which a radio-ligand (a radioactive marker), in this case [^{123} I]-5-I-R91150, with a high and selective affinity for 5HT-2a receptors is used to label the neurons. This makes it possible to assess the density of these neurons. Five participants comprised the MDMA group (having used MDMA on at least 50 occasions, but with an average lifetime dose of 218 tablets, and average abstinence period of 4.6 months), and 9 people were in the non-MDMA group. In most brain areas the [^{123} I]-5-I-R91150 binding ratios were higher in ecstasy users than in nonusers, but this was only significant for the occipital cortex, and indicated an up-regulation of the post-synaptic 5HT-2a receptors. In addition, as mentioned in Chapter 3, section 3.6 the binding was significantly correlated with recall in the ecstasy group (but not the nonuser group). It is likely in this case that the up-regulation of the receptors is related to ecstasy neurotoxicity, as it is consistent with animal and human studies finding neurotoxicity in the occipital cortex only (Scheffel, Szabo, Mathews, Finley et al. 1998; Semple, Ebmeier, Glabus, O'Carroll et al. 1999).

In another study from the same laboratory, Reneman et al. (2001a) used a different radio-ligand: iodine 123-labeled 2β-carbomethoxy-3β-(4-iodophenyl) tropane (hereafter referred to as [^{123} I]β-CIT) to assess cortical 5-HT neuron density. In a sample of 22 recent ecstasy users (2.4 months mean abstinence period; average lifetime dose of 485 tablets), 16 previous users (29 months mean abstinence period; average lifetime dose of 268 tablets) and 13 non ecstasy-using controls, mean cortical [^{123} I]β-CIT binding was significantly lower in recent ecstasy users indicating decreased SERT density. Previous users performed similarly to controls, and although both groups of ecstasy users performed worse on the RAVLT, this wasn't

significantly correlated with cortical binding. In another study from the same laboratory, 29 ecstasy users (average lifetime dose of 324 tablets), 9 ecstasy and amphetamine users (average lifetime ecstasy dose of 358 tablets), and 15 nonuser controls were compared. [^{123} I]β-CIT was used to assess dopamine binding ratios in the striatum, as it is possible that ecstasy may also affect the dopaminergic system. [^{123} I]β-CIT binding ratios were significantly higher for ecstasy users than for controls. The binding ratios of the ecstasy + amphetamine group were significantly lower than the ecstasy only group, but did not differ from controls. Correlations between extent of amphetamine and ecstasy use and binding ratios were not significant. While the binding ratios suggest that amphetamine or combined ecstasy and amphetamine use may affect the dopaminergic system, this should be treated with some caution as correlations with drug use were non significant. (Reneman, Booij, Lavalaye, de Bruin et al. 2002).

Using the same radio ligand, Semple et al. (1999) assessed SERT densities in 10 long-term male ecstasy users (18 days abstinence period, lifetime dose of 672 tablets) and 10 ecstasy-naïve controls who used a range of other drugs. Using Regions-of-Interest (ROI) analysis, a reduction of [^{123} I]β-CIT binding was found in posterior cortical regions, and uptake in many regions was correlated with time since last dose of ecstasy, which remained significant after control for estimated lifetime dose. Performing further analysis of the data using a voxel-based method, the largest reductions were seen in the primary sensori-motor cortex, and significant correlations were also observed between the abstinence period from ecstasy and binding in the mid-line limbic areas.

Chang, Grob, Ernst, Itti et al. (2000) used SPECT to assess cerebral blood flow (CBF) in 21 ecstasy users (211 lifetime occasions of use) and 21 drug-naïve

controls. At baseline scans, the MDMA users only exhibited slightly lower CBF than the nonusers, and reductions in individual regions were also non-significant. Eight participants were administered MDMA and scanned 2 and 3 weeks later. At these scans, MDMA users exhibited decreased regional and global CBF compared to their baseline scans and the non-ecstasy group. The largest significant reductions were observed in the caudate, superior parietal cortices, and the right DLPFC. Furthermore, these decreases in CBF were more pronounced in the participants who had received larger doses of MDMA, and in those with more recent MDMA administration.

To summarise, those studies using SPECT have generally found ecstasy-related changes in SERT binding ratios (Reneman et al. 2000; Reneman et al. 2001a; Semple et al. 1999). One study also found that increases in post-synaptic binding (which the authors state reflects lower synaptic 5HT levels) were significantly correlated with recall in ecstasy users (Reneman et al. 2000), although this was not supported by a later study (Reneman et al. 2001a). In the two studies that used the radioligand [^{123} I]β-CIT, recency of ecstasy use appeared to be an important factor in the extent of 5HT reductions- in one study recent ecstasy users had lower binding ratios than former users and nonusers (Reneman et al. 2001a), and in another binding was significantly correlated with abstinence period (Semple et al. 1999). Recency of use was also significantly correlated with decreased CBF in ecstasy users (Chang et al. 2000). However, it appears that amphetamine use is a more important contributor to decrements in dopaminergic function than ecstasy use (Reneman et al. 2002). To summarise, SPECT studies in ecstasy users have reported decrements in serotonin function which if present among the ecstasy users to be investigated in the chapters that follow, might be responsible for any possible decrements in cognitive function observed in this thesis.

4.2 Electroencephalogram (EEG) measures

EEG has also been used to assess brain function in ecstasy users, by using electrodes placed on the scalp to measure patterns of electrical activity in the brain.

Croft, Klugman, Baldeweg and Gruzelier (2001b) examined the relationship between an index of 5HT function (the intensity of evoked auditory potentials) and frequency of MDMA use and cumulative lifetime dose. In the primary auditory cortex, 5HT is thought to protect against loud auditory stimuli by attenuating cortical response. If 5HT is intact in the primary auditory cortex, it would be expected that the attenuation to loud stimuli would be greater than if the 5HT was not intact (and thus it may be expected that ecstasy users do not show such great attenuations). Twenty-two MDMA users (total lifetime dose of 226 tablets), 19 cannabis users, and 20 drug-naïve participants were compared. The MDMA users had significantly larger evoked potentials than the cannabis users and nonusers (although the latter two groups did not differ significantly. Total ecstasy use was found to be a significant predictor of the evoked potential, although frequency of use was not.

Using the same rationale Tuchtenhagen, Daumann, Norra, Gobbele et al. (2000) performed an auditory evoked potentials study in 28 ecstasy (lifetime dose of 93.4 tablets; abstinent for 41 days) users, 28 cannabis users (abstinent for 4 days), and 28 nonusers. Ecstasy users and cannabis users were comparable for cannabis use. As with Croft et al's study, the ecstasy users exhibited significant increases in evoked auditory potentials. Although the main effect of group was marginally non-significant, the interaction between stimulus intensity and group was significant. Post-hoc tests revealed that while group differences were not apparent at the lower intensities, at 80dB the ecstasy users differed significantly from the cannabis users (but not the nonusers), and at 90 dB the ecstasy users differed significantly from both the control

groups. However there were no significant correlations between indices of ecstasy and cannabis use, and evoked auditory potentials. Both of these studies therefore support the notion that ecstasy users present degraded serotonergic functioning.

In another study (Gijsman, van Gerven, Verkes, Schoemaker et al. 2002) alpha, delta and theta EEG waves were assessed following administration of dexfenfluramine (a serotonin releaser) every hour for 6 hours. Nonusers, moderate users and heavy users were assessed. Dexfenfluramine produced a concentration dependent decrease in slow wave EEG activity (this effect was greater in heavy users). Dexfenfluramine was also associated with decreased alpha activity in frontal/central areas in heavy ecstasy users compared with moderate users and controls. So it appears that ecstasy is associated with changes in electrical brain activity.

EEG power in different brain areas has also been shown to correlate with extent of ecstasy use. In a correlational study, Dafters, Duffy, O'Donnell and Bouquet (1999) evaluated different EEG frequencies in 23 ecstasy users (having used an average of 14 tablets in the previous year). There was a positive correlation between ecstasy use in the last 12 months and EEG power in the alpha frequency band (all brain areas with the exception of the right anterior quadrant of the brain), and also a positive correlation with the beta frequency band in the left-posterior quadrant only. There was also a significant negative correlation with low frequency delta EEG waves across the brain.

EEG studies have revealed that serotonin function may be degraded in the frontal cortex, with one study finding that total lifetime ecstasy dose was a significant predictor of evoked potentials (Croft et al. 2001b) and another study finding a non-significant trend towards higher evoked auditory potentials (Tuchtenhagen et al.

2000). The non-significant result in the latter study may reflect the lower lifetime dose than the former study. EEG power in different brain areas was also correlated with ecstasy use in the last 12 months.

4.3 Magnetic Resonance Imaging (MRI) & Magnetic Resonance Spectroscopy (MRS)

4.3.1 Magnetic Resonance Imaging (MRI)

In an MRI scan a large cylindrical magnet creates a magnetic field around the participant's head, and radio waves are sent through the magnetic field. Sensors then read the signals and an image of the brain is constructed using a computer. Functional MRI (fMRI) is used to assess brain function while performing an action, and relies on the magnetic properties of blood (thus enabling researchers to image blood flow in the brain while participants are performing tasks).

Cowan, Lyoo, Sung, Ahn et al. (2003) performed structural MRI scans on 31 ecstasy-polydrug users (having used ecstasy at least 5 times; abstinent for 3 weeks) and 29 nonusers and compared scans using voxel-based metamorphy (VBM), to assess regional brain grey and white matter concentration[3]. It was hypothesised that only grey matter would reveal ecstasy-related differences as it is believed that ecstasy primarily affects unmyelinated axons from the dorsal raphe nucleus (e.g. Ricaurte et al. 1988). Ecstasy users had decreased grey matter in several brain regions, which were localised to the neocortex in bilateral Brodmann's area (BA) 18, left BA 21, left BA 45 in addition to bilateral cerebellum and midline brainstem. It is suggested that these decrements may be responsible for the neuropsychiatric impairments observed in ecstasy users. More specifically both left BA 45 and left BA 21 play important

[3] VBM employs gray/white matter segmentation and statistical parametric mapping analysis to calculate a voxel-wise comparison of matter concentration.

roles in the retrieval from semantic memory (e.g. Booth et al. 2002; Lee et al. 2002). This may be particularly relevant to this thesis as access to semantic memory is one of the key areas under investigation.

To try and elucidate any structural differences apparent during different aspects of information processing, Jacobsen et al. (2003) used fMRI to scan 6 ecstasy users (average lifetime exposure of 10 occasions) and 6 nonusers, while performing a verbal working memory task (the N-back task at 1- 2- and 3-back conditions). The main finding was that ecstasy users had abnormal function in the left hippocampus during the task (they failed to deactivate the left hippocampus normally during high verbal working memory load). Correlational analysis also revealed that there were strong negative relationships between left hippocampal activity and MDMA abstinence period, with the strongest correlation occurring under the highest memory load. However, total lifetime episodes of MDMA use and age of onset were not significantly correlated with hippocampal activity, suggesting that changes are related to recency of use and may be reversed with prolonged abstinence. The observation of abnormal hippocampal activity in the left hippocampus is consistent with previous studies in ecstasy users in which specific memory deficits have been observed (e.g. Parrott & Lasky, 1998; Gouzoulis-Mayfrank et al. 2000; Fox et al. 2001), although as the n-back task supposedly loads on prefrontal resources, this is somewhat surprising.

Reneman, Majoie, Habraken and den Heeten (2001c) used MRI to assess cerebral volume ratios in 8 ecstasy users (lifetime dose of 154 tablets; average abstinence period of 14.6 weeks) and 6 nonusers. Diffusion and perfusion MRI were used, allowing apparent diffusion coefficient and cerebral volume maps to be

constructed. Apparent Diffusion Coefficient values and relative cerebral volume ratios were significantly higher in the globus pallidus of ecstasy users compared to nonusers, and the increases in cerebral volume in this area were significantly positively correlated with extent of previous ecstasy use, suggesting that this was an ecstasy-related effect and not a premorbid difference. Reneman et al. (2001c) suggest that this is a distinct possibility considering that serotonin is believed to have a vasoconstrictory role in the brain (Cohen, Bonvento, Lacombe & Hamel 1996), and if ecstasy does decrease serotonergic function, then it would be expected that vasodilation would occur, thus increasing CBV ratios. In terms of the possible functional correlates of such CBV changes in this thesis, the globus pallidus is part of the basal ganglia and is involved in word fluency (access) tasks and syllogistic reasoning (e.g. Fisk & Sharp, 2002).

Overall, MRI has revealed some abnormalities in the brain structure of ecstasy users. Participants (who were only required to have used ecstasy 5 times) showed significant decreases in grey matter in the globus pallidus (Cowan et al. 2003) while ecstasy use also appears to increase cerebral blood volume (Reneman et al. 01c). As with studies mentioned in the previous sections, it appears that recency of use may be an important factor in abnormal brain structure. Jacobsen et al. (2003) found that ecstasy users failed to deactivate the left hippocampus during a high load working memory condition, although there was a significant negative correlation between abstinence and activity suggesting some recovery of function over time.

4.3.2 Magnetic Resonance Spectroscopy (MRS)

Proton magnetic resonance spectroscopy (^{1}H MRS) is a non-invasive technique that can measure concentrations of N-acetylaspartate (NAA- a neuronal marker) or myo-inositol (MI- a tentative glial marker). Chang, Ernst, Grob and Poland

(1999) used this method to evaluate 21 ecstasy users (average lifetime dose of 131 tablets; abstinent for 4 months) and 37 nonusers in mid-frontal, mid-occipital and mid parietal brain regions. The NAA ratios were normal in all brain regions in both groups. However, the MI ratio and the MI to creatine ratio were increased in the parietal white matter of ecstasy users. Cumulative lifetime dose of ecstasy had significant effects on MI concentration in the parietal white matter and the occipital cortex in ecstasy users. While the lack of a difference in NAA ratios in brain areas may reflect the lack of ecstasy-related neuronal damage, the increases in MI suggests an ecstasy-related increase in glial content.

Using the same method, Obergriesser, Ende, Braus and Henn (2001) assessed hippocampal function in 5 ecstasy users (having used an average of 100 doses; abstinent for at least 3 weeks) and 5 non-ecstasy users. Like Chang et al. (1999), no significant differences were observed between the two groups in terms of NAA and creatine metabolism in the hippocampus. Thus taken together, the findings of these two studies suggest that either ecstasy users do not exhibit decreases in neuronal function resulting from their use of the drug, or that NAA concentration assessed using MRS is not the most sensitive measure of evaluating neuronal damage (however this method has been shown to be sensitive in other populations).

4.4 Positron Emission Tomography

PET scanners measure emissions from radioactive chemicals (radioligands) that are usually injected in to the bloodstream of participants. Like MRI, this data can then be fed in to a computer which produces 2- and 3-D images of the brain.

Some studies use PET scanning to assess serotonin transporter (SERT) density in brain regions (as with SPECT). Thomasius et al. (2003) used this method in 30 regular ecstasy users (used for at least 20 weeks prior to participation), 29 polydrug

using controls (similar drug use to the ecstasy users with the exception of ecstasy), 31 former ecstasy users (lifetime exposure of at least 250 tablets; abstinent for 20+ weeks), and 30 drug-naïve controls. PET was performed with the 5HT transporter ligand [^{11}C] (+) McN5652, a tracer which has been demonstrated to provide a highly specific binding to 5HT transporters of the human brain in vivo (Szasbo, Kao & Scheffel, 1995), in the mesencephalon, putamen, caudate and thalamus. The Distribution Volume Ratios (DVRs) did not differ significantly between the groups in the control region (white matter) or the putamen. There were however significant group differences in the mesencephalon, caudate nucleus and thalamus: current ecstasy users exhibited significantly lower DVRs in the mesencephalon relative to all other groups, and in the caudate nucleus relative to polydrug users. Typical number of exposures to ecstasy was a significant covariate for DVRs of SERT in the caudate nucleus, and together with gender and LSD taken in the last year, was also a significant covariate for the thalamus. In the regression equation, DVRs of SERT were best predicted by parameters of ecstasy use, with typical exposures being the best predictor in the thalamus and caudate nucleus, and tablets taken in the previous year with the mesencephalon

McCann, Szabo, Scheffel, Dannals et al. (1998) used the same radio ligand as Thomasius et al. (2003) in 14 former heavy ecstasy users (having used 228 times over 4.6 years; 386 mg average dose; 6 times per month, but abstinent for 19 weeks) and 15 control participants. Ecstasy users were found to have significant global and regional (hypothalamus, midbrain, caudate, putamen, pons, cerebellum and the cingulate, frontal, occipital and parietal cortices) decreases in DVRs for specific binding of [^{11}C] (+) McN5652. This suggests that the ecstasy users had a lower brain density of 5HT transporter sites than participants in the control group. The cerebellum

in particular has been shown to play an important role in visuo-spatial judgement (e.g. Fink et al. 2000), which may be an important contributory factor to performance in syllogistic reasoning tasks (e.g Goel, Buchel, Frith & Dolan). In addition, decreases in 5HT transporter binding were significantly correlated with extent of previous ecstasy use, and there was no correlation between duration of abstinence and extent of binding.

Vollenweider, Gucker, Schonbachler, Kamber et al. (2000) measured 5HT uptake binding in healthy volunteers via PET with [^{11}C] (+) McN5652. Participants were scanned at baseline, after administration of 1.5 mg/kg MDMA, and at one month following administration. No differences in binding could be detected at one month following treatment, although on scan 2 (after administration) significantly decreased binding was observed in the ecstasy group in the caudate, putamen, thalamus, midbrain, and occipital, temporal, frontal and parietal cortices.

Using the same radioligand, Buchert, Thomasius, Nebeling, Petersen et al. (2003) compared 30 current ecstasy users (827 tablets lifetime dose over 54 months; abstinent for 24 days), 29 former users (793 tablets lifetime dose over 55 months; abstinent for 514 days), 29 drug-naïve participants, and 29 polydrug controls. In all SERT rich areas, the mean DVR was lowest in the group of current ecstasy users. In the mesencephalon, the DVR for current users was significantly lower than for all other groups, while in the caudate the DVR was significantly lower for current ecstasy users than for polydrug users. In the thalamus, the DVR was significantly smaller for the current ecstasy users than for drug-naïve participants and polydrug users. The mean standardised uptake volumes (SUV- the ratio of tracer uptake to injected dose per bodyweight) although non-significant were highest for drug-naïve participants in

all regions. The mean SUVs were similar for the current users and polydrug users, although former users had the lowest of all groups.

Gamma, Buck, Berthold, Hell et al. (2000) administered 1.7 mg/kg of MDMA to MDMA-naïve participants in a cross-over design. It was found (via statistical parametric mapping) that although there were main effects of drug and Continuous Performance Task (CPT) on regional cerebral blood flow ($_rCBF$ indexed by $H_2{}^{15}O$), the interaction was non-significant indicating that task had no significant effect on how ecstasy affected $_rCBF$ compared to placebo. MDMA produced significant bilateral increases in $_rCBF$ in the ventromedial prefrontal cortex (VMPFC), and the ventral anterior cingulate, inferior temporal lobe, medial occipital lobe, and widespread activation of the entire cerebellum. It also caused decreases in $_rCBF$ bilaterally in the pre- and para-central lobule, dorsal anterior and posterior cingulate, superior temporal gyrus, insula and thalamus. One-sided decreases were also found in the left amygdala and right parahippocampal formation and uncus.

Again trying to assess the relationship between brain activation and task, Gamma, Buck, Berthold and Vollenweider (2001) used [$H_2{}^{15}O$]-PET to compare blood flow in 16 regular ecstasy users (270 tablets lifetime dose) and 17 non-ecstasy using controls. Participants were scanned at baseline and twice while performing a continuous performance task (CPT). While in both groups the CPT produced alterations in $_rCBF$, no ecstasy-related differences were observed, and there were no significant correlations between extent of ecstasy use and $_rCBF$.

Obrocki, Schmoldt, Buchert, Andresen et al. (2002) used PET labelled with 2-[18F]-fluoro-2-deoxy-D-glucose (FDG) in 94 ecstasy users (438 tablets cumulative lifetime dose; 6.4 months abstinence) and 27 controls. Glucose metabolism as indexed by uptake of FDG was reduced in ecstasy users compared to controls in the cingulate,

BA11, putamen, caudate, amygdala and the hippocampus bilaterally. These differences were only significant for the putamen and caudate bilaterally and the left amygdala. Although no significant relationship was detected between cumulative lifetime dose and FDG uptake, there was a statistically significant relationship between FDG uptake and abstinence period in the left cingulate and right amygdala. In a pilot study from the same laboratory, 7 ecstasy users were found to have reduced glucose metabolism rates in the hippocampus and striatum compared to controls (Obrocki, Buchert, Vaterlein, Thomasius et al. 1999).

In terms of significant findings most studies using PET scanning in ecstasy users find abnormal functioning. Three studies found significant decreases in SERT binding in ecstasy users with two of these finding that the decreases were significantly related to extent of previous ecstasy use (McCann et al. 1998; Thomasius et al. 2003). The other study showing decreases in SERT binding found that former ecstasy users had the lowest binding ratios of all groups (Buchert et al. 2003), supported by the non-significant correlation with abstinence in McCann et al's study. In contrast with this Vollenweider et al. (2000) found that there were differences in SERT binding immediately after administration of MDMA but no such differences were apparent after one month. Contrasting findings were also shown in relation to cerebral blood flow with one study finding ecstasy-related increases and decreases in certain brain areas (Gamma et al. 2000) and one finding no differences in blood flow (Gamma et al. 2001). One study also found decreases in glucose metabolism in ecstasy users (Obrocki et al. 2002). The final section of this chapter focuses on decrements in serotonin metabolites.

4.5 Cerebrospinal Fluid (CSF) metabolites

One way in which serotonergic function can be assessed is by measuring the metabolites of serotonin in cerebrospinal fluid. The rationale behind this being that if there are lower levels of serotonin due to ecstasy use, then there will also be lower levels of serotonin metabolite. In an early study Ricaurte, Finnegan, Irwin and Langston (1990) measured CSF levels of 5-hydroxyindoleacetic acid (5-HIAA- a serotonin metabolite) in 33 ecstasy users (lifetime dose of 64 tablets; abstinent for at least 2 weeks) and 24 nonusers. Ecstasy users showed a significant 26% decrease in CSF-5HIAA compared to nonusers, although correlations between CSF-5HIAA concentration and number of ecstasy exposures, duration of use and abstinence period were not significant. Such results are consistent with damage to the central serotonergic system in ecstasy users.

Another study found that memory impairments in abstinent ecstasy users were correlated with lower levels of CSF 5-HIAA. Specifically, amounts of 5-HIAA were assessed in 28 ecstasy users (lifetime use of 60 occasions; abstinent for 4 weeks) and 28 nonusers. Participants also completed a number of memory measures. The mean concentration of 5-HIAA was significantly lower for ecstasy users than for controls; the concentration of 5-HIAA was also significantly negatively correlated with ecstasy dose (mg/month). In addition CSF levels of 5-HIAA were significantly associated with delayed visual memory (the lower the concentration, the lower the memory score). Significant associations were also observed between 5-HIAA concentration and immediate figural memory and delayed visual reproduction (Bolla, McCann and Ricaurte 1998).

McCann, Eligulashvili, Mertyl, Murphy et al. (1999) also assessed CSF-5HIAA levels in 22 ecstasy users (lifetime usage of 215 occasions; abstinent for 13.91 weeks) and 23 nonusers. Ecstasy users were found to have lower CSF levels of 5-

HIAA than nonusers, although concentrations of 5-HIAA were not significantly correlated with cognitive performance. An earlier study from the same laboratory (McCann, Ridenour, Shaham & Ricaurte, 1994) also found that ecstasy users had significant decreases in CSF 5-HIAA. While the 30 ecstasy users (lifetime exposure of 94.4 occasions; abstinent for 17.9 weeks) had lower metabolite concentrations than the 28 controls, there was also a significant group by gender interaction reflecting that in the ecstasy group females had a larger reduction in 5-HIAA than males (46% compared to 20%), and in the controls, males had lower levels than females. Levels of 5-HIAA were not significantly correlated with any indices of ecstasy use.

An early study of 5-HIAA concentration contradicts the preceding studies. Peroutka, Pascoe and Faull (1987) measured levels of the metabolite in 5 ecstasy users (with lifetime doses of 1, 17, 18, 22, and 33 tablets; abstinent for at least 6 weeks). When compared to the mean levels of metabolite for a control group, there were no significant differences, and there was no significant correlation between extent of ecstasy use and concentration of CSF-5HIAA.

By way of summary, the earliest study assessing levels of 5-HIAA (Peroutka et al. 1987) found no differences in levels of the metabolite, although the sample size and ecstasy doses were rather small in this study. Subsequent studies did find that ecstasy users had lower levels of 5-HIAA in their cerebrospinal fluid (Bolla et al. 1998; McCann et al. 1994; McCann et al. 1999; Ricaurte et al. 1990) with one finding that the decrease was greater in females than in males (McCann et al. 1994). Two of these studies also investigated the possible link between decreases serotonin metabolite levels and performance, with one finding that decrements were significantly related to poor performance (Bolla et al. 1998) and one finding that they were not related (McCann et al. 1999).

Chapter Summary

It appears that in some way the use of ecstasy degrades the serotonin system. Serotonin is known to be involved in memory and learning processes, whether directly or indirectly (through modulation of another neurotransmitter system e.g. dopamine) (see e.g. Buhot et al. 2000). Abstinence from ecstasy seems to be a particularly important confound in such studies with some finding that any observed decrements in the serotonin system may be reversible after prolonged abstinence, although a number of studies also found that former users (in some cases having not used for as long as 514 days- Buchert et al. 2003) had lower uptake ratios than current users. Some studies mentioned in Chapter 3 (e.g. Wareing et al. 2000) also find that the cognitive deficits observed in ecstasy users persist after prolonged abstinence. Therefore all participants in this thesis will be required to abstain from the use of ecstasy for at least 7 days prior to testing (in line with other studies in this area e.g. Wareing et al. 2000) although in most chapters, the average abstinence period was actually longer than this.

In Chapter 3 the use of other recreational drugs, especially cannabis, appear to be important contributors/mediators of the ecstasy-related deficits. For example, moderate cannabis use may offer some protection against the neurotoxic effects of ecstasy, while the use of drugs such as cocaïne may exacerbate the neurotoxic effects of ecstasy. In turn both the use of cannabis and cocaine have been implicated in deficits in their respective users over a range of tasks. The following chapter (Chapter 5) reviews evidence for cognitive deficits in cannabis and cocaine users, and discusses how might be the best way to statistically control for the use of these drugs.

Chapter 5: The effects of Cannabis and Cocaine on cognitive processes.

As previously reviewed in Chapter 3, the use of ecstasy has been associated with cognitive decline. Some studies reviewed in Chapter 3 (e.g. Croft et al. 2001a) highlighted the significance of using other recreational drugs at the same time as ecstasy (in Croft et al's study this was cannabis, which was found to be more responsible for the cognitive deficits than ecstasy use in their sample). There may therefore be interaction effects between ecstasy and cannabis (see Parrott, Gouzoulis-Mayfrank, Rodgers & Solowij, 2004 for review). In their own right, cannabis and cocaine have been implicated in cognitive deficits in their respective users, although in the case of the former it is unclear in some studies if deficits persist after 30 days of abstinence, and in the latter most studies assess individuals presenting for dependence at clinics (as opposed to recreational use). Chapter 5 presents evidence for cognitive deficits in cannabis and cocaine users, which provides a rationale for quantifying the use of these drugs as well as ecstasy in this thesis. As most of the participants in this thesis were infrequent users of other recreational drugs (e.g. psilocybin mushrooms, amphetamine, GHB, Ketamine), the focus of this review is cannabis and cocaine.

5.1 Cannabis

Marijuana comes from the plant *Cannabis Sativa.* The psychoactive properties of cannabis are mainly[4] due to its active ingredient Δ^9 tetrahydrocannabinol, hereafter referred to as THC. Just as with ecstasy use in Chapter 3, the use of cannabis has also been associated with cognitive deficits. A review of some of the literature is provided below.

5.1.1 Intelligence

[4] Marijuana does contain other cannabinoids e.g. cannabinol, cannabidiol, but these are not thought to contribute to its psychoactive properties.

Three studies pre-matched their group on IQ tests in an attempt to normalise performance. Whitlow, Liguori, Livengood, Hart et al. (2004) matched groups (long-term heavy cannabis users reporting daily use on 25 out of 30 days a month for at least 5 years, with an average abstinence period of 14.6 hours and controls reporting using cannabis 1-50 times, with none reported in the last year) on the WASI; Schwartz et al. (1991) matched groups (10 daily cannabis users, 8 light users reporting using less than 35 times in total and 9 nonusers) for IQ on an unspecified full-scale IQ test (all participants between 90 and 120 IQ); and Ehrenreich, Rinn, Kunert, Moeller et al. (1999) matched early onset cannabis users (26 hour abstinence period; 3.9 days/week frequency of use in the last six months; 4.6 years of use; estimated lifetime use of 1087.5 days), late onset users (33.4 hour abstinence period; 3.2 days/week frequency of use in the last six months; 3.9 years of use; estimated lifetime use of 709.8 days) and controls on a PMI test.

Other research suggests that cannabis users are not intellectually impaired relative to non-cannabis users. Millsaps, Arzin and Mittenberg (1994) used the WAIS-R to estimate full-scale and premorbid intelligence in a group of cannabis users. Fifteen cannabis dependent adolescents (length of use 29.13 months; 8.93 grams/week used; 27.2 days of abstinence) participated in the study. There were no significant differences between values obtained for each scale and both were within the normal range. Again using the WAIS-R, Pope et al. (1997) found no differences between light (N=30; smoking a median of 1 day in the last 30) and heavy cannabis users (N=25; smoking a median average of 29 days in the last 30). To further support this Varma et al. (1998) used the WAIS-R verbal IQ scale (incorporating the information, digit span, arithmetic and comprehension subtests) and found that the 26 long-term heavy cannabis users (regularly consuming cannabis for 5 years, 20+ times

a month, with a daily intake equivalent to 150mg Δ-9-THC) did not perform worse than 26 non-cannabis-using controls). Finally, in another study only the cannabis user group were tested on the WAIS verbal intelligence scale, so comparisons were not made with controls. Nevertheless, Intelligence scores in the cannabis-using group (N=12; 19, 200 occasions of use in lifetime; current use of at least 7 times/week) were not significantly correlated with any other measures (Kanayama, Rogowska, Pope, Gruber et al. 2004). Using the culture fair IQ test (scale three) and the Intelligence Structure Test (IST- measuring verbal memory and assessing learning efficiency) Kurzthaler, Hummer, Miller, Sperner-Untwenger et al. (1999) found no significant differences between controls and cannabis users at baseline, after cannabis administration, or on day three of the study. However, whereas controls showed an increase in performance from day one to day two, and day two to day three, the cannabis group only improved from day two to three indicating that they have not learned from their performance while on cannabis. Solowij, Stephens, Roffman, Babor et al. (2002) used a measure of full-scale IQ (Wide Range Achievement Test-Revised, Reading subtest), and premorbid IQ (North American Adult Reading Test-NAART) in fifty-one short-term cannabis users (10.2 years of use; smoking on an average of 28.3 days a month), 51 long-term users (23.9 years of use; smoking on an average of 27.4 days a month) and 33 of control participants; comparisons were also made between a combined group of the cannabis users (17.1 years of use; smoking on an average of 27.9 days a month; and an average of ¼ ounce per week in two large joints) and 33 nonuser controls. Neither intelligence measure was significantly different between the cannabis users and nonusers. One study also using a measure of fluid intelligence (Raven's Progressive Matrices) found that cannabis users and nonusers did not differ significantly (Varma, Malhotra, Dang, Das et al. 1998).

As with studies in ecstasy users, there appear to be few differences between cannabis users and nonusers in terms of intellectual functioning, indeed no studies reviewed above found that cannabis users and nonusers performed differentially, and none found dosage effects.

5.1.2 Attention/Concentration

Although there is evidence that cannabis use may be associated with deficits in attention/concentration, the studies outlined below reveal that this may be related to recent cannabis use, rather than being a long-term consequence of using the drug.

Pope, Jacobs, Mialet, Yurgelun-Todd et al. (1997) used a divided attention letter detection task requiring participants to monitor a 9 x 9 matrix and when one letter changed to an asterisk for 250 ms, they had to indicate which one it was (the target was either at the centre or the periphery of the display). The 25 heavy users (smoking a median average of 29 days in the last 30) and 30 light users (smoking a median of 1 day in the last 30) did not differ significantly on this task. Nicholson, Turner, Stone and Robson (2004) used a letter vigilance task to assess the differential effects of placebo, THC, or a mixture of THC and cannabidiol (another cannabinoid contained in marijuana that is not believed to contribute to its psychoactive properties). Eight participants took part in this cross-over design completing 3 separate sessions of testing after being administered 15mg THC, a combination of THC/cannabidiol, or placebo. Participants had to press a key when two letters in a random sequence on the screen matched the critical stimulus at the top. No performance differences were observed between the three groups. Using a test battery incorporating tests of visual scanning (participants have to indicate the presence or absence of a "O" shaped stimulus in a 100 x 100 matrix), tonic alertness (responding to a tone), phasic alertness (enhancing attention by expecting a tone) and divided

attention (dual-task in which participants have to divide their attention between visual stimuli and tones), one study found that cannabis users performed worse than nonusers on the phasic alertness, visual scanning and divided attention tasks. In addition, on the visual scanning task cannabis users with an early age of onset performed significantly worse than late onset users. Early age of onset was also the only significant predictor of performance, not THC urinary metabolites or cannabis use variables (Ehrenreich et al. 1999).

Kurzthaler et al. (1999) used a digit cancellation task requiring participants to go through a list of numbers and cancel every eighth zero, then every eighth one, etc. While performance at baseline and on day three of the study was comparable, those given 200 μg/kg of body weight of THC in a cigarette performed significantly worse than those who were not given it on day two, suggesting an on-drug impairment. In another study utilising a crossover design and using single (participants are presented with 400 numbers on a piece of paper and have to cross out all the "4"s as quickly as possible) and double (same as before, but with numbers "2" and "6") digit cancellation, participants were administered placebo, 7.5mg THC or 15mg THC on separate occasions. On single digit cancellation, there were no differences in time taken to complete the task, but errors showed a main effect of drug administration and time of testing (in days), although the interaction was non-significant. On the double digit cancellation task, the time taken to complete the task approached significance, with the drug group (i.e. on occasions participants were administered 7.5 or 15mg of THC) performing worse, and there was a main effect of drug administration on errors, as errors were increased by both doses of THC (Curran, Brignell, Fletcher, Middleton et al. 2002). D'Souza, Perry, MacDougall, Ammerman et al. (2004) used a Continuous Performance Task (CPT) requiring participants to attend to sequentially

presented numbers and push a key if a number one was preceded by a number nine, and a "distractibility" task, which was the same as the CPT except that the numbers were in three columns and participants were told to attend to the middle column only. All 22 participants (modal cannabis use of less than 5 times and 1-6 months of abstinence) performed 3 separate trials under placebo, 2.5 mg or 5 mg of THC. THC had no effect on omission or commission errors in the CPT task although there was a trend towards significance on response latencies. On the distractibility task, there were dose effects of THC on omission errors and latencies with larger doses giving rise to more errors. Finally, Curran et al. (2002) used the Rapid Visual Information Processing Task (RVIP- previously described in Chapter 3, section 3.4), and although differences between the THC trial and placebo trial were non-significant, there was a trend towards a main effect of drug administration.

A further study (Solowij et al. 2002) used the Paced Auditory Serial Addition Task (PASAT) to assess sustained attention. In this task, 61 random digits are presented sequentially on an audiotape, and participants have to add the last presented digit to the preceding number and say the answer aloud before moving on to the next digit. Long-term cannabis users were significantly slower than short-term users on trial one, and there were trends towards a significant effect on trial 2 and the sum of all trials. This was however reduced to below statistical significance following the removal of those with THC metabolites in their urine indicating that perhaps recency of cannabis use is a more important contributor to cognitive deficits than having ever used cannabis.

While it appears from some of the studies above that cannabis impairs cognitive functioning, this may due to the residual post-intoxication neuropsychological effects of the drug. Only one retrospective study (Ehrenreich et al.

1999) found a clear cannabis related effect with cannabis users performing worse than nonusers, while all those involving administration of THC found a significant effect of drug administration, or a trend towards a significant effect. To further support this, another study found that significant drug effects were reduced to below statistical significance following the removal of those with THC metabolites in their urine (Solowij et al. 2002).

5.1.3 Recall

As with ecstasy use, recall seems to be one area of cognition that does reveal cannabis-related deficits. Solowij et al. (2002) used the RAVLT immediate and delayed recall components (previously described in Chapter 3, section 3.6) and found that long-term heavy cannabis users, short-term users and controls did not differ significantly on immediate recall. The nonusers and short-term users did however perform significantly better than the long-term users on the delayed recall of words. The effects on delayed recall were reduced to below statistical significance following the removal of those participants with THC metabolites in their urine, although the heavy cannabis user group still performed significantly worse on the RAVLT total score. Nicholson et al. (2004) used immediate and delayed word recall tasks in which participants were required to recall a list of 16 words after 45 seconds, and after 76 minutes. On immediate recall, 15mg of THC impaired performance (recalling fewer words) compared to placebo. On delayed recall, 15mg of THC impaired performance compared to placebo and a 5mg dose of THC and cannabidiol, suggesting an on-drug dose related effect. D'Souza et al. (2004) used a similar word learning test with three trials (the first immediate recall, the 2nd and 3rd learning trials) of recall of a 12-item semantically categorised list, and 30 minutes later a delayed and cued recall trial.

THC administration significantly impaired immediate recall in a dose dependent manner across the three trials. THC also impaired delayed recall and cued recall in a dose related fashion. Another study also used a word recall test (the Buschke Selective Reminding Test) with similar trials to that of D'Souza et al. Immediate recall showed that there was a drug x trial interaction which reflected a lack of learning over trials under the higher dose of THC. In delayed recall, there were main effects of drug and time, although the interaction between the two only approached significance. There were dose dependent impairments by THC which were most marked at 2 hours (Curran et al. 2002).

Two studies also assessed Prose Recall in cannabis users. Schwartz (1991) used the prose recall test of the WMS in daily cannabis users, light users and nonusers. At the initial testing session immediate recall of the material was impaired in daily cannabis users relative to controls, and although slightly attenuated at 6-week retest, this remained significant. Curran et al. (2002) used a prose recall news story which participants had to recall immediately and after a 45-minute delay. On immediate recall there was a significant drug x time interaction, with the higher dose trial performing worse than the lower dose trial and placebo trial. For delayed recall the interaction between dose and time only approached significance, again with participants performing worse after administration of the higher doses than the lower doses and placebo.

One study (Varma et al. 1988) assessed visual recall using the Bender Visual-Motor Gestalt Test (BVMG) in which each participant is required to reproduce 9 designs on a piece of paper, and the Nahor-Benson Test (NBT) which again requires the reproduction of designs. No significant differences were observed between cannabis users and nonusers on the BVMG, but the cannabis users did give

significantly more errors on the NBT. Finally, Millsap et al. (1994) used the WMS delayed recall component (specific tests unspecified) to test 15 cannabis-dependent adolescents (using a mean average of 9 grams/week for and average of 29 months). The scores for full-scale IQ and delayed recall were standardised and the full-scale IQ score was significantly higher than the delayed recall score, although no between group comparisons were made.

To summarise, like research in ecstasy use, this seems to be one area in which cannabis users are impaired. Moreover deficits appear to be dose-related in all clinical studies (Curran et al. 2002; D'Souza et al. 2004; Nicholson et al. 2004), although may dissipate somewhat after prolonged abstinence (Schwartz et al. 1991; Solowij et al. 2002).

5.1.4 Executive functions

5.1.4.1 Access to Semantic Memory

One particular focus of this thesis is access to semantic memory. It is therefore particularly interesting to see if cannabis users exhibit impairments in this area. Two studies have assessed the effects of THC administration on access to semantic memory. D'Souza et al. (2004) used a category fluency task similar to the COWA (Chapter 3, section 3.3.2) requiring participants to generate as many words as possible in one minute, beginning with a specific letter. Administration of THC had no significant dose related effects on the number of words generated in a minute. There was however a trend towards significance for the number of perseverative errors given, which has been linked to deficits in mental set switching (e.g. Miyake et al. 2000). In another study, Curran et al. (2002) used a crossover design in which 15 males with some cannabis experience (although not regular users) took part in 3 sessions, one week apart on which they were administered either placebo, 7.5mg of

THC, or 15mg of THC. The test required participants to give as many words as possible beginning with a certain letter in one minute. There was a significant drug x time interaction and a main effect of time indicating that THC actually enhanced performance, especially at 6 hours after administration when the higher dose THC group gave significantly more words than the low dose group.

To sum up, results in this area are equivocal with one study finding no effect of THC administration, and another finding that THC administration actually enhanced performance. Thus it is possible that in this thesis, cannabis use in the sample as a whole may have some mediating effect of performance on access tasks, and this will therefore be investigated statistically.

5.1.4.2 Inhibition

Skosnik, Spatz-Glenn and Park (2001) used a negative priming task to assess attentional inhibition in current cannabis users (average use of 1.3 times/week, at least 48 hours abstinence), previous users (having used at least once in their lifetime, but not in the last 45 days) and controls. In this visuospatial task, pairs of prime and probe displays were presented on a computer screen. First a prime is presented in which the target stimulus ("O") must be located, and a distractor ("+") ignored. After this, the target is presented at the previously ignored position, and an increase in reaction time while participants ignore the previously relevant position is expected. Accuracy was non-significantly different between the groups, with all groups getting nearly 100% correct. Current cannabis users did however get a more positive negative-priming score, indicating disinhibition or absence of negative priming, while previous users and controls showed normal negative priming. Correlations between negative priming and the amount of cannabis consumed in a week was non-significant. Current cannabis users were also faster than controls and previous users on the task, but again

correlations with the amount of cannabis consumed in a week were non-significant. The other two studies that assessed inhibition in cannabis users used the Stroop task. Solowij et al. (2002) used the Stroop interference task (requiring participants to read a colour word, rather than say the colour of that word- colour read) and a more cognitively demanding modification of this task in which naming of the items depends on a special visual cue given with each item (colour word). There were significant within group differences with the short-term and long-term cannabis users performing more poorly on the colour-read than colour-word condition (perhaps due to increased inhibition resources), although there were no differences between users and nonusers. Duration of cannabis use was also negatively related to the number of items completed on the CR and CW conditions. All of the significant results on the Stroop test in this study were however reduced to below statistical significance following the removal of those with urinary THC metabolites, suggesting that performance may be more related to recency of cannabis use, rather than cumulative use or duration of use. Finally, Pope et al. (1997) used the Stroop different colour (analogous to the colour read condition) and opposite colour (where participants are instructed to say a certain response for each colour e.g. say "red" for "green) conditions. Differences between the groups were non-significant, although heavy users were slightly slower than light users.

While in general response inhibition does not appear to be affected by cannabis use, it is possible that deficits are related to recent cannabis use (Solowij et al. 2002). Inhibition is also a particular focus of this thesis so it may be that if cognitive deficits are observed in ecstasy users, that these are genuinely an ecstasy-related effect and not related to cannabis.

5.1.4.3 Reasoning/Decision Making

Like inhibition and access, reasoning is a particular focus of this thesis. Whitlow et al. (2004) used a computerised card gambling task where decks A and B have higher monetary gains but also higher losses, while decks C and D have smaller monetary gains but also smaller losses, and are therefore the more advantageous pack. Participants were instructed to win as much money as possible, and told that the person who won the most money would receive a $50 reward. The net score was significantly lower for long-term heavy cannabis users than controls. There was also a significant interaction between group and block that indicated that while nonusers had started to choose more cards from the advantageous pack on successive blocks, the cannabis users continued with the disadvantageous pack. Thus cannabis users sought greater monetary gains while ignoring the losses. Curran et al. (2002) used the Baddeley reasoning task in which participants have to verify a series of statements on a computer, for example "A does not precede B...BA" by pressing true or false. There was a trend towards a THC effect on response times with both 7.5mg and 15mg doses increasing response times compared to placebo at 1hr after administration, although the effects on errors were non-significant. Taken together, the results of these studies suggest that the use of cannabis may impair rational thinking. In one study the results were found one hour after THC administration (and were non-significant) so this should be treated with some caution (Curran et al. 2002). Whitlow et al. did find that long-term heavy cannabis users exhibited impaired reasoning. Consequently, as with access and inhibition it is necessary to control for the use of cannabis.

5.1.4.4 Updating

Again, updating is a particular focus of this thesis so it is important to review evidence of cannabis-related decrements in memory updating. Ehrenreich et al. (1999) used a task similar to the 1-back task (Chapter 3, section 3.3.5) in which a participant

has to press a key when the previous digit is the same as the one presented. There were no significant differences between early and late onset cannabis users and controls. In addition, performance on this task was not predicted by THC metabolites in the urine indicating that recency of cannabis use is not an important factor in memory updating deficits. Using a similar task (the digit memory recall task) requiring participants to state if a presented digit was the same or different from the preceding digit, there were no performance differences between those administered THC, placebo or a combination of THC/cannabidiol in terms of errors. The group that was administered THC/cannabidiol were however significantly slower than the placebo group on the day after administration (Nicholson et al. 2004). Solowij et al. (2002) used the Auditory Consonant Trigrams test, in which 3 consonants are presented and participants have to recall these after intervals of 0- 9- 18- and 36-seconds. During the 9- 18- and 36-second gaps participants were required to count aloud backwards in "3"s from a specified number, as a distraction task. Long-term users recalled significantly fewer consonants than short-term users, controls and published norms on this task, although performance was not significantly correlated with length of cannabis use. After removal of those participants with THC metabolites in their urine, this was only significant for the 9-second delay. Curran et al. (2002) used the Subtracting Serial Sevens (Chapter 3, section 3.3.5), however neither reaction time nor errors committed showed an effect of THC administration.

The lack of cannabis-related deficits in tests that assess memory updating may indicate that if ecstasy-related decrements are observed in memory updating in this thesis, then they reflect the use of ecstasy, rather than the use of cannabis (although an interaction effect cannot be ruled out).

5.1.4.5 Switching

Switching has also been assessed in cannabis users via methods similar to those used in this thesis. Using a task similar to that used in this thesis (the number/letter task) that required participants to switch between attending to two opposing stimuli (numbers/letters) on the left and right hand side of the screen, there were no observed group differences between early onset users, late onset users and controls. In addition, performance was not correlated with the presence of urinary THC metabolites suggesting that although the abstinence period was relatively short, recent cannabis use was not a predictor of performance (Ehrenreich et al. 1999). Kurzthaler et al. (1999) used the Trail Making Test-B (previously described in Chapter 3, section 3.3.1) and found that THC administration did not impair performance. However, the THC group did not improve from day 1-2 of the study (immediately after THC administration) while the controls did. The THC group only improved from day 2-3 suggesting that while under the immediate influence of THC, they were not capable of learning from their experience.

Solowij et al. (2002) used the Wisconsin Card Sort Task (WCST- previously described in Chapter 3, section 3.3.1) and the alphabet task (the nature of the switch part of this task is unspecified in the paper) to assess switching in long-term cannabis users, short-term users and controls. On the WCST, no significant differences were observed on any of the dimensions, but there was a trend towards significance in maintaining mental set: with long-term users failing to maintain set more often than short-term users and controls. Correlations between length of use and performance were however non-significant so this should be treated with caution. On the alphabet task, the time taken to complete the alternating condition of the task increased with increasing duration of use, as did the times taken on alternating and difference trials (which the authors state is an indication of interference and a lack of cognitive

flexibility). This was however reduced to below statistical significance following removal of those with THC metabolites in their urine, suggesting that it may be more related to recent cannabis use. Whitlow et al. (2004) used the CANTAB intra- and extra-dimensional shift task (previously described in Chapter 3, section 3.3.1), and found a trend towards a cannabis effect with users giving more errors than nonusers.

Again, it appears that cannabis use does not impair performance on switching tasks, with most studies finding non-significant effects, or a trend towards a cannabis effect. The only study that did find that cannabis users were impaired in switching was reduced to below statistical significance following control for those with THC metabolites in their urine, indicating that recency of cannabis use is an important factor.

5.1.5 Psychomotor Speed

To assess psychomotor speed, Varma et al. (1988) used the pencil-tapping test (a participant has to tap a pencil on a piece of paper as quickly as possible for 30-seconds). The mean number of taps was significantly lower for cannabis users than for nonusers indicating decreased psychomotor speed. Using the Gibson Spiral Maze Task (place a pencil on the arrow in the centre of a maze and then find the way out without touching the sides or circles around the maze) another study found that there was a main effect of time after administration of THC, and a significant drug x time interaction indicating that those who were administered 7.5mg and 15mg of THC were faster than nonusers. This was however at the cost of accuracy: a significant main effect of drug was observed with more errors being given under THC administration than placebo (Curran et al. 2002).

5.1.6 Reaction Time

Some studies used tests to assess simple and choice reaction time. Varma et al. (1988) used a task which required participants to listen to 20 words read out by the experimenter, repeat them as quickly as possible (one by one) and say what ideas came to mind. On this task, cannabis users were significantly slower than nonusers although it was not clear if this was due to the cannabis users being slower at the repeating of the word, or if they were perhaps slower at thinking of the related word. Whitlow et al. (2004) also found no differences between the groups on the CANTAB reaction time task. In Curran et al's (2002) study, a simple RT task requiring participants to press a key as soon as a target symbol appeared on the screen was used. There were trends towards significant effects of drug, time of administration and significant drug x time interactions with the higher dosage sessions reaction times, compared to placebo administration.

Three studies also used choice reaction time tasks. In one study, the task used required participants to press a key in response to one of three letters (A, Z, E) on a screen. "A" and "Z" appeared alternately on the left and right sides of the screen, and occasionally they were replaced by "E" (which participants were required to respond to). Differences between heavy (N = 25; smoked a median of 29 days in the last 30) and light (N = 30; smoked a median of 1 day in the last 30) users were non-significant although the mean scores showed that heavy users were faster than light users, but also made more errors (Pope et al. 1997). In Nicholson et al's (2004) study, participants had to press keys corresponding to the positions of asterisks on the screen. The performance of the eight participants in this crossover design did not differ under administration of 15mg THC, a combination of THC/cannabidiol, or placebo. Finally, Curran et al. (2002) used a task requiring participants to respond to 4 targets (ABCD) presented at different response-stimulus intervals, by pressing the

corresponding key as quickly as possible. There were no effects of drug administration on reaction time. There was however a significant main effect of drug on errors due to 15mg of THC increasing errors (at 1 hour after administration), and 7.5mg increasing errors (at 2 and 8 hours after administration).

Only one retrospective study found that cannabis users were slower than nonusers (Varma et al. 1998) although it is not clear if the task used is solely a simple RT task. Most studies found that THC administration had no effect on reaction time, although it may increase the number of errors given (e.g. Curran et al. 2002). One study suggests that while under the influence of cannabis, users may sacrifice accuracy in favour of speed (Pope et al. 1997).

5.1.7 Visuo-Spatial Working Memory

Pope et al. (1997) used the Checkerboard test in which a 6 x 6 matrix with randomly distributed shaded squares is presented on a computer screen, after which participants have to indicate which squares were shaded (ranges from 2-11 squares). The differences between light and heavy cannabis users approached significance for the total number correct, span length and number of errors. When the groups were further split by gender a highly significant effect emerged with heavy female users performing significantly worse than light female users, although light and heavy using men performed comparably. Schwartz (1991) used the Benton Visual Retention Test (Chapter 3, section 3.10.3), in which daily cannabis users performed significantly worse than light users and controls at the initial testing session, and following six weeks abstinence, providing some support that the cognitive deficits do persist. In another unspecified spatial working memory task, the same study found that daily cannabis users did not perform worse than nonusers.

Skosnik et al. (2001) used a task requiring participants to remember the location of a black dot on the circumference of an imaginary circle, and after presentation, they had to perform a verbal distractor task then touch the point where they believed the original target had been. There were no significant differences between current cannabis users, previous users and controls.

One study used fMRI during a task in which participants focused on a cross at the centre of a screen that was surrounded by three dots. The dots disappeared then after a 3-second delay a circle appeared and participants had to press a key once or twice to indicate if it marked the place where a dot had previously been. The 12 cannabis users and controls both demonstrated activation in certain brain areas (bilateral middle frontal gyrus, bilateral inferior frontal gyrus, right anterior cingulate). The activation in cannabis users was stronger than in nonusers, and cannabis users also activated other areas of the brain (3 areas of the lentiform nucleus, and 1 of the superior frontal gyrus), although correlations between activation and THC metabolites and lifetime cannabis were non-significant. Performance was not significantly different between the groups, which the authors suggest may represent a ceiling effect due to task simplicity, while they suggest that increases in activation in cannabis users may reflect attentional dysfunction (Kanayama et al. 2004).

In a study using a crossover design, with all 22 participants performing 3 separate trials under placebo, 2.5 mg or 5 mg of THC, the delayed match-to-sample task required participants to select 5 previously presented shapes from an array of 20 (easy and difficult trials were implemented depending on stimulus complexity). Administration of both doses of THC significantly decreased the number of correct responses in the easy subtest without affecting reaction time. In the hard subtest, there

was no effect of THC administration on errors, but there was a trend towards a THC effect on reaction times (D'Souza et al. 2004).

While it appears that cannabis use does not impair performance on some easier visuo-spatial memory tasks (Kanayama et al. 2004; Skosnik et al. 2001) the severity of use may be important. Two studies found that heavy use of cannabis causes deficits in visuo-spatial working memory (Pope et al. 1997; Schwartz et al. 1991), with the former finding that this effect was particularly evident in female heavy users but not male users.

5.1.8 Verbal Learning

As with studies in ecstasy users, recall seems to show cannabis-related effects. One study using the RAVLT found that long-term cannabis users performed worse overall than short-term users and nonusers. In addition, the percentage of participants with very poor learning ability (less than 3 words acquisition over 5 trials) was significantly greater among long-term users (13.7 %) than controls (0 %), but not short-term users (5.9 %). The long-term users also recalled less than 10 words on trial 5 compared to 8.5% of short-term users, and 3 % of controls. The differences in RAVLT total remained significant after removal of those with urinary THC metabolites (Solowij et al. 2002). In another study using a test similar to the RAVLT, THC administration had no effects on learning over three trials (D'Souza et al. 2004).

5.1.9 Information Processing Speed

In Varma et al's (1988) study, cannabis users committed significantly more errors on the TMT-A (Chapter 3, section 3.2), although two other studies using the Stroop-A task found no differences in reaction times between users and nonusers (Pope et al. 1997; Solowij et al. 2002). Solowij et al. (2002) used the Speed of Comprehension Test (Chapter 3, section 3.2) and found that cannabis users did not

differ significantly from controls in the number of items completed, but both short-term and long-term users did make more errors than controls (although they did not differ from each other). Nicholson et al. (2004) used the Digit Symbol Substitution Test (DSST, Chapter 3, section 3.2) and the Multiattribute Task (MAT) Battery, which contains four tasks that airline crew would be expected to perform (system monitoring, tracking, communications, fuel management). It was not reported in the paper if there were differences between administration of THC, THC/Cannabidiol or placebo on the MAT battery, and there were no significant differences in the number of substitutions made on the DSST.

5.1.10 Recognition

Kurzthaler et al. (1999) used the Benton Multiple Choice Form G in which participants have to recognise a previously presented stimulus from a choice of 15. There were no significant differences between the groups at baseline, after THC administration (day 2 of the study), or on day three of the study. Another study using the CANTAB pattern recognition task found that there were no performance differences between heavy long-term cannabis users and controls (Whitlow et al. 2004). Another study found no significant effects of administration of THC, placebo or THC/cannabidiol on a letter recognition task requiring participants to pick out previously presented letters from a random string (Nicholson et al. 2004). Similarly, D'Souza et al. (2004) found only a trend towards an effect of THC administration on the number of words recognised, false positive responses, and intrusions on a word recognition test (from the Hopkins Verbal Learning Battery). Using another word recognition task (the recognition of lists A and B from the RAVLT), Solowij et al. (2002) found that overall long-term cannabis users recognised fewer words from list A (the original list) and list B (the interference list), although long-term and short-

term users did not differ. Significantly more long-term users had recognised less than 12 words for list A, and also mis-assigned more words than short-term users and controls. All significant results in this case remained significant after the removal of those with THC metabolites in their urine. The same study also used the omitted numbers task in which participants have to recognise numbers omitted from a previously presented list. No significant differences were observed between short-term cannabis users, long-term users or controls in terms of recognition, and performance was not significantly correlated with cannabis use variables (this also remained non-significant after the removal of those with urinary THC metabolites).

To summarise, cannabis has been associated with mild decrements in a number of areas of cognition. However, unlike the studies in ecstasy users reported in Chapter 3, it appears that in cannabis users these decrements are more related to recent use. The next section reviews a number of studies examining aspects of cognition in cocaine users, as it is also possible that the use of cocaine may contribute to deficits observed in the ecstasy-users in this thesis.

5.2 Cocaine

Also a naturally occurring substance, cocaine has been used culturally for centuries. The use of cocaine among recreational drug users in the UK has risen in recent years (British Crime Survey 04-05) and like ecstasy, cocaine use has been associated with deficits in some areas of cognition.

5.2.1 Intelligence

Two studies in cocaine users have used the WAIS-R scale to assess intelligence. Gillen, Kranzler, Bauer, Burleson et al. (1998) used the verbal intellectual scale, performance IQ scale and full-scale IQ scale of this battery. On the verbal intellectual scale controls had significantly higher scores overall than the

cocaine users, due to them having significantly higher scores on the "information" and "vocabulary" subtests. In the same study, the controls also scored significantly higher on a visual intellectual measure, incorporating scores from a number of tests. Goldstein, Leskovjan, Hoff, Hitzemann at al. (2004) used the WAIS-R information and vocabulary subscales, Raven's Progressive Matrices, the Wide Range Achievement Test-Revised (WRAT-R), and the Woodcock-Johnson word attack test to assess IQ. Between group comparisons were not made for the separate tests although on an overall measure of verbal knowledge, the cocaine users were worse than the nonusers (on standardised scores). Other studies used different tests including the Shipley IQ scale (where the 12 cocaine abusers had significantly lower IQ scores than the 14 controls, although IQ was not a significant predictor of performance on a gambling task (see below), Stout, Busemeyer, Lin, Grant et al. 2004), and the New Adult Reading Test-Revised (where cocaine dependent participants who had been using for a minimum of six months did not differ significantly from controls, Berry, van Gorp, Herzberg, Hinkin et al. 1993). Finally, one study used the Barona IQ scale and the Shipley Institute for Living Scale (SILS) vocabulary and estimated IQ scales. The cocaine dependent participants had lower IQs than the alcoholic group and control group (Beatty, Katzung, Moreland and Nixon, 1995).

Unlike ecstasy and cannabis use, it appears that cocaine users perform worse on tests assessing IQ. It is unclear whether this reflects a difference in the sample that may pre-date drug use or a cocaine-related decrement. It is noteworthy that most studies in this area assess those presenting at clinics for treatment rather than recreational users (as with ecstasy and cannabis studies), thus those using cocaine in the studies reported in this section are likely to be chronic heavy users.

5.2.2 Attention/Concentration

To assess concentration, Berry et al. (1993) used the Paced Auditory Serial Addition Task (PASAT, previously described in section 4.1.2). Cocaine users were significantly worse at session one, but not session two, after a longer period of abstinence, although the group by trial interaction approached significance suggesting that the cocaine users did not improve to the same extent as the nonusers. On a combined deficit score for the PASAT and the WMS-III number-letter sequencing task (requiring the re-ordering of a sequence of numbers/letters to alphabetical and numerical order), cocaine users who did not use cannabis performed similarly to those who did and controls (Gonzalez, Rippeth, Carey, Heaton et al. 2004).

Two studies used the WAIS-R digit span and arithmetic subtests to assess attention. On one there was no difference between cocaine users and controls (Gillen et al. 1998). In the other study, the 42 cocaine and/or crack dependent participants (who had been dependent for at least two years, with 2 months of abstinence) performed significantly worse than controls on both tasks. Performance on the arithmetic subtest was predicted by the "drug problems" scale of the Personality Assessment Inventory (Rosselli et al. 2001). Beatty et al. (1995) found no significant performance differences between cocaine users and controls on the Distractibility Test from the Gordon Diagnostic Battery (requiring the detection of 2 target numbers in a sequence, presented against a background of other numbers). Similarly, cocaine users did not perform significantly worse on an "attention/executive" scale incorporating the WMS digit span task, and a letter cancellation task (Goldstein et al. 2004).

Cocaine use does therefore not appear to be degrading to the attentional system in the studies reviewed above (although this may be because some of these tasks are not reliant on attentional processes only).

5.2.3 Recall

A number of studies used the CVLT (see Chapter 3, section 3.6). In one study, cocaine users performed significantly worse than controls on the immediate and delayed recall scales, and performance on immediate recall was predicted by the "drug problems" scale of the Personality Assessment Inventory (Roselli, Ardila, Lubomski, Murray et al. 2001). Butler & Frank (2000) also found that on a combined measure of verbal recall, cocaine users performed worse than nonusers at an initial testing session, although this had improved significantly after one month of abstinence. However, Gillen et al. (1998) did not find any significant differences between cocaine users and nonusers on immediate and delayed recall. On a total score for the Arizona Battery for Communicative Disorders of Dementia (ABCD) incorporating a prose recall task, cocaine users were significantly worse than norms at one weeks abstinence, but after one month performance had significantly improved, although between group comparisons were not performed on separate subtests (Butler & Frank, 2000). Another study assessing prose recall found that cocaine users and alcoholics performed worse on immediate and delayed recall, and the cocaine users were also worse than the alcoholics on the delayed component. Performance also appeared to be related to amount of cocaine used: the Quantity of Cocaine Index was significantly negatively correlated with immediate recall of stories (Beatty et al. 1995).

Two studies specifically tested nonverbal recall: one found a trend towards a cocaine effect on the Rey-Osterrieth delayed recall at session 1, but the cocaine users were significantly worse at session 2, although the group by trial interaction was non-significant (Berry et al. 1993). Beatty et al. (1995) used the WMS-Figures subscale, but no differences were observed between controls, alcoholics and cocaine users on immediate and delayed recall. Two studies also used a range of recall tests and

analysed results as a whole. Goldstein et al. (2004) used the CVLT, WMS immediate and delayed recall, and the WMS visual reproduction immediate and delayed recall tasks. No separate analyses were performed for these tasks, but the cocaine users did not perform significantly worse on the "verbal memory" scale incorporating these measures. Gonzalez et al. (2004) used the HVLT-R delayed recall component (a word learning test similar to the CVLT and RAVLT), the BVMT-R delayed recall test, the story memory test, and the figure memory test. Those cocaine users who did not smoke cannabis performed significantly worse than controls on a total score for these measures (while those who did use cannabis did not differ significantly from controls).

Again, studies assessing recall in cocaine users yield mixed results. It may be that recent use of cocaine, like cannabis is an important contributor to deficits in recall as some studies found that performance improved after abstinence (e.g. Butler & Frank, 2000). It may also be that severity of cocaine use is important as heavy cocaine use produced worse deficits in some studies (e.g. Beatty et al. 1995).

5.2.4 Executive functions

5.2.4.1 Access to Semantic Memory

As with cannabis and ecstasy use most studies use the COWA task to assess access to semantic memory. Only one of the reviewed studies found that cocaine users performed worse than nonusers on this task (Gillen et al. 1998). In this study, the 19 cocaine dependent participants (using an average of 10.6 days and 15.8g in the last 30 days; an average of 6.3 years of use; 68.4% using freebase; average abstinence period of 181.7 hours) gave significantly fewer words than the 16 non-cocaine using controls. However, Butler & Frank (2000) and Berry et al. (1993) did not report significant differences on this task, and another study reported that cocaine users did

not perform worse on a "language" scale incorporating this task (Goldstein et al. 2004). Two studies used the COWA and a category fluency task (having to say as many types of animals as you can in one minute), with one finding no significant differences between cocaine users and nonusers (Rosselli et al. 2001). The other aimed to assess the possible neuroprotective properties of cannabis in chronic cocaine use. The 26 cocaine users who were only light cannabis users (median 2784g of cocaine in lifetime, 608 joints in lifetime) did not perform worse than the 27 heavier cannabis users (median 3462g of cocaine in lifetime, 3614 joints in lifetime) or the 41-nonuser controls (Gonzalez et al. 2004).

Three studies used the Boston Naming Test (BNT), or similar tasks requiring participants to match words to their pictorial representations. Gillen et al. (2001) found that there were no significant differences between the groups on this task, and Butler and Frank (2000) found that the cocaine only users did not perform worse than norms following one week or one month of abstinence on the Peabody Picture Vocabulary Test. Goldstein et al. (2004) did however find that cocaine users performed worse than nonusers on a "verbal knowledge" scale incorporating the BNT. Lastly, one study used the ABCD subtests for linguistic expression (comprising of tests of object description, generative naming, confrontational naming, and concept definition). The cocaine only users performed significantly worse than norms at one week of abstinence, although this improved significantly after one month of abstinence.

Access to semantic memory is a particular focus of this thesis. From the studies above, it is likely that neither cannabis or cocaine cause deficits in access. Indeed the only cocaine study that found cocaine users recalled fewer words on the COWA used a sample consisting of 68.4% free-base (crack cocaine) using

participants. As with recall it may be that heavier use is associated with greater functional deficits.

5.2.4.2 Inhibition

Three studies used the Stroop task. One found no differences between cocaine users and nonusers following one week and one month of abstinence (Berry et al. 1993), while another found that cocaine users did not perform worse on an "Attention/executive" scale incorporating this task (Goldstein et al. 2004). Rosselli et al. (2001) did however find that cocaine users were worse than nonusers on the colour word score of this task. Performance on the Stroop task in this study was predicted by the "drug problems" and "antisocial features" scales of the Personality Assessment Inventory (PAI).

5.2.4.3 Reasoning/Decision Making

Stout et al. (2004) used the Iowa gambling task described previously in the section on cannabis use (Chapter 5, section 5.1.7) to assess decision-making performance among cocaine users. While the control group gradually learned to choose from the advantageous deck, the cocaine group (reporting regular cocaine abuse and the use of other drugs- no values given) chose nearly equally from both packs and selected significantly fewer advantageous cards. This remained significant after control for age and IQ. Using Cognitive Modelling Analysis it was found that decision-making in cocaine users was less responsive to losses (as participants were offered a monetary reward, this may suggest that motivation processes are a possible source of decision-making differences in cocaine users). Cocaine users also responded more randomly with choices less likely to lead to payouts suggesting that the response process was also a source of differences. Learning and memory processes did not however distinguish the groups. Gillen et al. (1998) used the Porteus Maze Task, a

motor task that assesses foresight and planning ability, although no differences were observed between controls and cocaine users. Another study using the Conceptual Levels Analogy Task found that both cocaine users and alcoholics performed worse than controls (Beatty et al. 1993). One study assessed performance in 6 cocaine-only users (mean duration of usage 5.83 years) on the RIPA problem solving and abstract reasoning task and organisation and general knowledge task. On the problem solving and abstract reasoning task, the cocaine users did not perform worse than published norms after one week or one month of abstinence, nor did their scores at one week and one month differ significantly from each other. On the organisation and general knowledge test, the cocaine users were significantly worse than published norms following one week of abstinence; this had significantly improved after one month of abstinence, suggesting that differences at one week may be related to residual cocaine intoxication (Butler & Frank, 2000). Finally one study used the WAIS-R similarities subscale, which has been used in other papers as a measure of analogical reasoning (e.g. Verdejo-Garcia et al. 2005). No separate analysis was performed on this subscale, although the cocaine group did perform significantly worse on an overall scale for verbal knowledge which incorporated this measure (Goldstein et al. 2004).

5.2.4.4 Switching

Most tests in this area have used the TMT-B and the WCST (both described in Chapter 3, section 3.3.1), although one used the Halstead Category test (a test with similar principles to sorting tests such as the WCST). Beatty et al. (1995) found that cocaine users performed worse on the TMT-B than controls, and another study found that a cocaine-using group took significantly longer than controls, and performance was not predicted by PAI scores (Rosselli et al. 2001). Berry et al. (1993) used the TMT-B and found a significant main effect of group with the cocaine users

performing worse than the nonusers at the second session of testing (after 2 weeks abstinence), although the group by time interaction was non-significant indicating that abstinence was not an important factor in cocaine-related switching deficits. Another study using this test and the Halstead Category Test found that the cocaine-dependent group (without concomitant use of cannabis) did not perform worse on a "deficit score" for executive function incorporating these tests, (although the cocaine users were worse on a total measure of all tasks; Gonzalez et al. 2004). Similarly, again using this test both Gillen et al. (1998) and Goldstein et al. (2004) found no significant differences between cocaine users and controls. Cocaine users performed worse than controls on the WCST in both Rosselli et al's study (by giving more errors and correctly classifying fewer categories) and Beatty et al's study (where both alcoholics and cocaine users gave more perseverative responses and errors than controls). By way of contrast, Gillen et al. (1998) and Goldstein et al. (2004) did not observe cocaine-related deficits on these tasks.

5.2.5 Visuo-Spatial Working Memory

Three studies used the WAIS-R block design subtest. One finding a significant main effect of cocaine use at an initial testing session and after a month of abstinence, although the group by time interaction was non-significant indicating that although the cocaine users had improved over the month, they were still impaired relative to controls (Berry et al. 1993). Another study also observed deficits on this task, with the 23 cocaine users (average dose of 3 g/week, and using for an average of 7.1 years) performing worse than controls (Beatty et al. 1995). However, the third study found no differences between cocaine users and controls on this task (Gillen et al. 1998). Using a different visuospatial construction task requiring generative drawing and figure copying (from the ABCD), Butler and Frank (2000) found that the

6 cocaine only users did not perform worse than norms at one week, or after one month of abstinence. In two studies using spatial orientation tasks, one a line orientation task (Gillen et al. 1998) and the other a temporal orientation, spatial orientation and orientation to environment test, no significant differences were observed between cocaine users and controls/published norms in either study (in the latter deficits were not apparent at 1 week or 1 month following abstinence).

Two studies used the Rey Osterrieth Complex Figure copy test with both finding that cocaine users performed worse than nonusers (Berry et al. 1993; Rosselli et al. 2001). Two studies also used the Benton Visual Retention Test. Roselli et al. (2001) found that cocaine users performed worse than nonusers on this task and performance was predicted by the "drug problems scale of the Personality Assessment Inventory; but on a "visual memory" scale incorporating this task Goldstein et al. (2004) did not find any cocaine-related differences in the number correct and number of errors. Another study used the Brief Visuospatial Memory Test-Revised and the Figure Memory Test. Separate analyses of these two tests was not performed, but the methamphetamine dependent participants who did not use cannabis performed significantly worse on this measure (Gonzalez et al. 2004). Finally Roselli et al. (2001) found that cocaine users did not perform worse on the Hooper Visual Organisation Task.

5.2.6 Verbal Learning

As in Chapter 3, a number of studies used list-learning tasks such as the CVLT and RAVLT to assess learning. Berry et al. (1993) found that cocaine users performed worse than controls at an initial testing session and also following 18 days abstinence on the RAVLT trials 1-5 total. There was a significant group by trial interaction indicating that learning processes in cocaine users differed from the patterns evident

in controls. Three studies used the CVLT and found no differences between cocaine users and nonusers (Gillen et al, 1998; Rosselli et al. 2001). Similarly no differences were observed following one month of abstinence (Butler & Frank, 2000).

One study used a combined verbal and visual paired associates task in which 12 black and white photos of faces with highly concrete names were presented to participants for 10 seconds each. Then each face was shown in turn and participants had to recall the name that went with that face. Both cocaine users and alcoholics were worse than controls, getting fewer correct at trials 1 and 6. The quantity of cocaine index was also significantly positively correlated with performance on trial 1 (Beatty et al. 1995). Two studies also used a combination of tests. Using the Hopkins Verbal Learning Test-Revised total recall score and the story memory test learning score, those who used cocaine but not cannabis performed significantly worse than controls, although the cocaine users who did use cannabis did not differ significantly from either group (Gonzalez et al. 2004). In another study, cocaine users did not perform worse on a "verbal memory" scale incorporating the WMS paired associates task and the CVLT (Goldstein et al. 2004).

5.2.7 Information Processing Speed

All reviewed studies assessing processing speed used the TMT-A and/or the DSST (both previously described in Chapter 3, section 3.2). Berry et al. (1993) found a trend towards significance at the initial testing session on the DSST, and in Beatty et al's (1995) study, the cocaine users and alcoholics performed significantly worse than controls, while Gillen et al. (2004) found no significant differences between cocaine users and controls, and in Goldstein et al's (2004) study the cocaine users did not perform worse on an overall measure of attention/executive functioning (although

separate between group comparisons were not made for each test comprising the scale).

For the TMT-A, one study found that cocaine users did not differ significantly from controls at the initial testing session, although there was a significant group by time interaction indicating that the cocaine group did not improve as much as the controls (Berry et al. 1993). One study found that cocaine users performed worse than controls on this task (Beatty et al. 1995), while another found that the performance of 42 cocaine users did not differ from that of controls (Roselli et al. 2001). In another study, cocaine users were actually faster on the TMT-B than nonusers (Gillen et al. 1998). Finally, one study found that cocaine users did not perform significantly worse on an "attention/executive" scale incorporating this measure, although separate comparisons were not made for the individual components (Goldstein et al. 2004).

Chapter Summary

It is therefore apparent that the use of cannabis or cocaine may result in cognitive deficits in users of these drugs. Given the fact that most ecstasy users are not solely users of ecstasy, using a range of other drugs at different stages of their night out, it is possible that other drugs might be responsible for any apparent ecstasy-related deficits. This chapter therefore provides a rationale for assessing the impact that cannabis and cocaine use might have on cognitive deficits relative to ecstasy use. As with a number of studies in this area, it is likely that while the ecstasy users will use a range of other drugs, the use of drugs in the non-ecstasy group will be mainly limited to the use of cannabis. This raises a problem when using ANCOVA to control for indices of illicit drug use. Thus correlations (and where appropriate, part correlations) are used to assess the impact of ecstasy, cannabis and cocaine on the cognitive deficits in ecstasy users. In addition all participants were required to be drug

free for at least 24 hours, although actual abstinence periods in each Chapter were longer than this.

To summarise thus far the aim of this thesis is to study the separability of executive function deficits in recreational ecstasy users. If any such deficits are observed then it is possible that these reflect the drug's neurotoxic potential. In addition, it is possible that cocaine and cannabis use may contribute to any executive function deficits observed in ecstasy users. The next chapter is the first of the empirical chapters. Chapter 6 assesses performance of ecstasy users and nonusers on a letter-updating task.

Chapter 6: Working Memory Updating

6.1 Chapter Overview:

Chapter 3 reviewed evidence for cognitive deficits in ecstasy users. A key aim of this thesis is to assess ecstasy-related cognitive deficits within Miyake et al's conceptualisation of executive processes, and this Chapter will explore memory-updating deficits in ecstasy users. Twenty-nine ecstasy users and 35 nonusers were assessed using a running memory task requiring them to remember the final six presented letters in lists varying in length (either 6, 8, 10, or 12 letters). On each trial, participants were unaware of the number of letters that would be presented. The interaction between ecstasy use and list length was non-significant although there was a main effect of ecstasy use on the task. Separate ANOVAs revealed that this was due to ecstasy users performing worse on the intermediate list lengths (8 and 10 letters). While indices of ecstasy use were significantly correlated with performance on chain lengths of 10 letters, cannabis was significantly correlated with chain lengths of 8 letters, and cocaine with 6 letters. The results of this chapter suggest that ecstasy/polydrug users are impaired on a running memory-updating task, with different drugs impacting on different aspects of the task.

6.2 Introduction

The updating component of the central executive requires monitoring and coding incoming information, assessing its relevance, and reviewing the contents of working memory. This involves deleting information that is no longer relevant, and replacing it with more recent salient information. The fundamental nature of memory updating is that it requires active manipulation of relevant information, rather than acting as a short-term store (Lehto, 1996; Miyake et al. 2000; Morris & Jones, 1990).

Indeed to support this dissociation, neuroimaging studies show differences in activation between tasks requiring passive storage of information (parietal lobes) and those requiring the active manipulation of information (Dorsolateral Prefrontal Cortex- DLPFC) (Jonides & Smith, 1997). Moreover, as the usefulness of working memory as a whole is related to the efficiency with which we maintain, monitor, and edit the online contents, the updating component is one of the most often used functions in cognition (Carretti, Cornoldi, De Beni, & Romano, 2005). Within the context of Miyake et al's conceptual framework, this aspect of executive functioning is under investigated in ecstasy users, with only two studies using tasks that are key indicators of the framework (Fisk et al. 2004; Wareing et al. 2004b).

How may this updating of information be achieved? Ruiz, Elosua and Lechuga (2005) suggest that a recency strategy is used (remembering those items that one saw most recently via phonological rehearsal). Ruiz et al. found a clear recency effect on letter and word memory-updating tasks, which increased with increasing list length (i.e. the recency strategy was more likely to be used for longer list lengths). However, Morris and Jones (1990) found that memory updating on a running memory task was not affected by articulatory suppression, and consequently concluded that updating was not performed by the articulatory loop but rather by the central executive. Furthermore, Baddeley and Hitch (1993) maintain that recency is a short-term memory phenomenon and is not related to working memory. Nevertheless, it is possible that remembering items at the minimum task requirement (6 letters) may require a different strategy to remembering items at list length +2 items (8 letters), list length +4 items (10 letters), and list length +6 items (12 letters), with the former requiring a passive storage mechanism, and the longer list lengths requiring the updating of items. Therefore as it is likely that an updating strategy will be recruited

on the longer list lengths, it is expected that executive deficits, should they exist, will be found on these, relative to the shorter lengths.

A complicating factor emerges in recent research that suggests that in cognitive ageing, updating the contents of working memory is mediated by information processing speed. Indeed Fisk and Sharp (2004) found that all of the age-related variance in updating was reduced to below statistical significance following control for processing speed. This appears to be a consistent finding in the cognitive ageing literature (e.g. Fisk & Warr, 1996; Salthouse & Babcock, 1991). However the same may not be true for users of ecstasy. Wareing et al. (2005) found that differences in computation span remained significant after control for differences in processing speed. To summarise the preceding paragraphs it is likely that if ecstasy users are impaired on the letter updating task then this will reflect a genuine updating deficit, although it remains a possibility that it is due to ineffective use of a phonological recency strategy.

As discussed in Chapter 3, cognitive deficits in ecstasy users are reported frequently over a wide range of tasks. The focus of this chapter is the updating of working memory. A number of studies have found that ecstasy users and nonusers perform comparably on tests believed to tap the updating executive component process (see Chapter 3, Section 3.3.5 for full review). Using backward digit span, which requires participants to listen to a string of digits and recite them to the experimenter in reverse order thus recruiting executive updating resources, no performance differences were observed in most studies (Bhattachary & Powell 2001; Gouzoulis-Mayfrank et al. 2003; McCardle et al. 2004; Thomasius et al. 2003). One study did find that ecstasy/cannabis users were impaired on the backward digit span task. Gouzoulis-Mayfrank et al. (2000) found that ecstasy/cannabis users performed

worse than nonuser controls. They were not impaired relative to cannabis only users (matched for cannabis use), and cannabis only users did not differ significantly from controls. Cumulative lifetime ecstasy dose and age of onset of cannabis use were significantly correlated with performance on this task. Thus it appears that some aspect of cannabis use may also affect performance on this task. This was supported by Croft et al's (2001a) study in which no performance differences were observed between 11 ecstasy/cannabis users (with a cumulative lifetime ecstasy dose of 42 tablets, and cannabis of 10965 joints), 18 cannabis only users (with a cumulative lifetime cannabis dose of 7762 joints), and 31 drug-naïve controls on the backward digit span task. After forming a single drug-using group (by combining the ecstasy/cannabis and cannabis only users), this group performed worse than controls, which the authors propose was more related to the use of cannabis rather than ecstasy. Although this proposition may seem quite plausible considering the estimated lifetime doses of each drug in the study, as there were no significant differences between the cannabis only users and nonusers before the groups were combined, it may be that the new significant difference between the groups reflects a decrease in the error variance due to the integration of the user groups and/or an increase in the main effect mean square due to the reduced degrees of freedom.

In the same way as backward digit span, Subtracting Serial Sevens (SSS) also recruits updating resources. Curran and co-workers have found ecstasy users make significantly fewer subtractions than nonusers on this task (Curran & Travill 1997; Curran & Verheyden 2003), while Morgan et al. (2002) found that ecstasy users made significantly more errors on the task. The possibility that these differences in terms of errors indicate an updating function deficit should be treated with some caution as the

authors suggest that the increased number of errors in ecstasy users reflects heightened impulsivity, not a specific memory updating impairment.

Some studies have also used established indicators of memory updating, similar to the operation span task used by Miyake et al. (2000). Wareing et al. (2004b) used computation and reading span tasks, analogous to Miyake et al's operation span task. Although no group differences were observed on the reading span measure, ecstasy users were significantly impaired on the computation span. From the same laboratory, Fisk et al. (2004) also used the computation span task and found that current ecstasy users attained a lower level than the nonusers. This remained significant after control for the use of other drugs indicating that memory updating performance is related to the use of ecstasy in this study. Dafters et al. (1999) used a similar working memory span task requiring the recall of words following distraction with a mathematical problem. Although no control group was employed, in the ecstasy user group (N=23), performance on this task was not significantly correlated with ecstasy use in the previous 12 months.

Another task that recruits executive updating resources is the N-back task. Gouzoulis-Mayfrank et al. (2003) used the 2-back version of the task, with both digit and figure versions. There were no significant differences between the heavy ecstasy users, moderate users and nonusers (indices of ecstasy use presented earlier in this thesis) in terms of reaction time or number of correct responses. Daumann et al. (2003) used a 0-back (having to press a key in response to a pre-specified target), 1-back and 2-back condition. Again, there were no significant differences in terms of correct responses and reaction times between the pure ecstasy users and polyvalent ecstasy users. In terms of fMRI activation during the 1-back task, polyvalent ecstasy users did not differ significantly from controls, however pure ecstasy users presented

lower activations than controls in the inferior temporal and angular region; additionally, pure users had lower signal changes in the striate cortex, and a higher BOLD response in the premotor cortex compared to polyvalent users. During the 2-back condition, again pure users showed lower activation relative to both controls and polyvalent users, mainly in the angular gyrus. A further study also found evidence for decreased activation in the left hippocampus of 6 ecstasy users relative to 6 nonusers, which significantly negatively correlated with length of abstinence from ecstasy (Jacobsen et al. 2004). Using a similar task (the Tic-Tac-Toe task), Alting von Geusau et al. (2004) found that users were unimpaired (although in male users there was a significant interaction indicating that they performed worse under high demand conditions).

Alting von Geusau et al. (2004) also used an arithmetic based memory updating task (mental counters) in which male ecstasy users were significantly slower than male nonusers, although there was no interaction between working memory load and ecstasy use.

Finally, Verdejo-Garcia et al. (2005) used a combined measure of updating (incorporating the backward digit span task, the arithmetic subtest from the WAIS-III, and the letter-number sequencing from the WAIS III) and found that ecstasy use was an important contributory factor in deficits in working memory updating among a clinical sample of poly-substance abusers. Indeed, severity of ecstasy use was the best predictor of performance on this dimension.

From the research set out above, it remains unclear whether or not ecstasy users are impaired in memory updating tasks. Many of the studies employed tasks with a strong arithmetic/numerical component. It has been suggested by Wareing et al. (2004b) that ecstasy-related deficits were evident in computation but not reading

span in their study, because ecstasy use impacts number processing and not verbal working memory updating. Thus one aim of the present study was to use a purer measure of memory updating, supposedly reliant on executive prefrontal resources (Van der Linden, Collette, Salmon, Delfiore et al. 1999) while being free of numerical abilities. The task used has featured in the evaluation of adult age differences in working memory capacity (e.g., Fisk & Sharp, 2004; Van der Linden et al. 1994), and also in evaluation of executive functioning in dyslexia (Smith-Spark, Fisk, Fawcett & Nicholson, 2003). In the context of executive functioning, Miyake and co-workers also used this measure to investigate the idea that executive processes are in fact separable rather then unitary in nature (Miyake et al. 2000). This test which is a key indicator of the updating executive construct within Miyake et al's conceptual framework has not been used before in a sample of ecstasy users. Furthermore, deficits in updating may support an MDMA related deficit in the dorsolateral prefrontal cortex (Goldman-Rakic, 1996; Postle, Berger, Goldstein, Curtis et al. 2001) or the left fronto-polar cortex (Van-der-Linden et al, 1999). It is now widely supported that ecstasy use has adverse effects on the serotonin system in animals (e.g. Hatzidimitriou et al. 1999), and also in humans (e.g. Ricaurte et al. 1990). In turn, research in other clinical populations has shown that those with similar 5HT dysfunctions (e.g. depression) are also impaired in memory updating tasks (e.g. Porter, Gallagher, Thompson & Young 2003). Thus it seems reasonable to expect that ecstasy users will be impaired on a "pure" measure of memory updating.

Given the nature of ecstasy poly-drug use, it is possible that any observed deficits in cognitive functioning may be in part attributable to the concomitant use of "other" drugs (e.g. Croft et al. 2001a). Indices of the frequency and intensity of other

drug use will be collected and where possible, we shall attempt to evaluate the impact of these on the executive measures included in the present study.

To summarise, this chapter investigated the updating executive component process. It was predicted that ecstasy users would perform worse than non-users on a memory-updating task (a running memory task). The letter-updating task is widely accepted as an established pure measure of the memory updating function (Miyake et al. 2000; Morris & Jones 1990). The task is a key indicator of Miyake et al's conceptual framework, and has not been used in research with ecstasy users before. It was expected that ecstasy users would perform worse on the longer list lengths as these recruit greater executive resources.

6.3 Method

6.3.1 Design.

With regard to the updating, mixed ANOVA was used, with ecstasy user group (2 levels) as the between groups variable, and list length (number of letters correctly recalled at 6, 8, 10, and 12 letter lengths) as the within participants variables. Subsequent ANOVAs were used to analyse performance on separate list lengths. Letter span was also measured and incorporated into ANCOVA, to remove the potentially mediating effects of differences in simple span.

6.3.2 Participants[5]

Twenty-nine ecstasy users (mean age 21.62; 16 male) and 35 non-user controls (mean age 21.69; 10 male) completed the updating task. Participants were recruited via direct approach to university students, and the snowball technique (Solowij et al, 1992). With 29 ecstasy users, the present sample is sufficient to detect a difference of 0.75σ for $\alpha = .05$ and $\beta = .20$ (Hinkle, Wiersma & Jurs, 1994).

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[5] Due to the nature of the studies, there is some overlap in terms of the participants in each Chapter. See Appendix 1 for specific numbers in each study.

Participants were requested to refrain from ecstasy use for at least 7 days and ideally 10 days prior to testing (the mean period of abstinence was actually 5 weeks, median abstinence period 2 weeks). Participants were also requested not to use any other illicit drugs for at least 24 hours and ideally for 7 days prior to testing.

6.3.3 Materials

Patterns of drug use and other relevant lifestyle variables were investigated via means of a background questionnaire[6]. The questionnaire gauged the use of ecstasy and other drugs, as well as current age, years of education, general health and other relevant lifestyle variables. In relation to other drugs, participants were asked a range of questions including frequency and duration of use and the last time that they had used each drug. Participants were also questioned concerning their history of drug use, and using a technique employed by Montgomery, Fisk, Wareing, Newcombe et al. (2005), these data were used to estimate total lifetime use for each drug. Average weekly dose and the amount of each drug consumed within the previous 30 days were also calculated.

Sleep Quality: Research has shown that ecstasy users exhibit altered sleep patterns, with less total sleep time and qualitative changes in the characteristics of Stage 2 sleep (Allen, McCann & Ricaurte, 1993). As it has been suggested that ecstasy-related cognitive deficits may be in part due to differences in other lifestyle variables such as sleep quality (Cole, Sumnall & Grob, 2002) a screening questionnaire and the Epworth Sleepiness Scale (ESS, Johns, 1991) were used to investigate any group differences in sleep quality. The ESS is a measure of subjective daytime sleepiness and contains eight items, which a participant has to score on a scale of 0 (would never doze off in this situation) to 3 (high chance of dozing off in

[6] See Appendix 2 for a copy of the questionnaire.

this situation). A total score of all eight items was used in the analysis, and a high score was indicative of increased subjective daytime sleepiness. The screening questionnaire contained a number of questions on sleep quality, e.g. hours per night.

Letter Span: Consonants were presented sequentially on a computer screen for 1.25 seconds. Participants were then required to recall the letters in the order in which they were presented. The task commences with three sets of two letters, and is then increased to three sets of three, four, five etc., until the individual fails on at least two out of three trials.

Consonant Updating: This task was based on the running memory task (Morris and Jones, 1990). In this computer-based task, the participant was presented with a random sequence of between 6 and 12 consonants on a computer screen. Twenty-four such lists were presented, and in each case, the participant was unaware of the number of consonants to be presented. The task was always to recall the most recent six consonants in the order in which they were presented. An answer book was provided for this purpose. The participant experienced six trials at each of the four list lengths: 6, 8, 10, and 12 items, and the order in which the lists were presented was randomised.

Raven's Progressive Matrices (Raven, Raven & Court, 1998): Each of the problems in Raven's Standard Progressive Matrices (SPM) was presented in the form of a sequence of symbolic figures. Participants were required to understand the nature of the relationships within each sequence and select one figure that completes each sequence. The Standard (SPM) consists of 60 problems divided into five sets of 12. In each set the first problem is self evident, the others becoming progressively more difficult. The test yields a total score out of 60 with a high score being indicative of good performance, and has been used extensively as an indicator of fluid intelligence.

The National Adult Reading Test (NART) (Nelson, 1982): The NART is an oral word reading test assessing premorbid intelligence. The test consists if 50 words of atypical phonology, whose pronunciations cannot be derived from standard grammatical rules (e.g. ache; gaoled). The total number correct was calculated for each participant, with a high score being indicative of high premorbid intelligence.

6.3.4 Procedure

Participants were informed of the general purpose of the experiment, and written informed consent was obtained. The tests were administered under laboratory conditions, and a computer running MS-DOS was used for the computer based tasks. The tests were administered in the following order: background questionnaire, sleep questionnaires, NART, letter span, consonant updating, and Raven's progressive matrices. Participants were fully debriefed, paid £15 in store vouchers, and given drugs education leaflets. The study was approved by the Ethics Committee of Liverpool John Moores University, and was administered in accordance with the ethical guidelines of the British Psychological Society.

6.4 Results

Scores for background variables are set out in Table 6.1. The t test revealed that the ecstasy users did not differ significantly from the nonusers in terms of age, self-rated health, number of years of education, intelligence (Raven's and NART scores), number of hours sleep per night, and letter span. The ecstasy users did however report significantly higher average weekly alcohol consumption than nonusers, $t(38.58) = 3.86$, $p<.001$, and also a significantly higher score on the Epworth Sleepiness Scale, $t(61) = 2.23$, $p<.05$, indicating increased daytime sleepiness (for alcohol consumption Levene's test was significant so degrees of freedom have been adjusted accordingly). Gender distribution was also significantly

different between the groups, with the ecstasy users being predominantly male and the nonusers predominantly female, χ^2 (df. 1, N=64) = 4.65, p<.05.

Table 6.1: Age, Years of Education, Intelligence and Sleep Quality for Ecstasy Users and Nonusers.

	Ecstasy users		Nonusers	
	Mean	S.D.	Mean	S.D.
Age (years)	21.62	1.63	21.69	1.94
Years of Education	16.00	1.41	15.69	2.08
Raven's Progressive Matrices (Max. 60)	49.76	4.45	48.26	5.11
NART (Max. 50)	29.66	6.11	30.49	6.23
Units of Alcohol (per week)	23.60	16.63	10.58	7.79
Hours of Sleep per night	8.14	1.64	7.90	1.45
Epworth Sleep Scale (Max. 24)	6.89	3.31	5.26	2.51
Self Report Health*	3.72	0.80	3.97	0.89
Letter Span Score	5.21	0.56	5.26	0.74
Weeks Since Last Used Ecstasy	5.28	7.31	-	-

* The self report health measure scores range from 1 (very poor) to 5 (very good)

Table 6.2 shows that the ecstasy users scored lower than nonusers on all four list lengths. The data were entered into repeated measures ANOVA. Mauchly's test of Sphericity was non-significant for list length, $p>.05$, so the sphericity assumed values were used. There was a significant main effect of length indicating that all participants had performed worse on the longer list lengths, $F(3,186) = 11.95$, $p<.001$. It was predicted that ecstasy users would perform worse at the longer list lengths, but analysis revealed that the list length by user group interaction was non-significant indicating that ecstasy users did not perform worse at the longer list lengths as

originally predicted, $F(3,186) = 0.96$, $p>.05$. However, the main effect of ecstasy use on letter updating was statistically significant, $F(1,62) = 5.44$, $p<.05$ with an effect size (partial Eta squared) of 0.081. To ascertain which aspects of letter updating were affected by ecstasy use, ANOVAs were performed with each list length. This revealed that ecstasy users and nonusers performed comparably on the 6-letter lists $F(1,62) = 0.98$, $p>.05$, and 12-letter lists, $F(1,62) = 1.05$, $p>.05$. Ecstasy users did perform worse than nonusers on the 8-letter lists, $F(1,62) = 4.16$, $p<.05$, and 10-letter lists, $F(1,62) = 9.52$, $p<.01$. The lack of an updating deficit across all list lengths was not associated with a significant interaction. It was predicted that ecstasy users would perform worse at the longer list lengths, while no deficit would be evident at list length 6. The lack of a significant interaction argues against this proposition.

Covariate Analyses

As ecstasy users scored significantly higher than non-ecstasy users on the ESS, reported drinking significantly more units of alcohol per week, and were predominantly male, it was possible that some or all of these factors may have contributed to the observed group differences on the letter-updating task. Thus these variables were incorporated into mixed ANCOVA.

Table 6.2: Mean Numbers of Letters Recalled and Significance Levels (F values) For Main Effects.

	Ecstasy Users		Non Ecstasy Users		F
	Mean	S.D.	Mean	S.D.	
Chain Length 6	2.56	0.79	2.76	0.73	0.98
Chain Length 8	2.06	0.59	2.41	0.76	4.16*
Chain Length 10	1.93	0.56	2.40	0.64	9.52**
Chain Length 12	2.07	0.82	2.26	0.68	1.05

* $p<.05$, two-tailed
** $p<.01$, two-tailed

After control for all three covariates, the main effect of ecstasy use on letter updating was slightly intensified, $F(1,56) = 8.47$, $p<.01$ (with a partial Eta squared of 0.131) and the length by user group interaction remained non-significant, $F<1$. While the univariate analyses revealed that the group differences on the chain length 6 trials were still non-significant, differences on the chain length 12 items were now significant, $F(1,56) = 2.80$, $p<.05$ (one-tailed).[7] The ecstasy-related differences on chain length 8 remained significant after control for these covariates, $F(1,56) = 5.71$, $p<.05$, as did the differences on chain length 10, $F(1,56) = 10.15$, $p<.01$.

Although there were no significant group differences in letter span, it was possible that the effect of ecstasy use on the letter-updating task could in part be mediated by letter span. To address this possibility letter span was entered as a covariate. The main effect of ecstasy use on letter updating remained significant $F(1,61) = 5.31$, $p<.05$, although the interaction between chain length and user group

[7] See Appendix 3 for adjusted means following ANCOVA.

was still non-significant. The differences in chain length 8 and chain length 10 proved more robust and remained significant after control for differences in letter span, $F(1,61) = 4.00; 9.29$, $p<.05$ and $p<.01$ respectively. Homogeneity of regression was achieved with respect to all covariates, $p>.05$ for the group by covariate interaction.

Table 6.3: Indicators of Drug Use Among Ecstasy Users and Non Ecstasy Users

	Ecstasy Users			Non Ecstasy Users		
	Mean	S.D.	N	Mean	S.D.	N
Total Use						
Ecstasy (Tablets)	329.83	358.22	29	-	-	-
Amphetamine (grams)	4.08	4.22	6	4.00	-	1
Cannabis (joints)	2503.48	2503.70	20	1291.98	1494.15	15
Cocaine (grams)	19.59	23.64	12	-	-	-
Frequency of Use (times per week)						
Ecstasy	0.42	0.36	29	-	-	-
Amphetamine	0.03	0.03	3	-	-	-
Cannabis	2.57	2.58	20	0.93	0.92	15
Cocaine	0.32	0.23	12	-	-	-
Amount Used During Previous 30 Days						
Ecstasy (tablets)	3.25	3.32	28	-	-	-
Amphetamine (grams)	2.00	3.46	3	-	-	-
Cannabis (joints)	22.66	36.04	19	8.89	11.49	14
Cocaine (grams)	1.68	1.83	10	-	-	-
Average Weekly Dose						
Ecstasy (tablets)	1.79	1.41	29	-	-	-
Amphetamine (grams)	0.20	0.25	5	0.09	0	1
Cannabis (joints)	9.69	9.24	19	6.13	10.74	15
Cocaine (grams)	0.17	0.26	12	-	-	-
Number Ever Used						
Amphetamine	12	-	-	2	-	-
Cannabis	26	-	-	20	-	-
Cocaine	22	-	-	5	-	-

Indices of Drug use

It is clear from Table 6.3 that while the ecstasy users were also regular users of other drugs, in the nonuser group this was restricted mainly to the use of cannabis. The ecstasy users smoked cannabis significantly more often than nonusers (2.57 times a week compared to 0.93), $t(24.95) = 2.63$, $p<.05$. Other indices of cannabis use were comparable between the groups: differences in total use were non-significant, $t(31.65) = 1.78$, $p>.05$; as were differences in amount used in the last 30 days, $t(31) = 1.37$, $p>.05$; and differences in average weekly dose, $t(32) = 1.04$, $p>.05$[8]. The non-ecstasy users had actually used cannabis more recently than the ecstasy users (average abstinence period of 5.16 weeks for nonusers, and 10.54 weeks for ecstasy users), although not significantly so, $t(41) = 0.70$, $p>.05$.

Correlations with Indices of Drug Use.

Aside from cannabis, due to the small number of illicit drug users among the non ecstasy user group it was not possible to control statistically for the effects of other drugs through the use of ANCOVA. Therefore it is possible that some or all of the ecstasy-related effects might have been attributable to the effects of other drugs. To address this possibility, non-parametric correlations were performed with different measures of ecstasy, amphetamine, cannabis and cocaine use. Measures of lifetime use of each drug, the number of times each drug was consumed each week, the amount of each drug consumed within the last 30 days, and the average weekly dose (i.e. total amount consumed divided by the length of use in weeks) were all included[9]. For each of these a value of zero was entered for nonusers of the drug in question. In

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[8] Although in this and subsequent chapters some of the differences between ecstasy users and nonusers regarding drug use were non-significant, it is noteworthy that in most cases the ecstasy users had substantially larger means. However the large standard deviations inflated the error variance and rendered these differences non-significant.

[9]Those in the nonuser group who reported that they had ever used amphetamine or cocaine (N= 2 and 5 respectively) felt that they were unable to estimate their pattern of use accurately.

addition, for each illicit drug, a categorical variable in which users and nonusers of each drug were coded as 0 or 1 respectively was included.

A full Bonferroni correction is not appropriate in this case, as the performance measures are intercorrelated (Sankoh, Huque & Dubey, 1997). However multiple comparisons remain potentially problematic, therefore an intermediate level of correction has been used, with correlations being evaluated at $p<.01$. The results, set out in Table 4, show that ecstasy use was significantly correlated with a number of the performance measures. The correlations revealed an interesting dissociation of the effects of different drugs on letter updating. While total lifetime dose of ecstasy, frequency of ecstasy use, average dose, and having ever used ecstasy were all significantly correlated with chain length of 10 letters, total use of cannabis, frequency of cannabis use, average dose and having ever used cannabis were all significantly correlated with chain length of 8 letters. In addition, total lifetime dose of cocaine and amount used in the last 30 day were significantly correlated with chain length of 6 letters. Indices of amphetamine use were not significantly correlated with any of the letter updating measures.

Table 6.4: Correlations between Measures and Indices of Drug Use.

		Ecstasy	Cannabis	Cocaine	Amphetamine
Total use	N	64	53	49	53
Chain Length 6		-0.106	-0.257	-0.349**	0.009
Chain Length 8		-0.170	-0.371**	-0.130	0.002
Chain Length 10		-0.306**	-0.070	-0.132	0.013
Chain Length 12		0.005	-0.064	-0.165	0.073
Frequency of Use	N	64	53	49	53
Chain Length 6		0.135	-0.178	-0.298	-0.117
Chain Length 8		-0.226	-0.321**	-0.180	-0.071
Chain Length 10		-0.309**	-0.073	-0.149	0.008
Chain Length 12		-0.040	-0.062	-0.185	0.012
Average dose	N	64	52	49	56
Chain Length 6		-0.110	-0.232	-0.331	-0.044
Chain Length 8		-0.199	-0.338**	-0.125	-0.037
Chain Length 10		-0.310**	-0.056	-0.130	-0.027
Chain Length 12		-0.040	-0.028	-0.168	0.025
Current Use	N	64	64	64	64
Chain Length 6		-0.078	-0.092	-0.297**	-0.086
Chain Length 8		-0.148	-0.199	-0.012	-0.055
Chain Length 10		-0.208	0.045	-0.037	-0.041
Chain Length 12		0.001	0.035	-0.119	0.175
Ever Used	N	64	64	64	64
Chain Length 6		0.136	0.245	0.155	0.072
Chain Length 8		0.257	0.374**	0.116	-0.018
Chain Length 10		0.374**	0.092	0.107	0.054
Chain Length 12		0.110	-0.020	-0.037	-0.065

** Correlation significant at p<.01

Implications of Chapter 6

The results of Chapter 6 support an ecstasy-related deficit in memory updating that is not related to gender, alcohol use, subjective daytime sleepiness, or amphetamine use. The interaction between list length and ecstasy use was non-significant indicating that ecstasy users did not perform worse at the longer list lengths under increased working memory load. Interestingly, there was a dissociation between the effect of ecstasy, cannabis, and cocaine on the letter updating task, with indices of ecstasy use being correlated with chain length 10, cannabis with chain length 8, and cocaine use with 6. It is possible that this reflects the different strategies (e.g. a recency strategy or an updating strategy) used by ecstasy users, cannabis users, and cocaine users, this proposal will be discussed at length in Chapter 12. Chapter 6 has shown that ecstasy users are impaired in a letter-updating task, a key indicator of Miyake et al's conceptual framework. As discussed in Chapters 2 and 3 there are four postulated executive functions under investigation in this thesis. The next Chapter will investigate possible ecstasy-related differences in the switching and inhibition components of Miyake et al's model.

Chapter 7: Mental set switching and response inhibition

7.1 Chapter overview

Chapter 6 showed that ecstasy users were impaired in a memory-updating task; the present chapter assessed the postulated executive functions of switching and inhibition. Fifty-one ecstasy users and 42 nonusers completed tasks that assess mental set switching (number/letter task and plus/minus task) and response inhibition (random letter generation). Unexpectedly, ecstasy users performed significantly better on the inhibition task producing more letters than nonusers. No group differences were observed on the switching tasks. Correlations between indices of ecstasy use and number of letters produced were significant. The surplus evident on the inhibition task should be treated with some caution as this was limited to a single measure and has not been supported by previous research (e.g. Fisk et al. 2004; Wareing et al. 2000).

7.2 Introduction

As discussed in Chapter 3, "switching" or "shifting" refers to a participant's ability to shift the focus of their attention between different tasks or different elements of the same task. Neural substrates have been identified with reference to both switching and inhibition, and any observed deficits in either could indicate a possible structural change in the brains of ecstasy users. For example, while poorer performance of ecstasy users on switching tasks may be linked to the anterior cingulate cortex (Posner and Raichle, 1994), the left frontal lobe (Rogers, Sahakian, Hodges, Polkey et al, 1998) and the bioccipital and parietal lobes (Moulden, Picton, Merran, Stuss et al, 1998), performance on a response inhibition task may be linked to the pre-frontal cortex (Casey, Trainor, Orendi, Schubert et al, 1997; Kiefer,

Marzinzik, Weisbrod, Scherg et al, 1998), and damage to the inferior frontal gyrus (Aron, Sahakian & Robbins 2003).

Some studies have shown that ecstasy users exhibit impairments in task switching by longer response latencies in a switching condition as opposed to a non-switch condition, while some have revealed an ecstasy-related inability to switch set when a certain rule changes (i.e. a perseverative error). Nonetheless it appears that ecstasy users are not generally impaired in task switching. Though as mentioned in Chapter 3 (See section 3.3.1 for full review), this may reflect the nature of the tasks used. The Trail Making Test-B (TMT-B) requires participants to alternately connect numbers and letters in numerical/alphabetical order (e.g. 1-A-2-B-3-C). The letters and numbers are randomly distributed on a piece of paper; hence the task requires switching attention between attending to number/letter stimuli. Ecstasy users were not generally impaired on this task (Krystal et al. 1992; McCardle et al. 2004; Semple et al. 1999; Thomasius et al. 2003). One study utilising this task did however find ecstasy-related effects. Morgan et al. (2002) found that ecstasy users made more errors on this task, although this was found to be more related to the use of mushrooms and LSD than ecstasy. The lack of group differences on the TMT-B may reflect the relative simplicity of the. Effects on this task are not dose related either, and it is not a key indicator within Miyake et al's conceptual framework.

McCann et al. (1999) used the Serial Add and Subtract Task from the Walter Reed Army Institute of Research Performance Assessment Battery (WRAIR-PAB). As described in Chapter 3 this computer based mental arithmetic task requires participants to perform an addition/subtraction for two numbers on the screen, enter the least significant number (while adding 10 if this is a negative number). Ecstasy users performed worse than nonusers on days 2 and 3 of the study. While part of this

task (the serial addition/subtraction) is similar to the one used in the present study (the plus/minus task), the task is made more complex by additionally requiring participants to identify the lower of the numbers and identify if that is a positive/negative response (i.e. a + or -). If the number is negative the participant then has to add 10 to it. Thus it is unlikely that this task solely measures task switching as it requires the coordination of a number of other aspects.

Alting von Geusau et al. (2004) used two tasks that are indicative of Miyake et al's conceptual framework. Both tasks are described in detail in Chapter 3, Section 3.3.1, but in short the dots-triangles task requires participants to switch between making judgements about the quantity of dots or triangles on a computer screen, while the local-global task requires participants to switch between attending to the local/global components of shapes. An interesting pattern of results were observed with male ecstasy users being significantly slower than male nonusers, and also having significantly higher switch costs than the male nonusers on both tasks, although this was not true of the female ecstasy users. However, in the dots-triangles task, the male ecstasy users were actually more accurate than the controls indicating that they had sacrificed speed in favour of accuracy (although the same was not true for the local-global task).

As mentioned in Chapter 2, another task that Miyake et al. (2000) found loaded on switching resources was the Wisconsin Card Sort Task (WCST). Ecstasy users were not generally impaired on this task (Alting von Geusau et al. 2004; Back-Madruga et al. 2004; Dafters et al. 1999; Dafters et al. 2004; Fox et al. 2001; Halpern et al. 2004; Thomasius et al. 2003; Verkes et al. 2001; Zakzanis and Young 2001b) although two studies (Alting von Geusau et al. 2004; Thomasius et al. 2003) did find that ecstasy users gave more perseverative errors than nonusers. However, as

literature suggests (e.g. Reitan and Wolfson, 1994) the WCST s a complex cognitive task which may require other resources in addition to the ability to switch sets, e.g. the ability to inhibit a previous rule (e.g. Ozonoff & Strayer, 1997).

To summarise the literature on task switching in ecstasy users, most studies do not find ecstasy-related deficits. Those that have found between group differences appear to have used harder tasks (Alting von Geusau et al. 2004; Fox et al. 2002; McCann et al. 1999). In Miyake et al's conceptual framework, the tasks used to assess switching were the number/letter task, the plus/minus task, the local-global task and the dots/triangles task. Thus it is possible that ecstasy users are impaired in task switching, but most tasks used in ecstasy users (with the exception of Alting von Geusau et al. 2004; Fox et al. 2002; McCann et al. 1999) do not solely tap this target function.

Switching the focus to inhibition, the Stroop task has been used to assess this aspect of executive functioning in ecstasy users. As reviewed in Chapter 3 (section 3.3.4), none of the studies using the Stroop task (Back-Madruga et al. 2004; Gouzoulis-Mayfrank et al. 2000; Morgan et al. 2002; Semple et al. 1999; Vollenweider et al. 1998) found ecstasy-related deficits, and as this task is not the focus of the present chapter the research will not be discussed again here. Alting von Geusau et al. (2004) also used the Stop Signal Reaction Time Task and the Eriksen Flankers Task, but as these are not key indicators of Miyake et al's framework, they are not discussed further here.

A number of studies in ecstasy users have used Random Letter Generation (RLG) to assess response inhibition in ecstasy users. Miyake et al. (2000) proposed that Random Number Generation loads on the inhibition and updating components of the central executive, whereas Fisk and Sharp (2004) propose that Random Letter

Generation loads solely on the inhibition component. Random generation is a relatively demanding cognitive process and is known for placing a continuous strain on executive resources (see Baddeley 1996). Participants are asked to produce letters in a random sequence avoiding alphabetical or well-known sequences (e.g., CIA, BBC, or FBI). They are also asked to try to produce each letter with the same overall frequency. The task is repeated three times with letters produced at one every four seconds, one every two seconds, and one per second (with 100 letters each time). Wareing et al. (2000) found that current ecstasy users and previous users were impaired relative to drug-naïve controls at the 1-second rate of production. One stipulation of the task was that participants were only allowed to produce consonants (i.e. no vowels), and Wareing et al. found that both user groups gave more vowel intrusions at all 3 rates. One problem with this study is that sample sizes were very small (N=10), and estimated lifetime dose of ecstasy was atypically high compared to other studies (see e.g. Halpern et al. 2004; Verkes et al. 2001). Another study from the same laboratory (Fisk et al. 2004) did not use the consonants only version of the RLG task. In this study, the ecstasy users (with a total lifetime ecstasy dose of 343 tablets- somewhat more modest than their first study) did not perform worse than the controls. Thus it may be that response inhibition under more difficult conditions (i.e. inhibiting alphabetical sequences and vowels) may require greater inhibitory control, and thus place greater demand on the central executive. As with the task switching data, this is an executive process that does not appear to be susceptible to the effects of ecstasy use. Nonetheless, one aim of this thesis was to use tasks that assess Miyake et al's conceptual framework, and thus inhibition, along with task switching formed the basis for this Chapter.

Tasks loading on the switching and inhibition component executive processes were administered. These included random letter generation. In this task participants were asked to produce letters in a random sequence avoiding alphabetical and well-known sequences (e.g., ABC, CIA, BBC, or FBI). They were also asked to try to produce each letter with the same overall frequency. The task was repeated three times with participants respectively generating a letter every four seconds, or every two seconds or one per second. Random generation yields a number of performance measures, (i) redundancy, which measures the extent to which each letter is produced with equal frequency, (ii) alphabetical, and (iii) repeat sequences (alphabetically ordered pairs or pairs of letters that are repeated). For all of these, a high score is indicative of poor performance. The fourth measure generated by the random generation task is the total number of letters generated. For this variable a high score is indicative of good performance. There is general agreement that alphabetic and repeat sequences load on the inhibition component executive process (Fisk & Sharp, 2004; Miyake et al, 2000). Consensus is lacking as to whether or not the redundancy measure loads on any of the component processes. While Miyake et al found that with random number generation, redundancy appears to load on the updating component process, Fisk and Sharp (2004) found that this was not the case with random letter generation. As we are using Random Letter Generation in the present study, it was deemed that as Fisk and Sharp found, this would load solely on the inhibition component

The two tasks chosen to tap shifting were the plus-minus task and number/letter task. Both require switching between mental sets, the plus-minus task by alternately adding and subtracting, and the number/letter task by switching attention between attending to numbers and letters. Previous research has shown that

the ability to switch sets involves temporal cost (indexed by increased response latencies on switch conditions as opposed to non-switch) (e.g. Rogers & Monsell, 1995). There is also growing evidence that this involves the frontal lobes (see beginning of Chapter).

It has already been shown in Chapter 6 that ecstasy users are impaired in the updating executive component process on a pure measure of updating. In light of the evidence set out above, it was unclear whether or not ecstasy users would perform worse than nonusers on measures of task switching and inhibition. Research suggests that both processes are executive prefrontal tasks. In turn, research (e.g. Renema et al. 2001a) has shown that the prefrontal cortex may be subject to the neurotoxic effects of ecstasy use. However, previous research has revealed mixed results on other tasks thought to assess both target functions. Thus using the measures outlined by Miyake et al. (2000) we assessed task switching and inhibition. It was not expected that ecstasy users would perform worse than nonusers, more specifically, both groups would have similar switch cost latencies, and similar numbers of alphabetical sequences, repeat sequences, similar redundancy, and would produce a similar number of letters.

7.3 Method

7.3.1 Design

A multivariate design was used for the switching measures with ecstasy user group (2 levels) as the between participants independent variable, and the shift cost latencies (seconds) as the dependent measures. For the random generation task,

MANOVA was used with ecstasy user group as the between participants variable, and the four random letter generation scores as the dependent measures.

7.3.2 Participants

Fifty-one ecstasy users (mean age 21.96, 27 male) and 42 nonuser controls (mean age 20.83, 9 male) were recruited via direct approach to university students, and the snowball technique (Solowij et al, 1992). With 42 nonuser controls, the present sample is sufficient to detect a difference of between 0.5 and 0.75 σ for α = .05 and β =.20 (Hinkle et al, 1994). Participants were requested to refrain from ecstasy use for at least 7 days and ideally 10 days prior to testing (the mean period of abstinence was actually 22 weeks, median abstinence period 4 weeks). Participants were also requested not to use any other illicit drugs for at least 24 hours and ideally for 7 days prior to testing.

7.3.3 Materials

Background questionnaires, intelligence tests and sleep quality tests were used as in Chapter 6.

Plus-minus task. The plus-minus task, adapted from Miyake et al (2000) consists of three lists of 30 two-digit numbers (the numbers 10-99, randomised). On the first list, participants were instructed to add three to each number, and write their answer in the box next to it. On the second list, participants were instructed to subtract three from each number. On the third list, participants were required to alternately add and subtract three from the list (i.e. add three to the first number, subtract from the second, and so on). List completion times were measured with a stopwatch. The cost

of shifting between adding and subtracting was calculated as the difference between the time for list three and the average of the times for lists one and two.

Number-Letter task. In the number-letter task, adapted from Rogers and Monsell (1995) and Miyake et al (2000), a number letter pair (e.g.D4) is presented in one of four quadrants on a computer screen. If the target is in the top half of the screen, the task is to indicate if the letter is a vowel (A, E, I, O or U) or a consonant. If the target is in the bottom half of the screen, the task is to indicate if the number is odd or even. Responses are made via pressing the key "Z" for odd and consonant and they key "/" for even and vowel. The practise version of the task comprises three sets. The target is presented in the top half of the screen for 12 trials, then the bottom half for 12 trials, and then in a clockwise rotation around all 4 quadrants for a further 12 trials. The main task follows the same structure, except there are 64 targets in each block. Therefore, the trials in the first two blocks required no switching, while the third set did. The shift-cost was the difference between the average decision times of the third block and the averages of the first two blocks.

Random letter generation. A computer display and concurrent auditory signal was used to pace responses. Participants were asked to speak aloud a letter every time the signal was presented. They were told to avoid repeating the same sequence of letters, to avoid producing alphabetical sequences, and to try to speak each letter with the same overall frequency. Individuals attempted to produce three sets of 100 letters; one set at a rate of one letter every 4 s, a second set at one letter every 2 s, and a third at one letter every 1 s. The order in which the sets were generated was randomised. The experimenter recorded the responses on an answer sheet. The test yields four scores. First, the number of alphabetically ordered pairs; second, a repeat sequences score corresponding to the number of times that the same letter pair is repeated; third,

a "redundancy" score, which measures the extent to which all 26 letters of the alphabet are produced equally often (0% being truly random); and fourth, the number of letters produced. In the first three cases, higher scores indicate poor performance; in the fourth the opposite is the case. The scores for each separate variable, at each of the three generation rates, were standardised. A single score was calculated for each variable by summing the score for each rate and dividing by three.

7.3.4 Procedure

Participants were informed of the general purpose of the experiment, and written informed consent was obtained. The tasks were administered under laboratory conditions, and a computer running MS-DOS was used for the computer based tasks. The tests were administered in the following order: background questionnaire, sleep quality questionnaires, NART, random letter generation, plus-minus task, number-letter task, and Raven's progressive matrices. Participants were fully debriefed, paid £15 in store vouchers, and given drugs education leaflets. The study was approved by the Ethics Committee of Liverpool John Moores University, and was administered in accordance with the ethical guidelines of the British Psychological Society.

7.4 Results

The scores for background variables are set out in Table 7.1. An initial t-test revealed that there were no significant differences between the groups in age, pre-morbid intelligence, Raven's Progressive Matrices, the Epworth Sleepiness Scale, sleep (hours per night), years of education, or self-rated health, so these are not discussed any further.

Table 7.1: Age, Years of Education, Intelligence and Sleep Quality for Ecstasy Users and Nonusers

	Ecstasy users		Nonusers	
	Mean	S.D.	Mean	S.D.
Age (years)	21.96	2.11	20.83	1.45
Years of Education	15.62	1.94	15.07	1.92
Raven's Progressive Matrices (max. 60)	46.66	6.53	47.83	5.47
NART (max. 50)	28.67	6.53	28.71	4.90
Hours Sleep per night	7.92	1.45	8.09	1.13
Epworth Sleep Scale (max. 24)	6.48	3.54	7.63	3.22
Self Report Health*	3.54	0.88	3.83	0.70
Weeks Since Last Used Ecstasy	22.15	40.71	-	-

* The self report health measure scores range from 1 (very poor) to 5 (very good)

Scores for the switching and inhibition tasks are set out in Table 7.2. Contrary to expectations, the main effect of ecstasy on inhibition was statistically significant, $F(4,88) = 2.63$, $p<.05$ for Pillai's Trace. Separate univariate analyses revealed that this was due to ecstasy users producing more letters than non-users, $F(1,91)= 8.29$, $p<.005$. There were no differences between the groups on the other random letter generation scores of alphabetic sequences, repeat sequences and redundancy, $F < 1$ in all cases. The main effect of ecstasy use on switching was also non-significant, $F < 1$ for Pillai's Trace. Separate univariate analyses revealed that there were no significant

between group differences in performance on the plus/minus task or the number letter task, $F < 1$ in both cases.

Table 7.2: Mean Random Letter Generation and Switching scores and Significance Levels for Measures

	Ecstasy Users		Non Ecstasy Users		F
	Mean	S.D.	Mean	S.D.	
Random Letter Generation (standardised scores)					
Alphabetic Sequences	0.0568	0.7719	-0.0720	0.7821	0.63
Repeat Sequences	0.0005	0.6453	-0.0007	0.6955	0.00
Redundancy	-0.0490	0.6341	0.0622	0.9591	0.45
Number of Letters	0.1967	0.4203	-0.2495	1.0137	8.29***
Switching Tasks					
Plus/Minus Switch Cost (seconds)	28.63	19.46	29.58	18.18	0.06
Number/Letter Switch Cost (seconds)	39.27	18.14	38.52	18.98	0.04

*** $p<.01$, two-tailed

Indices of Drug Use

Inspection of Table 7.3 shows that the use of other drugs among the non-ecstasy group was limited mainly to the use of cannabis, alcohol, and tobacco. The ecstasy users had a lifetime dose of cannabis many times that of the non-users (3544 joints to 368 joints), in addition to using it more frequently (2.78 times a week, compared to 0.94 times a week), having smoked more in the last 30 days (41.14 joints compared to 17.29 joints), and having a larger average weekly dose (9.10 joints compared to 1.91 joints). A t-test revealed that all these differences between the groups except amount used in the last 30 days were statistically significant: t(43.40;

40.80; 50.79) = 4.42; 3.27; 3.65, p<.005, for total, frequency and average dose respectively. (As Levene's test was significant, degrees of freedom have been adjusted accordingly).

Table 7.3: Indicators of Drug Use Among Ecstasy Users and Non Ecstasy Users

	Ecstasy Users			Non Ecstasy Users		
	Mean	S.D.	n	Mean	S.D.	N
Total Use						
Ecstasy (Tablets)	373.87	542.91	52	-	-	-
Amphetamine (grams)	90.85	127.19	16	-	-	-
Cannabis (joints)	3544.16	4410.04	40	367.54	622.96	13
Cocaine (grams)	57.12	92.39	21	-	-	-
Frequency of Use (times per week)						
Ecstasy	0.27	0.29	52	-	-	-
Amphetamine	0.04	0.13	14	-	-	-
Cannabis	2.78	2.65	40	0.94	1.36	13
Cocaine	0.71	1.57	21	-	-	-
Amount Used During Previous 30 Days						
Ecstasy (tablets)	2.18	3.17	52	-	-	-
Amphetamine (grams)	0.04	0.13	14	-	-	-
Cannabis (joints)	41.14	59.45	40	17.29	42.97	12
Cocaine (grams)	0.83	0.87	21	-	-	-
Average Weekly Dose						
Ecstasy (tablets)	1.46	1.40	52	-	-	-
Amphetamine (grams)	0.26	0.37	14	-	-	-
Cannabis (joints)	9.10	11.58	40	1.91	3.37	13
Cocaine (grams)	0.30	0.38	21	-	-	-
Number Ever Used						
Amphetamine	19	-	-	0	-	-
Cannabis	46	-	-	23	-	-
Cocaine	41	-	-	4	-	-

Correlations with Indices of Drug Use.

There was no evidence of any ecstasy-related deficit on the inhibition and switching measures, although it is possible that other illicit drugs might exert an influence. To address this possibility, correlations were performed with different measures of ecstasy, amphetamine, cannabis and cocaine use. Measures of lifetime use of each drug, the number of times each drug was consumed each week, the amount of each drug consumed within the last 30 days, and the average weekly dose (i.e. total amount consumed divided by the length of use in weeks) were all included[10]. For each of these a value of zero was entered for nonusers of the drug in question. In addition, for each illicit drug, a categorical variable in which users and nonusers of each drug were coded as 0 or 1 respectively was included.

As in Chapter 6, a full Bonferroni correction is not appropriate in this case, as the performance measures are intercorrelated (Sankoh et al. 1997). However multiple comparisons remain potentially problematic, therefore an intermediate level of correction has been used, with correlations being evaluated at $p<.01$. The results are set out in Table 7.4. Frequency of ecstasy use, average dose of ecstasy, and amount used in the last 30 days were significantly correlated with the number of letters produced ($p<.01$) . In all cases, increased ecstasy use was associated with more letters produced. No correlations with indices of other drug use were significant at $p<.01$.

[10] Those in the nonuser group who reported that they had ever used amphetamine or cocaine (N= 1 and 4 respectively) felt that they were unable to estimate their pattern of use accurately.

Table 7.4: Correlations with Indices of Drug Use

		Ecstasy	Cannabis	Cocaine	Amphetamine
Total use	N	93	76	67	85
P/M switch cost		-.015	-.136	.196	.106
N/L switch cost		.124	.143	.212	.077
Redundancy		.028	-.032	.051	.042
Repeat sequence		.084	.004	.131	.139
Alpha sequence		.080	.010	.113	-.137
Number of Letters		.228	.174	.018	.032
Frequency of Use	N	93	76	67	85
P/M switch cost		-.043	-.125	.108	.220
N/L switch cost		.071	.050	.144	.139
Redundancy		-.079	-.145	.041	.034
Repeat sequence		-.062	-.169	.100	.044
Alpha sequence		.106	-.110	.025	-.105
Number of Letters		.335*	.186	.078	-.051
Average dose	N	93	76	67	83
P/M switch cost		-.025	-.167	.186	.115
N/L switch cost		.060	.122	.210	.025
Redundancy		.035	-.056	.048	-.029
Repeat sequence		.053	-.017	.129	.097
Alpha sequence		.071	.033	.120	-.159
Number of Letters		.283*	.199	.018	.034

Current Use	N	Ecstasy 93	Cannabis 93	Cocaine 93	Amphetamine 93
P/M switch cost		-.106	-.045	.133	.197
N/L switch cost		.041	.062	.068	-.025
Redundancy		-.109	-.100	-.057	.013
Repeat sequence		-.155	-.033	.075	.055
Alpha sequence		-.021	-.048	.062	-.071
Number of Letters		.344*	.116	.000	.102
Ever Used	N	93	92	92	92
P/M switch cost		.051	.118	-.007	-.073
N/L switch cost		-.063	-.062	-.176	-.052
Redundancy		.028	.050	-.142	.077
Repeat sequence		-.022	.055	-.118	-.056
Alpha sequence		-.134	.069	-.029	.129
Number of Letters		-.258	-.037	-.018	-.023

* correlation significant at p<.01.

Implications of Chapter 7

To summarize, the results of Chapter 7 suggest that ecstasy-related group differences are not apparent in task switching. Ecstasy users did however produce significantly more letters on the inhibition task, although there were no group differences on the three other inhibition measures. This finding is not supported by previous research and should thus be treated with caution. Thus far, the pattern of results suggests that ecstasy users are impaired in Miyake et al's updating component, but not the switching and inhibition components. This may in part reflect the different neural substrates activated during performance on each task. The next chapter will assess performance on the fourth postulated executive function: access to long-term memory.

Chapter 8: Access to Long-term Memory

8.1 Chapter Overview

Thus far, it appears that while ecstasy users are impaired in memory updating (Chapter 6), the same is not true for shifting and inhibition (Chapter 7). This chapter assess the fourth executive function postulated in Chapter 2, access to long-term memory. Twenty-Seven ecstasy users and 34 nonusers were assessed on tasks to tap access to long-term memory (a semantic fluency test and the Chicago Word Fluency Test). MANOVA revealed that ecstasy users performed worse on the Chicago Word Fluency Task (C- and S-letter fluency), but not on the semantic fluency task. However, notwithstanding the significant ecstasy-group related effects, indices of cocaine and cannabis use were also significantly correlated with performance on the "C" and "S" letter tasks. Further analyses revealed that effect sizes for ecstasy use were marginally larger than for cocaine use for "S" and "C" letter fluency. This chapter provides further support for ecstasy/polydrug related deficits in access to long-term memory. Of the four executive functions assessed, it appears that updating and access are affected by ecstasy use.

8.2 Introduction

The focus of this chapter is access to semantic memory (hereafter referred to as "access"). Although access is not a key component of Miyake et al's conceptual framework, Baddeley (1996) has noted that one of the key functions of the executive is the temporary activation of long-term memory. In a study of cognitive ageing, Fisk and Sharp (2004) provided further support for the three components of Miyake et al's model. Factor analysis revealed that certain tasks loaded on each of the three components identified by Miyake et al., but there was also a distinct executive

function loading on another factor which Fisk and Sharp termed access to long-term memory (although age was not a significant predictor of performance on "access" tasks). It is not surprising that word fluency requires the activation of long-term memory as it requires participants to retrieve as many words as possible from long-term memory; this has been supported in previous research where performance on a word fluency task was significantly correlated with long-term recall (Ruff et al. 1997).

Word fluency has been used extensively as an indicator of prefrontal/executive function, and is believed to be particularly sensitive to lesions in the prefrontal lobes (especially the left prefrontal lobe) (Benton, 1968; Milner, 1964; Perret, 1974). There is also a dissociation between the neural correlates of semantic and letter fluency tasks, with semantic fluency being related to temporal lobe lesions (e.g. Monsch et al. 1994) and letter fluency being related to lesions in the frontal lobes (Monsch et al. 1994; Stuss, Alexander, hamer & Palumbo 1998). As reviewed in Chapter 4, it is likely that humans, like animals, are subject to lesions in the prefrontal cortices following ecstasy administration, and accordingly it is expected that ecstasy users will perform worse than nonusers, especially on the letter fluency tasks.

Some studies have shown that ecstasy users exhibit deficits in word fluency (see Chapter 3, Section 3.3.2 for full review). In investigating the effects of ecstasy use nearly all researchers have used the Controlled Oral Word Association test (COWA), or similar tests, to assess access to long-term memory. The task requires participants to generate as many words as possible in 60-seconds beginning with a certain letter (usually F, A, S- although some studies alternated between a variety of consonants (e.g. Curran & Verheyden, 2003). Only three of the 12 studies assessing word fluency (Bhattachary & Powell, 2001; Fox et al. 2002; Hefferman et al. 2001a) found that ecstasy users retrieved fewer words than nonusers. Some studies also use a

semantic fluency task, requiring the retrieval of as many words as possible from a certain category (e.g. animals, fruit). On the semantic fluency task, one study found that group differences were only apparent in a combined drug-using group (Croft et al. 2001a), which the authors concluded was more related to cannabis use rather than ecstasy use. One found a trend towards an ecstasy effect (Morgan et al. 2002), while another found that ecstasy users performed worse than nonusers (Heffernan et al. 2001a). The present chapter will assess access via the Chicago Word Fluency Task. Although this area is already well researched in ecstasy users, most studies have used the same task. It is possible that a one-minute task of word retrieval does not recruit executive resources in such a way that ecstasy users would be impaired. Indeed testing other areas of cognition, it becomes apparent that ecstasy users are only impaired in the more difficult aspects of some tasks while easier tasks seem to be unaffected (e.g. Fox et al. 2002, 3D-IDED). The present chapter aimed to assess this proposal by using a longer version of a word fluency task, and a semantic fluency task. It was expected that ecstasy users will perform worse on both the semantic fluency task (as many animals as possible in 4 minutes) and also the first part of the CFWT (as many words as possible beginning with "S" in 5 minutes), as greater executive resources will be recruited (see below). The second part of the CFWT imposes further restrictions on participants' retrieval by asking them to generate as many four-letter words as possible beginning with the letter "C". Only one study in ecstasy users has imposed further restrictions such as this. In Heffernan et al's (2001a) study participants were asked to recall as many household items as they could beginning with the letter "T" in one minute. On this task the ecstasy users performed worse than nonusers, so we have reason to believe that the deficit will be even more pronounced in the longer version of the task used in the present study. With reference

to which part of the task will be most affected by ecstasy use, research suggests that "animals" is one of the best-retrieved semantic categories, and in one study number of words retrieved on the animals category was higher than for "S" letter (for a one minute recall) in normal participants (Baldo & Shimamura, 1998). It is therefore expected that retrieval will be highest on the semantic task (with between group differences being less evident), while larger performance deficits will be observed on the "S" letter task, and most pronounced on the "C" letter task.

One aim of the present chapter was to establish the separability of a specific deficit in access, as opposed to access being mediated by working memory capacity. Previous research has shown that individual capacities of working memory are reflected in performance on a word fluency task. For example, Engle and Rosen (1994) found that those with high working memory span were impaired by performing a concurrent task with semantic fluency (animal names) whereas those with low span were not. It also seems reasonable to expect that those with a high working memory span would have higher activation of access to long-term memory and thus be more efficient at this process. This may be reflected in the present study (and indeed previous studies) by ecstasy users performing worse on an access task, due to reduced working memory capacity. Consequently we will control for working memory capacity in the present chapter. With reference to which aspect of Miyake et al's model of executive functioning may be related to performance on the CWFT, Shimamura (2001) suggests that retrieval from long-term memory requires an ability to monitor previously retrieved items after each response, and consequently keep these in mind for future selections so that mistakes will not be made. From this it is possible that different aspects of Miyake et al's model may impact on performance in different ways. While inhibition may be related to errors on the task (writing down

words that do not meet the specific criteria), shifting may be related to the occurrence of perseverative errors (in the case of the word fluency task, making the same response more than once, whether it complies with the criteria or not). The updating component however may be more generally involved in the process of retrieval, through monitoring past choices and thus facilitating the retrieval of future ones. It was deduced that the updating component of Miyake et al's model was most likely to relate to word fluency performance in the present chapter. In keeping with this, Chapter 6 of this thesis found that ecstasy users performed worse on a memory updating task, but not on tasks that assess switching and inhibition (Chapter 7).

It was predicted that ecstasy users would perform worse than non-users on measures of access to long-term memory (a semantic and category fluency task) Although word fluency has been assessed in samples of ecstasy users (e.g. Bhattachary and Powell, 2001; Fox et al, 2002), the task used in the present study is more likely to recruit executive prefrontal resources as it is a longer version than previously used and places further constraints on the categories thus making it harder for participants. Cohen and Stançzak (2000) found that the Chicago Word Fluency Test (CWFT- also known as the Thurstone Word Fluency Test) has high test-retest reliability over 6 weeks, high inter-rater reliability, and good construct validity. In addition, performance on this task was also significantly correlated with performance on the COWA and FAS tasks previously used with ecstasy users. The CWFT differs in that longer time limits are imposed on participants (5 minutes for "S" letter words, and 4 minutes for 4-letter "C" words). Consequently, it seems reasonable to expect that with the constrained categories and longer time limits the task imposes greater demands on access to semantic memory. Indeed, Cohen and Stanczak (2000) found

that attention and memory contribute to performance on this task. In the present chapter, we have controlled for differences in memory updating (computation span) and attention (digit span). To our knowledge, this task has not been used in research with ecstasy users before. It seems reasonable to expect that semantic knowledge, more specifically available word knowledge is necessary for optimum performance on a word fluency task (this is evidenced by correlations between WAIS-R vocabulary scores and COWA scores, Ruff et al. 1997). Consequently verbal IQ and level of education will be controlled for.

8.3 Method

8.3.1 Design.

A multivariate design was used for the word fluency tasks, with ecstasy user group as the between participants independent variable, and the three word fluency scores (semantic, "S" letter, and C" letter) as the dependent variables.[11] To ascertain the extent to which memory and attention may play a role in the word fluency deficits observed in the present study, ANCOVA was used with computation span and digit span as covariates. Where group differences were observed in terms of background variables, these were also incorporated into ANCOVA.

8.3.2 Participants

Thirty-six ecstasy users (mean age 21.72; 19 male) and 62 non-user controls (mean age 21.32; 18 male) completed the word fluency tasks. Participants were recruited as in Chapter 6. With 36 ecstasy users, the present sample is sufficient to detect a difference of between 0.5 and 0.75σ for $\alpha = .05$ and $\beta = .20$ (Hinkle et al, 1994). Participants were requested to refrain from ecstasy use for at least 7 days and

[11] Data in this Chapter are analysed in a multivariate design. Appendix 4 contains supplementary analyses for a mixed design incorporating the same variables.

ideally 10 days prior to testing (the mean period of abstinence was actually 5 weeks, median abstinence period 2 weeks). Participants were also requested not to use any other illicit drugs for at least 24 hours and ideally for 7 days prior to testing.

8.3.3 Materials

Patterns of drug use, sleep quality, fluid intelligence, premorbid intelligence, and other relevant lifestyle variables were investigated as described in Chapter 6 (section 6.3.3).

Semantic Fluency: In the semantic fluency task, participants were required to produce as many animal names as they could think of. This could be different species, or breeds within species. Participants were given four minutes for this task.

Chicago Word Fluency Test (CWFT). Participants were instructed not to write any place names, peoples name or plurals in this test. Firstly participants were given five minutes to write down as many words as they could, beginning with the letter "S". Secondly, they were given four minutes to write down as many four-letter words beginning with "C" as they could. As plurals were not allowed words such as " cats", and repetitions of words were excluded. Scores for all three fluency tasks were the number of appropriate words in each case. For both semantic fluency and the CWFT participants wrote their responses in an answer booklet provided for this purpose.

Digit Span: Digits were presented sequentially on a computer screen for 1.25 seconds. Participants were then required to recall the digits in the order in which they were presented. The task commences with three sets of two digits, and is then increased to three sets of three, four, five etc., until the individual fails on at least two out of three trials.

Working memory updating. The computation span measure was used to assess these aspects of cognitive functioning. Computation span has been used as an indicator of working memory functioning in the cognitive ageing literature (Fisk & Warr, 1996; Salthouse & Babcock, 1991) and it is similar to the operation span measure used by Miyake et al. (2000) in their investigation of executive processes. In addition, it has been shown to be sensitive to the effects of ecstasy use (Fisk et al. 2004). Participants were required to solve a number of arithmetic problems (e.g., 4+7 = ?) by circling one of three multiple-choice answers as each problem was presented. They were also required to simultaneously remember the second digit of each presented problem. At the end of each set of problems the second digits had to be recalled in the order in which they were presented. The number of arithmetic problems that the participant had to solve, while at the same time remembering each second digit, gradually increased as the test proceeded. For each of the first three trials only a single problem was presented. For the next three trials, two problems were presented. Subsequently, the number of problems presented per trial increased by one every third trial. In order to proceed, the participant was required to be correct in at least two of the three trials at the current level. Computation span was defined as the maximum number of end digits recalled in serial order, with the added requirement that the corresponding arithmetic problems had been solved correctly.

8.3.4 Procedure

Participants were informed of the general purpose of the experiment, and written informed consent was obtained. Completed under laboratory conditions, the tests were administered in the following order: background questionnaire, sleep questionnaires, NART, semantic fluency, computation span, word fluency, and

Raven's progressive matrices. Participants were fully debriefed, paid £15 in store vouchers, and given drugs education leaflets. The study was approved by the Ethics Committee of Liverpool John Moores University, and was administered in accordance with the ethical guidelines of the British Psychological Society.

8.4 Results

The scores for background measures are set out in Table 8.1. The t-test revealed that there were no significant differences between the groups in age, pre-morbid intelligence, sleep (hours per night), subjective daytime sleepiness, years of education, self-rated health, digit span, or computation span[12]. Group differences on Raven's Progressive Matrices approached significance, $t(95) = 1.92$, $p = 0.058$. Ecstasy users also reported significantly higher average weekly alcohol consumption (21.65 units compared to 11.82 units), $t(48.21) = -3.27$, $p<.01$, than nonusers (as Levene's test was significant, degrees of freedom have been adjusted accordingly). Gender distribution was also significantly different between the groups, with the ecstasy users being predominantly male, and the nonusers predominantly female, χ^2 (df. 1, $N = 98$) = 5.47, $p<.05$.

[12] Although the lack of a significant difference on computation span in this chapter suggests that ecstasy users may not be impaired in updating, this is not consistent with the majority of chapters and should therefore be treated with caution.

Table 8.1: Age, Years of Education, Intelligence and Sleep Quality for Ecstasy Users and Nonusers.

	Ecstasy users		Nonusers	
	Mean	S.D.	Mean	S.D.
Age (years)	21.72	1.63	21.32	1.80
Years of Education	15.77	1.85	15.34	2.13
Raven's Progressive Matrices (max. 60)	50.00	4.76	47.97	5.16
NART (max. 50)	28.94	6.03	29.89	5.77
Hours of Sleep per night	8.08	1.55	8.00	1.27
Epworth Sleep Scale (max. 24)	6.46	3.42	5.82	2.83
Self Report Health*	3.67	0.79	3.85	0.81
Units of Alcohol Consumed in a Week	21.65	16.57	11.82	9.14
Digit Span	6.5	1.03	6.5	1.05
Computation Span	3.89	1.60	4.24	1.29
Weeks Since Last Used Ecstasy	15.79	39.24	-	-

* The self report health measure scores range from 1 (very poor) to 5 (very good)

Table 8.2 shows that ecstasy users retrieved fewer words on all three access tasks although the deficit was not as evident on the semantic fluency task. The main effect of ecstasy use on word fluency was significant, $F(3,94) = 4.55$, $p<.01$ (all multivariate effects reported in the results section relate to Pillai's Trace). This was due to ecstasy users' poorer performance on the "S" letter, $F(1,96) = 6.44$, $p<.05$, and

the "C" letter categories, $F(1,96) = 13.70$, $p < .001$. There were no significant differences between the groups on the semantic fluency task, $F(1,96) = 1.65$, $p > .05$

Table 8.2: Word Fluency Scores and Significance Levels (F values) For Main Effects.

	Ecstasy Users		Non Ecstasy Users		F
	Mean	S.D.	Mean	S.D.	
Semantic Fluency	40.64	8.87	43.19	9.83	1.65
"S" Letter	40.94	10.30	46.58	10.76	6.44*
"C" Letter	11.64	5.29	15.98	5.77	13.70***

* $p < .05$, two-tailed
*** $p < .001$, two-tailed

Covariate Analyses.

As there was a gender imbalance between the groups, and ecstasy users also reported consuming significantly more alcohol than nonusers, while group differences on Raven's Progressive Matrices approached significance (indicating that ecstasy users had a higher IQ), it was possible that some or all of these factors may have influenced ecstasy-related group differences in access to long-term memory. ANCOVA was conducted to investigate the possible mediating effects of alcohol consumption, intelligence, and gender on word fluency. The main effect of ecstasy use was intensified after control for these three covariates, $F(3,87) = 5.70$, $p < .001$. In addition, after ANCOVA to control for alcohol, gender and fluid intelligence, group differences in all three word fluency scores were significant: $F(1,89) = 4.00$, $p < .05$ for

semantic fluency; $F(1,89) = 6.18$, $p<.05$, for "S" letter fluency; and $F(1,89) = 15.97$, $p<.001$ for "C" letter fluency.

Although there were no significant group differences in NART scores, it was possible that the effect of ecstasy use on access to long-term memory could in part be mediated by verbal IQ, and hence NART scores. Using Pearson's correlations it was found that NART scores were significantly correlated with semantic fluency ($r = 0.231$, $p<.05$), "S" letter fluency ($r = 0.240$, $p<.05$), and "C" letter fluency ($r = 0.326$, $p<.01$). To address this possibility NART scores were entered as a covariate. The main effect of ecstasy use on word fluency remained significant after control for NART scores, $F(3,92) = 4.41$, $p<.01$. Group differences in semantic fluency remained non-significant ($p>.05$), but differences in "S" and "C" letter fluency remained significant, $F(1,94) = 5.92$; 13.22, $p<.05$ and $p<.001$ respectively. Homogeneity of regression was achieved with respect to all covariates, $p>.05$ for the group covariate interaction. Correlations between years of education and semantic fluency, "S" letter fluency, and "C" letter fluency were non significant ($r = 0.070$; 0.154; 0.097 respectively, $p>.05$). Nonetheless, it was possible that ecstasy group differences in word fluency may be mediated by available word knowledge, and thus be related to education. The main effect of ecstasy use on access remained significant after control for years of education, $F(3.93) = 4.99$, $p<.01$, although differences in semantic fluency were still non-significant, $F(1,95) = 1.86$, $p>.05$. Ecstasy-related differences in "S" and "C" letter fluency were actually intensified after control for number of years spent in education, $F(1,95) = 7.57$, $p<.01$ and $F(1,95) = 14.81$, $p<.001$ respectively.

As mentioned in the introduction, it is possible that access to semantic memory may be mediated by differences in working memory capacity and attention.

To evaluate the impact of working memory capacity on access, computation span was entered as a covariate. The main effect of ecstasy use remained significant after control for computation span, $F(3.93) = 4.01$, $p<.01$. Differences in semantic fluency remained non-significant, $F(1,95) = 1.22$, $p>.05$. Although very slightly attenuated, differences in "S" letter fluency remained significant, $F(1,95) = 5.03$, $p<.05$, as did differences in "C" letter fluency, $F(1,95) = 12.01$, $p<.001$. After entering digit span as a covariate, the main effect of ecstasy use was slightly intensified, $F(3,93) = 4.80$, $p<.01$, as were group differences in "C" letter fluency, $F(1,95) = 14.48$, $p<.001$. Differences in Semantic fluency remained non-significant, $F(1,95) = 1.66$, $p>.05$. There was also no change in differences in "S" letter fluency following control for digit span, $F(1,95) = 6.48$, $p<.05$. Homogeneity of regression was achieved for all covariates, $p>.05$ for the group by covariate interaction.

To summarise, ecstasy-related differences in access do not appear to be mediated by differences in intelligence, lifestyle factors, working memory capacity or attention.

Indices of Drug Use

Inspection of Table 8.3 shows that the use of other drugs was limited mainly to the use of cannabis among the non-ecstasy group. The ecstasy users had a lifetime dose of cannabis twice that of the non-users (2620 joints to 1083 joints), in addition to using it more frequently (2.69 times a week, compared to 0.77 times a week), having smoked more in the last 30 days (25.31 joints compared to 7.91 joints), and having a larger average weekly dose (8.77 joints compared to 5.14 joints). In relation to the cannabis measures, t-test revealed that the group difference was statistically significant for total lifetime dose, frequency of use, and amount used in the last 30 days: $t(40.40) = -2.36$, $p<.05$; $t(35.98) = -3.56$, $p<.001$; and $t(33.62) = -2.36$, $p<.05$

respectively (As Levene's test was significant, degrees of freedom have been adjusted accordingly).

Table 8.3: Indicators of Drug Use Among Ecstasy Users and Non Ecstasy Users.

	Ecstasy Users			Nonusers		
	Mean	S.D.	n	Mean	S.D.	N
Total Use						
Ecstasy (Tablets)	314.93	326.23	36	-	-	-
Amphetamine (grams)	47.11	129.38	9	4	-	1
Cannabis (joints)	2620.46	2888.46	27	1082.54	1439.33	18
Cocaine (grams)	18.10	21.57	16	-	-	-
Frequency of Use (times per week)						
Ecstasy	0.39	0.34	35	-	-	-
Amphetamine	0.04	0.04	5	-	-	-
Cannabis	2.69	2.61	28	0.77	0.90	18
Cocaine	0.25	0.23	16	-	-	-
Amount Used During Previous 30 Days						
Ecstasy (tablets)	3.14	3.39	35	-	-	-
Amphetamine (grams)	1.20	2.68	5	-	-	-
Cannabis (joints)	25.31	35.51	27	7.91	11.04	16
Cocaine (grams)	1.20	1.71	14	-	-	-
Average Weekly Dose						
Ecstasy (tablets)	1.94	1.67	36	-	-	-
Amphetamine (grams)	0.32	0.52	8	0.09	-	1
Cannabis (joints)	8.77	8.81	26	5.14	10.01	18
Cocaine (grams)	0.15	0.23	16	-	-	-
Number Ever Used						
Amphetamine	17	-	-	3	-	-
Cannabis	33	-	-	30	-	-
Cocaine	29	-	-	7	-	-

Correlations with Indices of Drug Use.

Due to the small number of illicit drug users among the non ecstasy user group it was not possible to control statistically for the effects of other drugs through the use of ANCOVA. Therefore it is possible that some or all of the ecstasy-related effects might have been attributable to the effects of other drugs. To address this possibility, correlations were performed with different measures of ecstasy, amphetamine, cannabis and cocaine use. Measures of lifetime use of each drug, the number of times each drug was consumed each week, the amount of each drug consumed within the last 30 days, and the average weekly dose (i.e. total amount consumed divided by the length of use in weeks) were all included[13]. For each of these a value of zero was entered for nonusers of the drug in question. In addition, for each illicit drug, a categorical variable in which users and nonusers of each drug were coded as 0 or 1 respectively was included.

A partial Bonferroni correction was applied as in Chapter 6. Specifically a value for alpha of 0.01 was selected. The results, set out in Table 8.4, show that ecstasy use was significantly correlated with a number of the performance measures.

[13] Those in the nonuser group who reported that they had ever used amphetamine or cocaine (N= 3 and 7 respectively) felt that they were unable to estimate their pattern of use accurately.

Table 8.4: Correlations between Word Fluency Measures and Indices of Drug Use

		Ecstasy	Cannabis	Cocaine	Amphetamine
Total use	N	98	80	78	88
Semantic Fluency		-0.114	-0.113	-0.156	0.041
"S" letter		-0.274**	-0.119	-0.307**	0.075
"C" letter		-0.369**	-0.272**	-0.420**	-0.028
Frequency of Use	N	97	81	78	83
Semantic Fluency		-0.044	-0.106	-0.201**	0.145
"S" letter		-0.176	-0.084	-0.279**	0.054
"C" letter		-0.304**	-0.259**	-0.426**	-0.065
Average dose	N	98	79	78	87
Semantic Fluency		-0.068	-0.092	-0.151	0.004
"S" letter		-0.262**	-0.100	-0.300**	0.035
"C" letter		-0.381**	-0.236	-0.420**	-0.046
Current Use	N	98	98	98	98
Semantic Fluency		-0.046	-0.163	-0.205	0.022
"S" letter		-0.164	-0.104	-0.224	-0.048
"C" letter		-0.329**	-0.253**	-0.249**	-0.094
Ever Used	N	98	98	98	98
Semantic Fluency		0.095	0.033	0.154	-0.021
"S" letter		0.248**	0.096	0.226**	-0.046
"C" letter		0.370**	0.231	0.357**	0.072

** Correlation significant at p<.01

Total ecstasy use, average dose of ecstasy, and having ever used ecstasy were all significantly correlated with "S" letter fluency (at p<.01), while total lifetime dose, frequency of use, average dose, amount used in the last 30 days, and having ever used ecstasy were all significantly correlated with "C" letter fluency.

In relation to other drugs, total lifetime cannabis dose, frequency of use, and amount used in the last 30 days were all significantly correlated with "C" letter

fluency. Total lifetime cocaine dose, frequency of cocaine use, average weekly cocaine dose, and having ever used cocaine were all significantly correlated with "S" letter fluency, while like ecstasy, total lifetime dose, frequency of use, average weekly dose, amount used in the last 30 days, and having ever used cocaine were all significantly correlated with "C" letter fluency.

While correlations with ecstasy were all stronger than those for cannabis use, this was not the case for correlations with cocaine use (with the exception of having ever used and amount used in the last 30 days on "C" letter fluency, where ecstasy was higher), and it is clear from the correlations that aspects of cocaine use may have contributed or possibly caused the observed ecstasy-related deficits in word fluency. To evaluate the potentially confounding effects of cocaine we performed several analyses with a categorical cocaine user/nonuser independent variable, with those reporting that they had ever tried cocaine, N=36 versus those who reported that they had never tried cocaine, N=62, which would enable us to compare effect sizes for ecstasy versus cocaine analyses. There was a main effect of cocaine use on access to long-term memory, $F(3,94) = 4.62$, $p<.01$, and separate univariate analyses revealed that cocaine users performed significantly worse on the "S" and "C" letter fluency tasks, $F(1,96) = 5.82$; 13.38, $p<.05$ and $p<.001$ respectively, while cocaine-related differences on semantic fluency approached significance, $F(1,96) = 3.52$, $p = 0.064$. To try and compare cocaine and ecstasy group-related effects on word fluency, we compared the effect sizes for the two sets of analyses. The multivariate effect size was marginally larger for cocaine user than for ecstasy user (partial Eta squared of 0.129 and 0.127 respectively), as was the semantic fluency effect size (partial Eta squared of 0.035 and 0.017 respectively). Effect sizes on the other indices of access to semantic memory were however marginally smaller for cocaine that for ecstasy: partial Eta

squared of 0.057 compared to 0.063 for "S" letter fluency, and partial Eta squared of 0.122 compared to 0.125 for "C" letter fluency. This is consistent with either an ecstasy-related word fluency deficit, or an exacerbated cocaine/ecstasy deficit in access to long-term memory.

Supplementary to the effect size analyses, part correlations were performed between ecstasy use and word fluency after control for indices of cocaine use. The results are summarised in Table 8.5. Although slightly attenuated following control for cocaine use, most of the significant correlations with ecstasy use remained significant.

Table 8.5 Part correlations after control for cocaine use indices

	Semantic fluency	"S" Letter Fluency	"C" Letter Fluency
Control for Total Cocaine			
Total ecstasy Use	-0.167[a]	-0.128	-0.158[a]
Frequency of ecstasy Use	-0.104	-0.072	-0.172[a]
Current Ecstasy Use	-0.072	-0.076	-0.157[a]
Average Ecstasy Dose	0.046	-0.116	-0.258**
Ever used Ecstasy	0.051	0.118	0.301**
Control for Cocaine Frequency			
Total ecstasy Use	-0.137	-0.095	-0.038
Frequency of ecstasy Use	-0.037	0.051	0.042
Current Ecstasy Use	0.005	0.037	0.026
Average Ecstasy Dose	0.054	-0.126	-0.180[a]
Ever used Ecstasy	0.044	0.099	0.212*
Control for Current Cocaine			
Total ecstasy Use	-0.065	-0.174*	-0.198*
Frequency of ecstasy Use	0.008	-0.093	-0.195*
Current Ecstasy Use	0.007	0.005	-0.189*
Average Ecstasy Dose	0.061	-0.163[a]	-0.261**
Ever used Ecstasy	0.020	-0.176*	0.303**
Control for Average Cocaine			
Total ecstasy Use	-0.228*	-0.208*	-0.213*
Frequency of ecstasy Use	-0.145	-0.121	-0.204*
Current Ecstasy Use	-0.127	-0.138	-0.197*
Average Ecstasy Dose	-0.012	-0.169[a]	-0.288**
Ever used Ecstasy	0.104	0.173[a]	0.330**
Control for Ever Used Cocaine			
Total ecstasy Use	-0.138	-0.194*	-0.115
Frequency of ecstasy Use	-0.052	-0.104	-0.115
Current Ecstasy Use	-0.087	-0.044	-0.137
Average Ecstasy Dose	0.063	-0.135	-0.171*
Ever used Ecstasy	-0.011	0.119	0.160[a]

* denotes correlation significant at p<.05

** denotes correlation significant at p<.01

[a] denotes correlation approached significance.

Implications of Chapter 8

This chapter supports an ecstasy-related deficit in access to long-term memory that is not related to gender, intelligence, alcohol use, cannabis use or

amphetamine use. However, it is possible that access to long-term memory (as indexed by the word fluency scores) is also sensitive to aspects of cocaine use. Indeed Table 4 reveals that among ecstasy users, in the majority of cases outcome measures were more related to aspects of cocaine use than they were to the equivalent indices of ecstasy use. Working memory updating and attention do not appear to be important mediating factors of word fluency deficits in ecstasy users, suggesting the presence of a specific access deficit in users, rather than a lower level attentional deficit. To summarise the results of this thesis so far, ecstasy users exhibit impairments in tasks that tap memory updating and access, but not switching and inhibition. It is possible that these differences in updating and access may mediate a range of other cognitive abilities. Reasoning is one area that is under-investigated in research in ecstasy users. The next Chapter will assess reasoning competence in ecstasy users via a syllogistic reasoning task. The impact of differences in memory updating and access on syllogistic reasoning will also be investigated.

Chapter 9: Syllogistic Reasoning

9.1 Chapter Overview

The aim of this chapter was to assess reasoning deficits in ecstasy users and the contribution of access and updating to performance on reasoning tasks. Previous research has demonstrated working memory and executive deficits in recreational users of ecstasy. In turn, both of these constructs have been implicated in syllogistic reasoning performance. Thirty ecstasy users and 30 non-ecstasy user controls were tested on syllogisms of varying difficulty, and on measures of updating (computation span) and access (word fluency). Ecstasy users were significantly impaired in aspects of syllogistic reasoning. However, the ecstasy-related variance was reduced to below statistical significance following control for group differences in working memory span. The results are consistent with the possibility that ecstasy-related deficits in aspects of executive functioning result in impaired reasoning performance among ecstasy users.

9.2 Introduction

Syllogistic reasoning performance in normal populations has been shown to rely on working memory and executive resources (Fisk & Sharp, 2002; Gilinsky and Judd, 1994). The purpose of this chapter was to establish whether ecstasy-related deficits in working memory might give rise to reasoning deficits. Since syllogistic reasoning is generally regarded as an indicator of the capacity for rational thought, ecstasy-related deficits on this measure raise the possibility that extensive use of ecstasy might be associated with impaired rational thinking. However, the possibility that ecstasy users might be impaired in reasoning, and more specifically in syllogistic reasoning, has not yet been investigated.

Johnson-Laird (1983) has proposed that rather than using some logical propositional calculus to solve reasoning problems, we generally construct mental models of the problem. Johnson-Laird (1983) suggests that individuals generally go through three stages when attempting to solve a syllogism. The first stage involves forming a mental model of the first premise of the problem, then incorporating the second premise into this model. The second stage involves using their mental model to propose a conclusion to the problem. In the third stage, individuals supposedly test their conclusion by searching for possible alternative models, and if none are available the conclusion is accepted as valid. If the conclusion is not valid, then another conclusion is deduced, and again tested against the models. Some syllogisms however have no valid conclusions. Syllogistic reasoning requires a participant to draw valid inferences from a set of premises. For Example the pair of premises:

Some A are B,

and

All B are C

can be accommodated within a single model, from which it follows that:

Some of A are C

as there is no alternative model of the premises that violates the conclusion.

On the other hand, the pair:

All of B are A

and

None of B are C

initially gives rise to a model that is consistent with the proposition that

No A are C

This in turn then requires the construction of a second model, which remaining consistent with the premises, falsifies this conclusion. The second model however leaves open the propositions that:

Some of the C are not A

and

Some of the A are not C

which in turn requires the construction of a third model, leaving only the second of these conclusions as valid (see Johnson-Laird, 1983, pp. 98-100).

Johnson-Laird (1983) maintains that reasoning involves constructing mental models of the premises and testing conclusions against these models. As described above, constructing a single model may solve some problems, while others may require up to three models. The more complex the problem, the greater number of models required and the greater the load on working memory and executive resources.

Among the different measures of reasoning competence, syllogistic reasoning is perhaps one of the best known. It was central in the development of Johnson-Laird's mental models theory (Evans, Handley, Harper & Johnson-Laird, 1999; Johnson-Laird, 1983). Within a developmental context, it has been used as a key indicator of reasoning competence in early childhood (Lourenco & Machado, 1996) and over the adult lifespan (Gilinski & Judd, 1994; Fisk & Sharp, 2002). Syllogisms have also featured prominently in the debate on human rationality (e.g., Stanovich & West, 2000). Syllogistic reasoning is also believed to utilise resources outside of working memory, for example relations between linguistic concepts such as 'all', 'some' and the logical operator 'not', as well as spatial representations of class inclusion relationships (see, for example, Ford, 1995).

Some studies in ecstasy users have assessed decision making/reasoning (see Chapter 3, Section 3.3.3 for full review). While one study (McCann et al. 1999) found that ecstasy users were impaired in logical reasoning, another found that ecstasy use was a significant predictor of poor performance on an analogical reasoning task (Verdejo-Garcia et al. 2005). Of the other studies that assessed logical reasoning, most used tasks that also supposedly tap other functions (e.g. the Revised Strategy Application Task used by Halpern et al. 2004 may be reliant on shifting and inhibition, as well as planning and reasoning). The majority of studies in ecstasy users have utilised planning tasks (e.g. the Tower of London Task: Alting von Geusau et al. 2004; Fox et al. 2001; Lamers et al. 2003; Morgan 1998; Schifano et al. 1998) to assess planning/reasoning skills. There were mixed results on tasks of planning ability, with some studies finding that ecstasy users exhibited longer planning times (Fox et al. 2001), and some that they exhibited shorter planning times (Alting von Geusau et al. 2004). However, the constructs underlying of the Tower of London (TOL) task are not well established. While the TOL is used to assess planning/decision making, Miyake et al. (2000) found that performance on the TOH (which is similar to the TOL) was related to the inhibition component of executive functioning. Indeed it was suggested that participants did not generally use a "planning strategy", but a "perceptual strategy" to solve the TOL task. This entailed making a move that would bring the present state of the task closer to the goal state, rather than a move which may temporarily take them away from the goal state, but result in arriving at their goal sooner (e.g. moving a disk away from the final peg). In this scenario, it is the inhibition of a prepotent response to move closer to, and not away from, the goal that may be impaired rather than a planning strategy itself (Goel & Grafman, 1995). Miyake et al. also postulate that if a planning strategy is

implemented as opposed to a perceptual strategy, then task performance may be more related to the updating component, which is involved in the management of goal information.

With reference to which aspects of executive functioning might be related to syllogistic reasoning in the present study, Gilhooly and co-workers (Gilhooly et al. 1993; Gilhooly et al. 1999) have found that concurrent random number generation (which Miyake et al. postulate is related to inhibition and updating) impaired performance on a syllogistic reasoning task, indicating that the two tasks may share the same modality. In addition, a number of studies have found that syllogistic reasoning performance is related to working memory capacity. One study investigating the extent to which performance on a syllogistic reasoning task can be predicted by working memory capacity in normal populations used the operation span task, a key indicator of Miyake et al's conceptual framework. It was found that those with larger working memory capacities performed better, which the authors conclude indicates a greater ability to effectively utilise mental models (Copeland & Radvansky, 2004), and thus performed better on the task. It is also possible that due to the linguistic nature of the task, requiring the understanding of relationships such as "some" "all" and "none" that linguistic abilities may be related to syllogistic reasoning performance (Ford, 1995). To summarise, inhibition, updating and access components of central executive functioning have been implicated in syllogistic reasoning deficits in normal populations. As Chapters 6 and 8 revealed that ecstasy users exhibit deficits in updating and access respectively, it was possible that these components may underpin syllogistic reasoning performance in the present study. In contrast, no deficits were observed on the inhibition task. Consequently, the present

chapter will ascertain if deficits in access and updating (indexed by word fluency and computation span) are responsible for ecstasy-related deficits in syllogistic reasoning.

While the preceding paragraphs suggest that reasoning in general, and syllogistic reasoning in particular are well researched outside the area of Psychopharmacology, an important area of cognitive functioning that has not been directly addressed with regard to ecstasy users is reasoning. Of the broad range of intellectual abilities that has been investigated, reasoning is perhaps the most cognitively demanding. There is cause to believe that among the many illicit drugs commonly in use, ecstasy in particular has the potential to disrupt reasoning processes. The drug is believed to have long-term adverse effects on the serotonin system (Morgan, 2000). In turn, the serotonin system is believed to underpin the operation of working memory processes through its modulation of the dopaminergic systems that support prefrontal executive processes (Luciana, Collins, & Depue, 1998; Robbins 2000). Indeed in his review of the literature, Morgan (2000, page234) has noted that 'it has been proposed that it [serotonin] may play an orchestrating role in cognition'. Given that ecstasy use has been associated with impaired working memory and executive functioning (As in Chapter 6 of this thesis; Wareing et al. 2000; Wareing et al. 2004b), and that these cognitive constructs are believed to underpin syllogistic reasoning performance (e.g., see Fisk & Sharp, 2002; Gilhooly, Logie and Wynn, 1999), it seems reasonable to expect that ecstasy users might be impaired on this measure of reasoning ability.

To sum up, it is expected that ecstasy users will perform worse compared to controls in a syllogistic reasoning task and that consistent with Johnson-Laird's mental models theory, the ecstasy related deficit will be most pronounced on the two and three-model syllogisms, as these load most heavily on working memory and

executive resources. ANCOVA will be used to investigate the extent to which ecstasy-related differences in syllogistic reasoning are related to group differences in working memory capacity and executive functioning. Updating and access will be assessed through a computation span task and through word fluency. It is also possible that the use of other drugs may play a part in the observed syllogistic reasoning deficits, accordingly correlations will be performed between indices of drug use and syllogistic reasoning.

9.3 Method

9.3.1 Design.

A mixed design was used with ecstasy user group (with two levels, user/non-user) as the between participants variable, and level of difficulty of the syllogism (again with two levels, low and high) as the within participants variable. Level of difficulty was based on the number of models required to derive a solution. Thus one-model syllogisms were low in difficulty. Since the NVC and three-model syllogisms require a similar number of models to produce a solution, responses for these types were combined to form the high difficulty level. The dependent variable was the number of correct solutions for the low and high difficulty syllogisms (maximum score was eight in both cases). We also sought to determine whether the main effect of user group was qualified by a user-by-difficulty interaction. ANCOVA was used to statistically control for group differences in updating and access as indexed by computation span and word fluency.

9.3.2 Participants

Thirty ecstasy users (mean age 21.37, 16 male) and 30 non-ecstasy user controls (mean age 21.3, 10 male) were recruited[14]. With 30 participants in each group, the present sample is sufficient to detect a difference of 0.75σ for $\alpha = .05$ and $\beta = .20$ (Hinkle et al, 1994). As in Chapter 6 participants were initially recruited through direct approach to Liverpool John Moores University undergraduate students. Participants were requested to refrain from ecstasy use for at least 7 days and ideally 10 days prior to testing (the mean period of abstinence was actually 12.70 weeks, median 2 weeks). Participants were also requested not to use any other illicit drugs for at least 24 hours and ideally for 7 days prior to testing. Participants were paid 15 UK pounds in store vouchers for their participation.

9.3.3 Materials.

Background data on drug use, fluid intelligence, premorbid intelligence, sleep patterns and other relevant lifestyle variables was collected as described in Chapter 6 (section 6.3.3).

Syllogistic reasoning. The syllogisms were presented in abstract form as in the example set out above. Participants attempted to generate solutions for four one-model syllogisms, four three-model syllogisms, and four syllogisms for which there was no valid conclusion (NVC). The syllogisms were the same as those used by Fisk and Sharp (2002). Scores were based on the number of correct solutions, or in the case of the NVC syllogisms, a response was deemed correct when the participant indicated that no valid conclusions were possible. According to Johnson-Laird (1983), NVC syllogisms require either two or three mental models in order to derive the correct solution. In the present study, two of the NVC syllogisms were two-model and

[14] Due to an oversight, only 15 ecstasy users and 18 nonusers completed the access tasks.

two were three-model. Therefore, in terms of the number of models required, three-model and NVC syllogisms were the hardest, and one-model the easiest. The syllogisms used in the study were presented in random order. The test was administered following the procedure outlined by Fisk and Sharp (2002).

Working Memory Updating: Computation span was used as described in Chapter 8. Since computation span is reliant on both phonological and executive processing resources, a simple digit span task (Fisk & Warr, 1996) was also administered so that it could be ascertained that any observed ecstasy related deficits were not simply a result of lower level non executive impairments (i.e., the phonological loop).

The Chicago Word Fluency Test and a Semantic Fluency Test (Animals) were used to assess access as in Chapter 8.

9.3.4 Procedure.

Informed consent was obtained. The tests were administered under controlled laboratory conditions. A computer, using MS-DOS was used for the computation span test. Tasks were administered in the following order: Health/education questionnaire, drug use background questionnaire and sleep questionnaires, word fluency tests, computation span test, syllogistic reasoning test, NART, and finally Ravens progressive matrices. The order of the access, computation span and syllogistic reasoning tests was rotated, to eliminate order effects. The study was approved by the Ethics Committee of Liverpool John Moores University, and was administered in accordance with the ethical guidelines of the British Psychological Society.

9.5 Results

Background Variables.

Average age, years of education, fluid intelligence, premorbid intelligence, and other background variables for the two groups are set out in Table 9.1. A t-test revealed that there were some significant group differences among the background variables. Ecstasy users performed worse than non-users on the computation span test, $t(56) = -3.50$, $p<.001$, and also reported consuming more alcohol than nonusers in an average week, $t(58) = 2.24$, $p<.05$. Unlike group differences evident in chapter 8, ecstasy users did not perform significantly worse than nonusers on the access tasks, although the difference approached significance for "C letter fluency, $t(31) = -1.99$, $p = 0.055$. In this study, the gender distribution of the groups was comparable, χ^2 (d.f. 1, N=60) = 2.44, $p>.05$.

Table 9.1: Performance of ecstasy users and nonusers on Background Variables

	Ecstasy Users		Nonusers	
	Mean	S.D.	Mean	S.D.
Age (Years)	21.37	1.65	21.30	1.62
Years of Education	15.10	2.77	15.80	1.85
Raven's Progressive Matrices (max. 60)	48.40	6.13	48.31	5.81
NART (max. 50)	28.07	6.72	29.67	5.86
Units of Alcohol consumed in a week	22.40	12.21	14.71	13.90
Hours of Sleep per Night	8.30	1.45	8.25	1.01
Epworth Sleepiness Scale (max. 24)	5.76	3.14	6.50	2.45
Self-report Health[1]	3.50	0.78	3.83	0.83
Computation Span	3.33	1.56	4.77	1.61
Semantic Fluency[2]	43.13	6.93	41.50	9.73
"S" Letter Fluency[2]	39.80	9.48	46.00	10.88
"C" Letter Fluency[2]	11.07	4.74	14.78	5.78
Weeks since last used Ecstasy	12.70	33.79	-	-

[1] On a scale of 1 = poor to 5 = good health
[2] Mean numbers of words

Main Analysis

Table 9.2 reveals that ecstasy users performed worse than non-users both on the one-model and on the three-model/NVC syllogisms although in the latter case the group difference was much less pronounced. Mixed ANOVA yielded a significant models by user interaction, $F(1,58)=5.56$, $p<.05$, and a main effect of ecstasy use, $F(1,58) = 5.76$, $p<.05$. Subsequent analyses revealed that ecstasy users performed significantly worse on the one-model syllogisms, $F(1,58) = 8.02$, $<.01$, but there was

little difference between the groups on the NVC/three-model problems, $F(1,58) = 0.97$, $p>.05$.

Correlations also revealed that although there were only group differences on the one-model syllogisms, not the three-model/NVC syllogisms, performance on the two in the sample as a whole was significantly correlated ($r = 0.355$, $p<.01$ one-tailed).

Table 9.2: Average number of correct responses for syllogistic reasoning task

	Ecstasy Users		Nonusers	
	Mean	S.D.	Mean	S.D.
One-Model Syllogisms	3.73	2.01	5.10	1.71
Three-model/NVC Syllogisms	1.33	1.88	1.77	1.50
Total Percentage Correct	31.63		42.94	

Note: for the four one-model problems (for which there were two valid conclusions per syllogism), and the eight three-model/NVC syllogisms (for which there was one valid conclusion per syllogism), the maximum possible score was eight. A one-sample t-test was conducted to see if performance of ecstasy users and nonusers was above chance on the syllogisms, with chance level of performance being one out of eight correct. For the one-model syllogisms, the ecstasy users and nonusers both performed well above chance, $t(29) = 2.80$, $p<.01$ and 13.14, $p<.001$ respectively. However, only the nonusers performed significantly better than chance on the three-model/NVC syllogisms, $t(29) = 7.43$, $p<.001$.

Covariate Analyses.

Working memory and executive functioning. It is possible that the observed ecstasy-related deficit in syllogistic reasoning might be mediated by executive

components. One aim of this thesis was to ascertain the extent to which ecstasy-related deficits in syllogistic reasoning are mediated by updating and access. Ecstasy users performed significantly worse than nonusers on the computation span measure, although no group differences were observed on the access tasks (Table 9.1). Nevertheless, as access may still have contributed to syllogistic reasoning deficits in the present sample, this was incorporated into ANCOVA. ANCOVA generated a non-significant result with respect to computation span $F(1,57) = 2.00$, $p>.05$. However, the ecstasy user group by models interaction was reduced to below statistical significance following control for computation span, $F(1,57) = 1.00$, $p>.05$. The main effect of user group was also reduced to below statistical significance, $F<1$. By way of contrast, ANCOVA with word fluency as a covariate generated a non-significant result with respect to all three word fluency measures, $p>.05$ in all cases. The interaction effect between group and models on syllogistic reasoning was however reduced to below statistical significance following control for access, $F(1,28) = 0.10$, $p>.05$. The ecstasy-related differences in syllogistic reasoning remained significant after control for access, $F(1,28) = 5.72$, $p<.05$. In both analyses the group by covariate interactions were non-significant, $F< 1$, indicating that homogeneity of regression was obtained (with the exception of semantic fluency).

To ascertain the extent to which computation span, word fluency, and having ever used ecstasy might be responsible for differences observed in reasoning, linear regression analysis was performed. Computation span emerged as the only significant predictor of performance on 1-model syllogistic reasoning problems $t(32) = 2.60$, $p<.05$.

As ecstasy users reported drinking significantly more alcohol in an average week than nonusers, this was also incorporated into ANCOVA. The models by

ecstasy user group interaction was reduced to below statistical significance, $F(1,55) = 1.65$, $p>.05$. On the contrary, the main effect of ecstasy use on syllogistic reasoning was actually slightly intensified after control alcohol use, $F(1,55) = 7.01$, $p<.05$.

Indices of Drug Use

As in Chapters 6, 7, and 8 inspection of Table 9.3 reveals that the use of "other" drugs was commonplace among ecstasy users, while among non-ecstasy users, drug use was mainly limited to alcohol. Ecstasy users reported a larger total lifetime dose of cannabis (3790 joints compared to 1141 for nonusers), using cannabis more frequently (2.62 times per week compared to 0.70), having smoked more in the 30 days prior to testing (55 joints compared to 6), and reporting a larger average weekly dose (12 joints compared to 4 joints for nonusers). Differences in total lifetime dose, and average weekly dose were non-significant, $t(29) = 1.12$, and $t(25.04) = 1.91$, $p>.05$ respectively. Group differences in terms of frequency of use were significant, $t(25.17) = 3.15$, $p<.01$, as were differences in amount of cannabis used in the last 30 days, $t(20.49) = 2.49$, $p<.05$ (for average dose, frequency of use and amount used in the last 30 days, Levene's test was significant so degrees of freedom have been adjusted accordingly).

Table 9.3: Indices of Drug Use

	Ecstasy Users			Nonusers		
	Mean	S.D.	N	Mean	S.D.	N
Total Use						
Ecstasy (tablets)	277.45	328.63	30	-	-	-
Amphetamine (grams)	74.07	186.06	7	-	-	-
Cannabis (joints)	3789.77	6198.92	22	1141.44	1723.69	9
Cocaine (grams)	45.62	70.02	15	-	-	-
Frequency of Use (times per week)						
Ecstasy	0.40	0.37	22	-	-	-
Amphetamine	0.11	0.13	3	-	-	-
Cannabis	2.62	2.71	22	0.70	0.58	9
Cocaine	0.59	0.55	15	-	-	-
Use in last 30 Days						
Ecstasy (tablets)	5.86	7.38	29	-	-	-
Amphetamine (grams)	-	-	-	-	-	-
Cannabis (joints)	54.83	88.86	21	6.28	6.46	9
Cocaine (grams)	2.35	2.42	15	-	-	-
Average Dose						
Ecstasy (tablets)	2.56	3.65	30	-	-	-
Amphetamine (grams)	0.24	0.47	6	-	-	-
Cannabis (joints)	12.33	18.46	21	4.08	4.68	9
Cocaine (grams)	0.42	0.47	15	-	-	-
Number Ever Used						
Amphetamine	15			0		
Cannabis	29			15		
Cocaine	22			2		

It was necessary to establish whether the prevalence of polydrug use, especially among the ecstasy user group (see Table 9.3), contributed to the ecstasy-related differences in reasoning. As once again there were relatively small numbers of users of cannabis, amphetamine and cocaine in the non-ecstasy group, correlations were performed between indices of the use of ecstasy, cannabis, cocaine and

amphetamine to ascertain the extent to which each drug may contribute to reasoning performance.

Table 9.4: Correlations with Indices of Drug Use

		Ecstasy	Cannabis	Cocaine	Amphetamine
Total Use	**N**	60	47	51	52
One-model		-0.342**	-0.210	-0.258	-0.314
Three-model/NVC		-0.126	-0.078	0.050	-0.106
Frequency of Use	**N**	59	47	51	48
One-model		-0.257	-0.330	-0.294	-0.186
Three-model/NVC		-0.023	-0.061	0.083	-0.134
Use in last 30 Days	**N**	60	60	60	-
One-model		-0.201	-0.155	-0.240	-
Three-model/NVC		0.051	-0.030	0.141	-
Average Dose	**N**	60	46	51	51
One-model		-0.352**	-0.229	-0.262	-0.274
Three-model/NVC		-0.128	-0.072	-0.068	-0.161
Ever Used	**N**	60	60	60	60
One-model		0.343**	0.134	0.187	0.311**
Three-model/NVC		0.217	0.101	0.026	0.067

** Correlation significant at p<.01 one-tailed

A partial correction was used as in Chapter 6 to adjust for inflated error rates following multiple comparisons[15]. No indices of drug use were significantly correlated with performance on the three-model syllogisms at p<.01. With reference to 1-model syllogisms, total lifetime dose of ecstasy, average weekly dose, and having ever used ecstasy were all significantly correlated with performance. This was also

[15] Again, those in the nonuser group who had used cocaine (n=2) felt hat they were unable to accurately estimate their pattern of use.

true of having ever used amphetamine, although the correlation was higher for having ever used ecstasy than having ever used amphetamine, and as all participants on whom this analysis was based were also ecstasy users, the significant correlation may reflect some aspect of ecstasy use.

Implications of Chapter 9

The present chapter demonstrates an ecstasy related deficit in syllogistic reasoning. Ecstasy users performed worse on the one-model syllogisms, although there was little difference on the three-model/NVC syllogisms. The absence of differences on the three-model/NVC syllogisms provides further support for Evans et al's proposition that individuals only generally construct one mental model of premises (see general discussion). One aim of this chapter was to ascertain the role that the executive deficits observed in Chapters 6 and 8 might play in ecstasy-related differences in syllogistic reasoning. Following control for computation span, ecstasy-related differences in syllogistic reasoning were reduced to below statistical significance, although the same was not true for access to long-term memory (though this may reflect the reduced sample size in this analysis). This highlights the role of Miyake et al's updating component in contributing to syllogistic reasoning deficits in ecstasy users.

Syllogistic reasoning as assessed in this Chapter is a higher level cognitive process which is reliant on executive prefrontal resources (e.g. Goel, Buchel, Frith & Dolan 2000). Another aspect of cognition that utilises executive prefrontal resources is associative learning. While research suggests that the hippocampal formation may be important in associative learning performance (e.g. Collie et al. 2002), there is also clear evidence that the prefrontal cortex is involved in human associative learning (e.g. Moscovitch and Winocur 2002). This involvement may be especially evident

during the initial phases of learning or when pre-existing associations break down (i.e. forgetting) (Fletcher, Anderson, Shanks, Honey et al. 2001). Thus like syllogistic reasoning, associative learning is a higher-level cognitive process that may also rely on executive resources. The next chapter assesses possible ecstasy-related differences in associative learning and the contribution of updating and access to performance on these tasks.

Chapter 10: The Nature of Associative Learning Deficits

10.1 Chapter Overview

In view of the results of the preceding chapters, it was possible that ecstasy-related differences in associative learning may be mediated by differences in updating and access – this was explored in the present chapter. Research has revealed associative learning deficits among users of ecstasy; the present chapter explored the component processes underlying these deficits. Thirty-five ecstasy users and 62 non-ecstasy users completed a computer-based, verbal paired-associates learning task, requiring the learning of eight sequentially presented word pairs. After all eight had been presented, the first member of each pair was displayed and participants attempted to recall the second. Correct responses on each trial, forgetting at various levels of learning, perseveration errors and the rate at which the associations were learned (trials to completion) were all recorded. There was a main effect of ecstasy use indicating that ecstasy users performed worse overall and subsequent ANOVAs showed that users performed significantly worse on virtually all measures. Regression analysis revealed that over half of the ecstasy-group related variance in trials to completion was attributable to group differences in initial learning and forgetting. In relation to forgetting, it appears that cannabis use may be the primary determinant. In relation to rate of learning (trials to completion) and initial learning, both ecstasy and cannabis may be implicated. Unlike syllogistic reasoning, it appears that ecstasy-related differences in associative learning are not underpinned by group differences in updating and access. There appears to be abundant evidence of associative learning deficits among ecstasy users. However, it appears that a range of illicit drugs including cannabis and ecstasy may contribute to these deficits.

10.2 Introduction

Developing an understanding of relationships between concepts is a fundamental aspect of human learning. One key aspect of this is associative learning, which involves forming appropriate links between previously unrelated phenomena. The working memory system in general, and the executive in particular are essential components in learning new skills before they become automatic, so that learning and the acquisition of knowledge is dependent on working memory (Tanji & Hoshi, 2001). The term associative learning describes the process by which an organism develops or reinforces connections between stimulus representations (Rose et al, 2001). Ecstasy users have been shown to exhibit deficits in aspects of working memory functioning (e.g., Fisk et al, 2004; Wareing et al. 2004b) and in view of the role of working memory and executive processes in supporting associative learning (Collie et al. 2002) it is possible that users might also experience impairments in learning processes.

Much of the research in this domain has focussed on animal learning and to date the results have been equivocal. While some studies have found MDMA-related deficits in aspects of learning (Broening, Morford, Inman-Wood, Fukumura et al. 2001; Frederick, Ali, Slicker, Gillam et al. 1995; Taylor & Jentsch, 2001; Williams, Morford, Wood, Rock et al. 2003) others have not (Frederick & Paule 1997; Ricaurte et al. 1993; Romano & Harvey 1994; Winsaeur, McCann, Yuan, Delatte et al. 2002). In a study examining learning in rats, Robinson, Castaneda and Whishaw (1993) found that the extent of 5HT denervation (72.6%) was not sufficient to produce marked deficits (this may be a sign of neurocompensatory changes). More generally, it is possible that the apparent lack of MDMA-related deficits in some animal studies is because the tasks are too simple, and they do not mirror learning in humans.

Although some studies in human ecstasy users have investigated associative learning, this is an area that is still under investigated as a number of tasks used relate more to immediate and delayed recall, rather than the learning of associations (see Chapter 3, Section 3.10 for full review). Gouzoulis-Mayfrank et al. (2003) used the word-pair learning test of the LGT-3 test battery, which requires participants to memorise 20 word pairs consisting of a Turkish word and it's German translation. In the retrieval phase, participants had to identify the correct Turkish word corresponding to each German word (out of 5 possible answers). Heavy ecstasy users performed worse than non-users in the delayed recall of the word pairs, but not the immediate recall component. However, the effect was reduced to below statistical significance after control for general knowledge scores.

Croft et al (2001a) studied the relative contributions of ecstasy and cannabis to spatial and non-spatial Paired Associates Learning (PAL). Participants were required to learn associations between six spatial pairs (spatial) and six colour pairs (non-spatial), but no significant differences were observed between the ecstasy/cannabis group and the cannabis only group. A combined drug-user group performed significantly worse than controls on the non-spatial PAL. ANCOVA revealed that this effect was more due to cannabis than ecstasy. However, the average cannabis abstinence period was only 17 hours so it was possible that participants were still intoxicated. Also, Croft et al's participants only had a modest lifetime dose of ecstasy.

A further study (Fox et al. 2002) also used a spatial PAL task in which participants were required to learn the spatial locations of abstract patterns. No significant group differences were observed in the number of errors, the number of presentations required per trial, or the memory score (total number of patterns successfully located on initial presentation). The group by trial interaction approached

significance, and post hoc tests revealed that the ecstasy group made a greater number of errors on the 8 pair trials. Rodgers (2000) found that ecstasy users were unimpaired during the initial learning phase of the verbal and visual paired associates sub-tasks of the Wechsler Memory Scale. However, subsequent deficits in the delayed recall of the verbal and visual paired associates were apparent among ecstasy users but not among cannabis-only users.

In addition to deficits in associative learning, basic verbal learning deficits have also been observed using the Rey Auditory Verbal Learning Test (RAVLT) (see Chapter 3, Section 3.6 for full review). During trials 1-5, a list of 15 words is read to participants, and they are then required to recall as many words as possible in any order; in trial 6 this is repeated with a new list of words (interference). Trial 7 requires participants to again recall the original list. Finally, participants are given a list of words containing those from the first list with phonemic and semantic distractors, and required to circle words that appeared in the first list. McCardle et al. (2004) found that ecstasy users performed significantly worse than non-users trials 4 and 5, and Reneman et al. (2000) found that ecstasy users recalled significantly fewer words than non-users. In another study (Gouzoulis-Mayfrank et al. 2000) ecstasy users exhibited poorer learning performance over 5 trials than nonusers, and required more trials to learn all words than cannabis users and nonusers. However, two studies found that differences in list learning were more related to cannabis/polydrug use (Croft et al. 2001a; Thomasius et al. 2003).

Thus the aim of this Chapter is to determine if users of ecstasy exhibit deficits in associative learning. Only two studies (Gouzoulis-Mayfrank et al. 2003; Rodgers 2000) have assessed the learning of word pairs in ecstasy users, with both finding no significant differences between ecstasy users and nonusers. In addition to the

measures used by in previous research with ecstasy users, the test used in the present study assesses various measures of forgetting, perseverative errors, and the speed with which all associations are learned (trials to completion) which have not yet been systematically investigated in ecstasy research. The number of pairs repeated correctly on trial one gives a measure of initial learning, and the number of trials required for a participant to learn all associations ("trials to completion") gives an overall indication of speed of learning. Forgetting at each level will also be recorded, whereby forgetting a response that had previously been recalled correctly once would indicate forgetting at level one, forgetting a response that had previously been recalled two times would be forgetting at level two, and so on. In addition, the number of perseverative errors will be recorded (i.e. giving the same incorrect response on two or more consecutive trials). It was expected that ecstasy users would perform worse than controls in paired associate learning, more specifically, they will correctly recall fewer pairs on trial 1, forget more items, make more perseverative errors, and take more trials to learn all associations. An overall deficit in associative learning may provide further support for impaired executive function since optimal learning requires the effective use of strategies and self-monitoring meta processes. Furthermore, an increased number of perseverative responses might be associated with a failure to inhibit previously incorrect responses or with an inability to shift mental set, and may thus provide further support for specific executive deficits in ecstasy users (with reference to Miyake et al's model). Recalling fewer pairs on trial one may in part reflect hippocampal/medial temporal lobe impairment, while forgetting well-learned material would suggest a retrieval deficit (perhaps reflecting a deficit in access as in Chapter 8). As with Chapter 9, it was possible that the updating

and access deficits observed in Chapters 6 and 8 may have mediated deficits in associative learning. This relationship was explored in the current chapter.

10.3 Method

10.3.1 Design

Dependent variables were various measures of associative learning including trials to completion, initial learning (number of correct responses in trial 1), perseverative responses, and forgetting at various levels of learning. The independent variable was ecstasy user group (users versus non-users). MANOVA was used supplemented by separate univariate analyses for each dependent variable. ANCOVA was used to ascertain the extent to which working memory capacity, access and differences in background variables may mediate ecstasy-related deficits in associative learning. In addition to these analyses, the relationship between aspects of illicit drug use and associative learning performance was assessed through bivariate correlation.

In order to establish which of the learning processes shared variance with the ecstasy-user group variable, hierarchical regression analysis was used. In all cases, trials to completion was the dependent variable. The ecstasy user group related variance was estimated first by entering this measure as the sole independent variable. Next, measures of initial learning, perseverative responses and forgetting at various levels were entered as independent variables in separate regressions. In each case the measure of learning performance was entered first followed by ecstasy user group to establish how much of the ecstasy user-group related variance was accounted for by each learning sub-process.

10.3.2 Participants

As in previous Chapters, participants were initially recruited through direct contact with under-graduates from Liverpool John Moores University, and through the snowball technique. Sixty-two non-ecstasy users (18 male, mean age 21.32) and 35 ecstasy users (20 male, mean age 21.66) were recruited[16]. With 35 ecstasy users, the present sample is sufficient to detect a difference of between 0.5 and 0.75σ for α = .05 and β =.20 (Hinkle et al, 1994)Participants reported that they had abstained from ecstasy use for at least 7 days (mean = 12.16 weeks, median = 2 weeks), and other psychoactive drugs for at least 24 hours prior to testing. Participants were paid 15 UK pounds in store vouchers for their participation.

10.3.3 Materials

Patterns of drug use and other relevant lifestyle variables were investigated by means of a background questionnaire, and fluid intelligence, premorbid intelligence and sleep patterns were assessed as in Chapter 6 (section 6.3.3). The computation span and word fluency measures were administered as indicated in Chapter 8.

Associative Learning

This was assessed via a verbal paired associates task. Participants were presented sequentially with the same eight word pairs (taken from Fisk, 2003) on a computer screen. For example,

DOOR CASE

YEAR PAGE

[16] Participants completed all tasks with the exception of the access task, which was completed by 33 ecstasy users and 61 nonusers.

After each presentation, the participant was prompted with the first member of each pair and required to recall the second member. Eight such trials were administered. The order of presentation was randomised and changed for each trial. Measures included the number of correct responses in trial 1 (a measure of initial learning), forgetting at various levels, the number of trials required to learn all associations, and the number of perseverative errors (giving the same incorrect answer consecutively).

10.3.4 Procedure

The tests were administered under controlled laboratory conditions. A computer running on MS-DOS was used for the associative learning task. Tasks were administered in the following order: Health/education questionnaire, ecstasy and drug use background questionnaire, sleep questionnaires, associative learning, computation span, word fluency, NART and finally Raven's progressive matrices. Overall, testing took two to three hours per person. The study was approved by the Ethics Committee of Liverpool John Moores University, and was administered in accordance with the ethical guidelines of the British Psychological Society.

10.4 Results

Average age, years of education, fluid intelligence, premorbid intelligence and other background variables for the two groups are set out in Table 10.1. Statistical tests (ANOVA, t-test) revealed that there were no significant differences between the groups regarding these variables, so they are not discussed further in this chapter. The ecstasy users did however perform worse than the nonusers on the "S" fluency task, $t(93) = -2.35$, $p<.05$, and the "C" letter fluency task, $t(93) = 3.48$, $p<.001$.

Table 10.1: Age, Years of Education, Intelligence, and Sleep Quality.

	Ecstasy Users		Nonusers	
	Mean	S.D.	Mean	S.D.
Age (Years)	21.66	1.64	21.32	1.80
Years of Education	15.77	1.88	15.34	2.13
Ravens Progressive Matrices (max. 60)	49.94	4.55	47.97	5.16
NART (max. 50)	28.91	5.98	29.89	5.77
Hours of Sleep per Night	8.11	1.56	8.01	1.28
Epworth Sleep Scale (max. 24)	6.38	3.38	5.82	2.83
Self Report Health *	3.74	0.74	3.85	0.81
Units of Alcohol consumed in a week	22.81	16.46	11.82	9.14
Computation span	3.77	1.66	4.24	1.29
Semantic Fluency	41.36	8.38	43.19	9.83
"S" Letter Fluency	41.15	10.71	46.58	10.76
"C" Letter Fluency	11.76	5.36	15.98	5.77

* The self report health measure scores range from 1 (very poor) to 5 (very good)

Ecstasy users performed worse on all measures of associative learning. Users required more trials to learn the pairings; they scored lower on the measure of initial learning (the number of correct responses on Trial 1); and they made more perseverative responses. However, Table 10.2 reveals that the group differences were less pronounced for the measures of forgetting. Indeed, the means reported in the Table indicate that once the material had been learned to a moderate degree,

forgetting was a rare event among both users and nonusers. Thus, for example, once a response had been successfully learned for four or more consecutive trials, there was no occurrence of forgetting in the nonuser group and only seven of the 35 users forgot a previously learned response. MANOVA revealed that the ecstasy-related group difference on the measures of associative learning was statistically significant, $F(7,88) = 4.60$, $p<.001$. Furthermore, subsequent univariate analyses revealed significant group differences on each of the measures with the exception of forgetting at levels 2 and 4, although the latter approached significance ($p = 0.06$) (see Table 10.2).

Table 10.2: Performance on Associative Learning Measures

	Ecstasy Users		Nonusers		F (1,95)
	Mean	S.D.	Mean	S.D.	
Trials to Completion	6.11	1.94	4.33	1.47	26.96***
Number Correct on Trial 1	2.97	2.01	4.36	2.00	10.70**
Number of Perseverative responses	0.69	1.16	0.15	0.65	8.50**
Number Forgotten at:					
Level 1	0.86	1.03	0.40	0.76	6.35*
Level 2	0.26	0.66	0.10	0.35	2.39
Level 3	0.14	0.36	0.00	0.00	9.96**
Level 4	0.06	0.24	0.00	0.00	3.62

*** p<.001; ** p<.01; * p<.05

Covariate analyses

As gender and alcohol use were significantly different between the groups, and group differences on Raven's Progressive Matrices approached significance,

these were incorporated into ANCOVA. The main effect of ecstasy use on associative learning remained significant after control for these covariates $F(7,81) = 4.96$, $p<.001$. Table 10.3 shows the Univariate F values for each separate measure of associative learning following control for these covariates. In all cases, significant effects remained significant. Of particular note is the marked increase in the perseveration F value.

Table 10.3: F values after Control for Group Differences in IQ, Alcohol and Gender

	Alcohol, Gender & IQ	Working Memory Updating	Access
Trials to Completion	26.67***	23.13***	16.56***
No Correct on Trial 1	10.44**	9.69**	6.86**
Perseverations	12.36**	8.45**	7.16**
Number forgotten at:			
Level 1	6.60*	5.76*	4.46*
Level 2	2.23	2.01	0.21
Level 3	10.31**	7.94**	6.50*
Level 4	2.76	4.33*	3.68

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

Although no significant differences were observed between the groups in terms of updating and access, one aim of this chapter was to assess the contribution of updating and access to ecstasy-related differences in associative learning. After control for updating the main effect of ecstasy use remained significant $F(7,87) = 4.18$, $p<.001$. Table 10.3 shows that although slightly attenuated, group differences in measures of associative learning remained significant. Contrary to expectations,

control for updating actually intensified group differences in forgetting at level 4. The main effect of ecstasy use on associative learning also remained significant after control for access, $F(7,83) = 3.76$, $p<.001$.

Indices of Drug Use

Inspection of Table 10.4 reveals that the use of other drugs was commonplace among the ecstasy group, but was restricted mainly to the use of cannabis among the control group. The ecstasy users had a lifetime dose of cannabis nearly twice that of the controls (2128 joints compared to 1082 joints), in addition to using it more frequently (2.45 times per week, compared to 0.77 times), and having smoked more in the last 30 days (17.52 joints compared to 7.91 joints). There were significant group differences in the amount smoked in the last 30 days $t(37.74) = 2.07$, and the frequency of use $t(32.56) = 3.20$, $p<.05$ in both cases. However the difference in lifetime use was not statistically significant: $t(41.31)=1.80$, $p>.05$. (As Levene's test was significant, degrees of freedom have been adjusted accordingly.) The ecstasy group reported an average total lifetime dose of ecstasy of 315 tablets; of amphetamine, 4 grams (n=8); and of cocaine, 18.96 grams (n=15). The average frequency of use for ecstasy was 0.4 times per week, and for cocaine, 0.26 times per week (n=15).

Table 10.4: Indicators of Drug Use.

	Ecstasy Users			Non Ecstasy Users		
	Mean	S.D.	n	Mean	S.D.	n
Total Use						
Ecstasy (tablets)	315.30	330.10	35			
Amphetamine (grams)	4.00	3.86	8	4.00	-	1
Cannabis (joints)	2128.71	2401.96	26	1082.54	1439.33	18
Cocaine(grams)	18.96	22.03	15	-	-	
Frequency of Use (times per week)						
Ecstasy	0.40	0.34	35			
Amphetamine	0.04	0.04	5	-	-	
Cannabis	2.45	2.40	25	0.77	0.90	18
Cocaine	0.26	0.23	15	-	-	
Amount Used During Previous 30 Days						
Ecstasy (tablets)	3.38	3.58	34			
Amphetamine (grams)	1.20	2.68	5	-	-	
Cannabis (joints)	17.52	18.26	24	7.91	11.03	16
Cocaine(grams)	1.23	1.77	13	-	-	
Average Weekly Dose						
Ecstasy (tablets)	1.67	1.31	35			
Amphetamine (grams)	0.10	0.20	8	0.01	-	1
Cannabis (joints)	7.75	8.73	25	5.11	9.94	18
Cocaine(grams)	0.14	0.24	15	-	-	

It is possible that some or all of the ecstasy-related differences in associative learning might have been attributable to the effects of other drugs. Since the number of cocaine and amphetamine users among the non-ecstasy user group was small it was not possible to properly test for homogeneity of regression in relation to these measures via ANCOVA. Accordingly, bivariate correlations were performed to ascertain relationships between indices of drug use and performance measures. Evaluating the correlations at $p<.01$, Table 10.5 reveals that there were a number of

significant correlations between measures of ecstasy, cannabis and cocaine use and the measures of associative learning. Correlations were higher for ecstasy than for cannabis and cocaine (with the exception of frequency of cocaine use and perseverative errors) for trials to completion and perseverative responses, so it appears that these aspects of associative learning may be related more to ecstasy use. However, it appears that aspects of cannabis use are related to the number of correct responses on trial one (initial learning), and contrary to expectations indices of cocaine use were most related to forgetting at level one.

Table 10.5: Correlations Between Various Measures of Learning Performance and Measures of Illicit Drug Use.

	Ecstasy	Cannabis	Cocaine	Amphetamine
Total Use				
Trials to Completion	0.410**	0.270**	0.380**	0.116
Correct on Trial 1	-0.327**	-0.334**	-0.308**	-0.083
Perseverations	0.380**	0.073	0.367**	0.213(*)
Forgot at Level 1	0.280**	0.169	0.337**	0.058
Frequency of Use				
Trials to Completion	0.350**	0.257	0.337**	0.140
Correct on Trial 1	-0.233	-0.347**	-0.341**	0.077
Perseverations	-0.209	0.005	0.278**	0.244*
Forgot at Level 1	0.240**	0.100	0.275**	0.199
Use in last 30 Days				
Trials to Completion	0.292**	0.267**	0.163	-0.054
Correct on Trial 1	-0.156	-0.330**	-0.236**	0.120
Perseverations	0.182	0.087	0.167	-0.049
Forgot at Level 1	0.196*	0.138	0.175*	0.105
Average Dose				
Trials to Completion	0.405**	0.265**	0.381**	0.072
Correct on Trial 1	-0.319**	-0.338**	-0.313**	0.005
Perseverations	0.382**	0.077	0.364**	0.175
Forgot at Level 1	0.246**	0.168	0.339**	0.103
Ever Used				
Trials to Completion	-0.434**	-0.134	-0.291**	-0.118
Correct on Trial 1	0.317**	0.163	-0.345**	-0.182
Perseverations	-0.404**	-0.020	-0.209	-0.103
Forgot at Level 1	-0.280**	-0.033	-0.151	-0.046

N=97

** p<.001; ** p< .01; one tailed

One aim of this Chapter was to ascertain the component processes underlying ecstasy-related deficits in associative learning. ANCOVA revealed that differences in updating were not related to performance on this task. Regarding the ecstasy-group related variance in trials to completion, it is important to emphasise that the ecstasy-group related variance potentially arises from a range of sources. In addition to using ecstasy, a range of other drugs was also used and there may also be premorbid differences between the two groups, as well as differences in psychological affect. Thus the ecstasy-group related variance might have arisen from any one of these sources. The focus here is to establish which sub-processes were responsible for the difference in overall learning performance among this group of poly-substance abusers.

Table 10.6 reveals that the ecstasy-group related variance amounted to 21.8% of the total variance in trials to completion (as indicated by the R squared increment of .218). In subsequent analyses, ecstasy use was entered in the regression equation following the inclusion of each specific learning sub-process. This makes it possible to establish how much of the ecstasy-group related variance was accounted for by each of the learning sub-processes. Inspection of Table 10.6 reveals that following statistical control for group differences in initial learning (as measured by the number of correct responses in Trial 1), the residual ecstasy-group related variance amounts to 8.0%. Thus over half of the ecstasy-group related variance is accounted for by individual differences in the level of initial learning. Three other regression models were evaluated. Prior control for group differences in perseverative responses reduced the ecstasy-related variance from 21.8% to 13.0%. Inclusion of forgetting at level one and at higher levels in the first stage of the hierarchy removed at least half of the ecstasy-group related variance in both cases.

Table 10.6: Variance in Associative Learning Uniquely Associated with Ecstasy User Group Following Statistical Controls for the Effects of Other Independent Variables

Regression Model	Independent Variables in the Model Prior to the Inclusion of Ecstasy User Group	Total R squared	R squared increment associated with Ecstasy User Group
0	None	.215	.215***
1	Number of Correct Responses in Trial 1	.458	.080***
2	Number of Perseverative responses	.304	.130***
3	Number Forgotten at level 1	.440	.107***
4	Number Forgotten at levels 2, 3 and 4	.401	.089***

*** p<.001; ** p<.01; * p<.05

Implications of Chapter 10

This chapter provides evidence for associative learning deficits in ecstasy users. Individual differences in initial learning, perseverative responses and forgetting all appear to be important determinants of verbal associative learning deficits in these individuals. However, while some of these impairments appear to be related to ecstasy use, others may be attributable to other drugs such as cannabis and cocaine. It appears that unlike deficits in syllogistic reasoning, associative learning deficits in ecstasy users are not related to memory updating or access to long-term memory. The final chapter of this thesis assesses aspects of everyday memory in ecstasy users via self-reports. While ecstasy-related differences in syllogistic reasoning were related to

group differences in memory updating and to a lesser extent, access, the same was not true for associative learning. In the context of ecstasy-related differences Chapter 11 assessed the contribution of executive processes to everyday memory functioning.

Chapter 11: Everyday Memory

11.1 Chapter Overview

The aim of the present chapter was to assess the contribution that the deficits in access and updating observed in Chapters 8 and 6 have on ecstasy-related differences in everyday memory functioning. While research suggests that recreational drug use impacts aspects of "everyday" memory (e.g. remembering to do something in the future) the possible mediating effects of working memory capacity on such deficits has not been systematically investigated. Forty-three ecstasy-polydrug users and 51 non-ecstasy users completed the Cognitive Failures Questionnaire (CFQ) and Everyday Memory Questionnaire (EMQ). Of these, 28 ecstasy-polydrug users and 35 non-ecstasy users completed the Prospective Memory Questionnaire (PMQ). In addition, an objective measure of cognitive failures (the CFQ-for-others) was completed by friends of participants. There was a main effect of ecstasy-polydrug use on CFQ, EMQ, CFQ-for-others, LT-PM and internally cued PM scores. Some of these effects were attenuated or reduced to below statistical significance following control for access and updating. Correlations were found between the different indicators of everyday memory and various measures of illicit drug use. Cannabis featured prominently in this respect. In addition, all ecstasy-related deficits were reduced to below statistical significance following control for cannabis use. This Chapter provides further support for cannabis related deficits in aspects of everyday memory functioning. Ecstasy may also be associated with cognitive slips, but not to the same extent as cannabis. Reduced working memory capacity emerged as a mediator of everyday memory deficits in ecstasy-polydrug users, and future research should investigate the relationship between the two in drug users.

11.2 Introduction

This chapter assessed the relationship between slips in everyday memory and the updating and access executive functions in a sample of ecstasy users. Research suggests that ecstasy has adverse effects on human memory, but while there is substantial evidence of working memory impairments in users of ecstasy (See Chapter 3), the investigation of the effects of ecstasy on more everyday aspects of memory is relatively neglected. Crucial aspects of everyday memory include prospective remembering (i.e. remembering to do a certain thing at a certain time in the future) and the occurrence of "cognitive slips" (e.g. slips of memory, language and attention). The link between reduced working memory capacity as a mediator of such deficits has not been investigated in ecstasy users.

A number of laboratory studies have assessed self-reports of cognitive failures and prospective memory in ecstasy users. Heffernan et al (2001a) assessed Prospective memory in recreational drug users. In study one, ecstasy users reported more prospective memory errors on the subscales of short-term habitual prospective memory, long-term episodic prospective memory and internally cued memory than non-users, although there were no group differences in strategies used to aid remembering. This was replicated for short-term habitual and long-term episodic prospective memory in study two, where ecstasy users also performed worse on an executive function task. It was concluded that prospective memory and executive function are linked, although the possible link was not directly investigated. The findings of study one were replicated by Heffernan et al (2001b), where ecstasy users reported more errors in short-term habitual, long-term episodic, and internally cued prospective memory (although the mean occasions of ecstasy use for this study was at least 10 times per month, which is atypically high). There were no group differences

in strategies used to remember. In a study on the World Wide Web, Rodgers et al (2001) assessed everyday memory and prospective memory in drug users. It was found that while cannabis use was associated with "here and now" memory deficits in short-term habitual and internally-cued prospective memory, ecstasy use was associated with long-term memory problems, that were more related to storage and retrieval problems. In a second World Wide Web study, Rodgers et al (2003) found that long-term prospective memory deficits were associated with ecstasy use, while deficits in everyday memory were associated with frequency of cannabis use. Thus it is possible that different recreational drugs affect human memory in distinct ways. Ecstasy users also reported a higher incidence of cognitive slips than nonusers (Fox et al, 2001), although this was not replicated by Rodgers (2000), and no differences between ecstasy users, cannabis users and nonusers were reported on the cognitive failures questionnaire by Heffernan et al (2001a).

Although the World Wide Web is an effective way of collecting large amounts of data, and Rodgers et al (2001, 2003) have managed to attribute specific deficits in everyday memory to specific drugs, it is possible that individuals visiting drug websites may already believe that they have a memory problem, and thus are not representative of the drug-using population as a whole. Therefore one aim of this Chapter was to assess prospective memory, everyday memory and cognitive failures in recreational ecstasy users in a controlled laboratory setting.

The lack of evidence on self-reported cognitive failures and the inconsistent results with reference to the three subscales of the prospective memory questionnaire could reflect a metacognitive deficit in ecstasy users, whereby they do not realise their cognitive slips. Heffernan et al (2005) attempted to control for this by using a self-report and objective measure (video-based) prospective memory task. Ecstasy users

reported significantly more forgetting on the long-term prospective memory scale, and also recalled significantly fewer items on the video-based prospective memory task. However, Cohen (1996) argues that self-report questionnaires are assessed better by gaining an independent measure of everyday performance such as that provided by ratings by a third party. In the present study, this concern is addressed by the Cognitive Failures Questionnaire-for-others (CFQ-others), a questionnaire to be completed by individuals who have a significant relationship with the Cognitive Failure Questionnaire (CFQ) respondent. The CFQ-others provides a means of determining whether the self-reports of CFQ respondents are subjective, or whether their beliefs about their own cognitive failures are generally accurate. Broadbent et al. (1982) found that there was a good correlation between the judgements of CFQ respondents and CFQ-others respondents. The correlation suggests that individuals who report more cognitive slips do in fact produce more such errors. Thus the possibility of a metacognitive deficit in ecstasy users is investigated in this Chapter.

The suggested relationship between central executive and prospective memory functioning would be in line with the finding that performance of a concurrent central executive task impaired performance in a laboratory-based prospective memory task in non drug using participants (Marsh & Hicks, 1998). As noted above, ecstasy users exhibit deficits on a number of executive tasks, and consequently the deficits in prospective memory noted above could be due to reduced executive resources, rather than a specific prospective memory deficit. Conversely, this may not be the case: van den Berg et al. (2004) found that although executive resources are involved in the processing of cues for remembering items, manipulating memory load had no effects on prospective remembering.

To summarise, the aim of this chapter was to assess everyday memory via self-reports of cognitive failures, prospective memory and everyday memory in a laboratory setting. In addition, a more objective measure of cognitive failures was included (the CFQ-others). The differential effects of recreational drugs on aspects of everyday memory was also investigated. As it has been suggested that there is a link between everyday memory and executive function, the possible mediating effects of executive processes on everyday memory functioning were also investigated.

11.3 Method

11.3.1 Design

A multivariate design was used for the Everyday Memory Questionnaire (EMQ) and CFQ, with scores as the dependent variables. A univariate design was used for the CFQ-for-others and for the PM-strategies. A multivariate design was used for the PMQ, with the three subscales as the dependent measures (long-term episodic, short-term habitual, internally cued). In all analyses, ecstasy user/nonuser was the between participants variable. ANCOVA was used to assess the possible mediating effects of executive function (computation span, word fluency), gender, and strategies used to aid remembering on everyday memory. Correlations were used to assess the relationship between drug use variables and dependent variables.

4.3.2 Participants

Forty-three ecstasy-polydrug users (mean age 21.56; 24 male) and 51 nonusers (mean age 21.51; 17 male) completed the CFQ and EMQ. With 43 ecstasy users, the present sample is sufficient to detect a difference of between 0.5 and 0.75 σ for $\alpha =$ .05 and $\beta =$.20 (Hinkle et al, 1994). As the PMQ only became available to use after the start of data collection, only 28 ecstasy-polydrug users and 35 nonusers completed

the PMQ. Data collected on the CFQ-others relied on the partners/families of participants returning the questionnaire; the partners/families of 26 ecstasy-polydrug users and 31 nonusers returned the questionnaires. With 26 or 28 ecstasy users, the present sample is sufficient to detect a difference of almost 0.75σ for $\alpha = .05$ and $\beta = .20$ (Hinkle et al, 1994). Participants were recruited via direct approach to university students and the snowball technique (Solowij et al, 1992). Participants were requested to refrain from ecstasy use for at least 7 days and ideally 10 days prior to testing (mean abstinence period 8.82 weeks, median abstinence period 2 weeks). Participants were also requested not to use any other illicit drugs for at least 24 hours and ideally for 7 days prior to testing.

4.3.3 Materials

Patterns of drug use, sleep quality, fluid intelligence, premorbid intelligence, and other relevant lifestyle variables were investigated as in Chapter 6 (section 6.3.3).

Cognitive Failures: The Cognitive Failures Questionnaire and the Cognitive Failures Questionnaire-for-others (Broadbent et al. 1982) were administered. The 25-item CFQ is argued to measure the relationship between attentional performance and general cognitive functioning. The questions relate to different aspects of cognitive functioning and failure, such as perceptual failures (e.g. do you fail to notice signposts on the road?), misdirected actions (e.g. do you bump into people?) and memory failures (e.g. do you forget what you came to the shops to buy?) within the last 6 months. The term "cognitive failure" is an umbrella term to cover all three types of slip. Each questionnaire item required a number (0-4 inclusive) to be circled. Four corresponded to "very often" and 0 to "never" (25 items in total). The direction of scoring for the CFQ was unidirectional, since pilot studies by Broadbent et al. (1982) found that reversed wording on some items only confused the participants and there

were no differences in a small sample using reversed wording. In the case of the CFQ-for-others half of the items began with "very often" and half with "never" (8 items in total). In the original study, Broadbent et al. use family or partners of the participant, but due to the nature of student populations, "housemate" has been added to the list of significant others in the present study. Total scores and percentage of slips reported were calculated to enable comparison between the two measures.

Everyday memory: The Everyday Memory Questionnaire (EMQ, Sunderland et al. 1983) is a self-report measure of memory lapses in everyday activities. It consists of 27 statements, and in each case, participants respond on a 9-point scale ranging from "not at all in the last 6 months" to "more than once a day". Statements include: "forgetting where you put something"; "finding a television story difficult to follow"; a total score for everyday memory is calculated by summing the responses to all items.

Prospective memory: This was assessed using the Prospective Memory Questionnaire (PMQ), which is a reliable and valid self-report measure (Hannon et al., 1995). The PMQ provides measures of three aspects of PM on a scale of 1-9 for each scale. Fourteen questions measure short-term habitual PM, e.g. "I forgot to turn my alarm clock off when I got up this morning". Fourteen items measure long-term episodic PM, e.g. "I forgot to pass on a message to someone". Ten questions measure internally cued PM, e.g. "I forgot what I wanted to say in the middle of a sentence". In addition, 14 questions make up the "techniques to remember" scale, which provides a measure of the number of strategies used to aid remembering. Responses on the three PM scales range from 1 (little forgetting) to 9 (great deal of forgetting), and for the strategies scale from 1 (few strategies) to 9 (many strategies). For each of the 4 scales, a total score is calculated by summing the responses in each section, and

dividing by the number of items in that section (14 for ST-habitual, LT-episodic and strategies, 10 for internally cued). Thus scores on all 4 scales ranged from 1-9 with high scores being indicative of much forgetting, and many strategies used to aid remembering.

Computation Span was the same as was used in Chapter 8.

Word Fluency was the same as used in Chapter 8[17].

11.3.4 Procedure

Participants were informed of the general purpose of the experiment, and written informed consent was obtained. The tasks were administered under laboratory conditions, and a computer running MS-DOS was used for the computation span task. The tests were administered in the following order: background questionnaire, sleep quality questionnaires, NART, CFQ, EMQ, PMQ, word fluency, computation span, and Raven's progressive matrices. Participants were given the CFQ-for-others and asked to get someone that had a day-to-day experience with them to fill it in. The CFQ respondents were requested not to discuss the responses that they had made prior to completion of the CFQ-for-others. The CFQ-for-others was returned via post in a pre-paid envelope. Participants were fully debriefed, paid £15 in store vouchers, and given drugs education leaflets. The study was approved by the Ethics Committee of Liverpool John Moores University, and was administered in accordance with the ethical guidelines of the British Psychological Society.

11.5 Results

The scores for background measures are set out in Table 11.1. t-test revealed that there were no significant differences between the groups in age, self-rated health,

[17] Completed by 28 ecstasy users and 38 nonusers

random letter generation, fluid intelligence, pre-morbid intelligence, years of education, subjective daytime sleepiness, or average hours of sleep per night. Ecstasy-polydrug users did however report consuming significantly more units of alcohol per week, $t(76.99) = 3.60$, $p<.001$ (as Levene's test was significant, degrees of freedom have been adjusted accordingly). Ecstasy-polydrug users also attained a lower level on the computation span task, indicating reduced working memory capacity, $t(92) = -3.45$, $p<.001$, and also a lower level on the Chicago Word Fluency Task, $t(65) = 2.69$; 3.42, $p<.01$ and $p<.001$ for "S" and "C" letter fluency respectively.

Table 11.1: Mean age, intelligence scores and other background variables

	Ecstasy Users		Nonusers	
	Mean	S.D.	Mean	S.D.
Age	21.56	1.68	21.51	1.79
Units of Alcohol/week	23.62	15.69	13.11	11.71
Self-Rated Health	3.60	0.76	3.84	0.92
Sleep (Hours/night)	8.02	1.47	7.99	1.32
Epworth Sleepiness Scale	6.26	3.25	5.57	2.59
Years of Education	15.95	1.57	15.94	1.76
Raven's Matrices (Max. 60)	48.84	5.93	48.22	5.30
NART (max. 50)	28.95	6.91	30.27	5.74
Computation Span	3.60	1.61	4.71	1.49
Semantic Fluency	39.96	9.46	42.49	10.18
"S" Letter Fluency	40.00	10.70	46.79	9.85
"C" letter Fluency	11.32	5.34	16.31	6.24

The scores for everyday memory measures are set out in Table 11.2.

CFQ and EMQ: Table 11.2 shows that ecstasy-polydrug users scored higher than nonusers on the CFQ and EMQ, indicating a higher incidence of self-reported everyday memory and cognitive failure slips. There was a main effect of ecstasy-polydrug use on these measures, $F(2,88) = 4.61$, $p<.05$ for Pillai's Trace. Separate univariate analyses revealed that ecstasy-polydrug users scored significantly higher on both the EMQ and CFQ, $F(1,89) = 9.02; 6.05$, $p<.01$ and $p<.05$ respectively.

Table 2: Mean Scores on Everyday Memory Measures

	Ecstasy Users		Nonusers	
	Mean	S.D.	Mean	S.D.
Everyday Memory Questionnaire	97.24	35.34	77.28	28.07
Cognitive Failures Questionnaire	46.95	15.28	39.68	12.93
Cognitive Failures-Others	14.65	6.44	10.71	3.63
PM- Long-Term Episodic	3.06	1.52	2.52	0.76
PM- Short-Term Habitual	1.26	0.32	1.19	0.32
PM- Internally cued	2.92	1.25	2.30	0.76
PM- Strategies	3.29	1.65	2.84	1.41
CFQ-Percentage of Slips Reported	45.42	16.66	38.58	10.29
CFQ-others: Percentage of Slips Reported	45.79	20.14	33.47	11.36

CFQ-for-others: The relatives/significant others reported more cognitive slips among ecstasy-polydrug users than nonusers (means of 14.65 and 10.71 respectively). Univariate ANOVA revealed that this difference was significant, $F(1,55) = 8.44$, $p<.01$.

PMQ: Table 11.2 shows that ecstasy-polydrug users scored slightly higher than nonusers on the four subscales of the PMQ. The three memory measures (long-term episodic, short-term habitual and internally cued prospective memory) were incorporated into MANOVA. The main effect of ecstasy-polydrug use was non-significant, $F(3,59) = 2.00$, $p>.05$, as was the univariate ecstasy-related difference in short-term habitual PM, $F(1,61) = 0.61$, $p>.05$. Ecstasy-polydrug related deficits in long-term and internally cued PM were significant, $F(1,61) = 3.32$, $p<.05$ one-tailed, and $F(1,61) = 5.82$, $p<.05$ respectively. Univariate ANOVA revealed that ecstasy users did not use significantly more strategies to remember than nonusers, $F(1,61) = 1.35$, $p>.05$.

Interaction between CFQ and CFQ-for-others: To assess whether users' own perceptions of cognitive failures were similar in magnitude to the equivalent judgements produced by others, the CFQ and CFQ-for-others responses were compared for users and non users. The percentage of slips reported for each scale was calculated and analysed using a mixed design, with one within participants factor for "cognitive failures", (with two levels, self-report versus others), and ecstasy-polydrug user group between participants. Mean percentages of self-reported slips and other-reported slips were similar for each group (indicating that ecstasy users were self-aware of their cognitive failures). This was supported by a main effect of ecstasy use, $F(1,55) = 9.20$, $p<.01$. The interaction between cognitive failures and having used ecstasy was however non-significant indicating that ecstasy users were aware of their cognitive slips $F(1,55) = 1.36$, $p>.05$.

Covariate Analyses

Units of alcohol consumed in a week and gender composition were significantly different between the groups, thus these were incorporated into ANCOVA to control for the contribution of these factors to memory deficits.

EMQ and CFQ: After controlling for gender, the main effect of ecstasy use remained significant, $F(2,87) = 5.07$, $p<.01$, as did the univariate analyses, $F(1,88) = 9.18$; 8.05, $p<.005$ and $p<.01$ for EMQ and CFQ respectively. Following control for units of alcohol used in a week, the main effect of ecstasy use remained significant, $F(2,85) = 5.00$, $p<.01$. Ecstasy-related differences in EMQ and CFQ scores were intensified after controlling for alcohol use, $F(1,86) = 9.65$; 6.95, $p<.01$ in both cases.

CFQ-for-others: After controlling for gender, the main effect of ecstasy use remained significant, $F(1,54) = 8.23$, $p<.01$, and also after control for units of alcohol consumed in a week, $F(1,52) = 9.02$, $p<.01$.

PMQ: After controlling for gender, the main effect of ecstasy remained non-significant, $F(3,58) = 2.15$, $p>.05$, as did differences in short-term PM ($F<1$). The ecstasy-related differences in long-term PM and Internally cued PM remained significant after control for gender, $F(1,60) = 3.26$, $p<.05$ one tailed and $F(1,60) = 6.37$, $p<.05$ respectively. After controlling for average units of alcohol consumed in a week, the main effect of ecstasy use remained non-significant, $F(3,37) = 1.12$, $p>.05$, as did differences in short-term PM ($F<1$). Ecstasy-related differences in long-term PM were reduced to below statistical significance after control for alcohol use. Again, although slightly attenuated the ecstasy-related differences in internally cued PM remained significant after control for alcohol use, $F(1,59) = 3.31$, $p<.05$ one-tailed.

As it was also possible that strategies used to remember may have mediated the number of prospective memory slips (more strategies used may decrease the

number of slips), this was incorporated into ANCOVA. The main effect of ecstasy use remained non-significant, $F(3,58) = 1.71$, $p>.05$, as did short-term PM ($F<1$). Ecstasy-related differences in long-term PM were reduced to below statistical significance following control for strategies used to remember. After control for strategies used to remember, ecstasy-related differences in internally cued PM remained significant, $F(1,60) = 5.08$, $p<.05$.

Homogeneity of regression was obtained with respect to all covariates in this block, $p>.05$ for the group by covariate interaction.

Everyday Memory and Executive Function

One aim of this Chapter was to assess the possible mediating role of updating and access on deficits in prospective and everyday memory. Therefore, computation span and word fluency were also controlled for.

EMQ and CFQ: After controlling for updating the main effect of ecstasy use remained significant, $F(2,87) = 3.20$, $p<.05$. Although slightly attenuated, the ecstasy-related deficits in EMQ remained significant, $F(1,88) = 6.45$, $p<.05$, although group differences in CFQ scores now only approached significance $F(1,88) = 3.35$, $p = 0.071$. After control for access, the main effect of ecstasy use remained significant $F(2,60) = 3.52$, $p<.05$. For the univariate analyses, the opposite pattern of results emerged compared to control for updating: ecstasy-related differences in EMQ scores were reduced to below statistical significance $F(1,61) = 3.26$, $p = 0.076$, while differences in CFQ scores were intensified $F(1,61) = 7.16$, $p<.01$. Homogeneity of regression was obtained, $p>.05$ for the group by covariate interaction.

CFQ-for-others: The main effect of ecstasy use also remained significant after control for updating, $F(1,54) = 5.42$, $p<.05$ and access $F(1,34) = 4.89$, $p<.05$. Homogeneity of

regression was achieved with respect to access (F<1), but not computation span, so this result should be treated with some caution.

Prospective Memory: After controlling for updating the main effect of ecstasy remained non-significant, F(3,58) = 1.62, p>.05, as did differences in short-term PM (F<1). The ecstasy-related differences in long-term PM were reduced to below statistical significance after control for updating F(1,60) = 2.25, p>.05, although ecstasy-related differences in internally cued PM proved more robust and remained significant after control for updating, F(1,60) = 4.74, p<.05. A similar pattern of results emerged after control for access; the main effect of ecstasy use on PM remained non-significant F(3,55) = 2.26, p>.05, as did differences in short-term PM (F<1). Group differences in long-term PM were reduced to below statistical significance following control for access F(1,57) = 2.12, p>.05; differences in internally-cued PM remained significant, F(1,57) = 5.39, p<.05. Homogeneity of regression was obtained with respect to these covariates, p>.05 for the group by covariate interaction.

Results of the preceding analyses are summarised in Table 11.3.

Table 11.3: Summary of Chapter 11 MANOVA, AVOVA and ANCOVA results.

Covariate	None		Gender		Alcohol		PMQ-Strat		Updating		Fluency	
Dependent Variable	Manova	Anova	Manova	Anova	Manova	Anova	Manova	Anova	Manova	Anova	Manova	Anova
CFQ		✓		✓		✓+				×		✓+
EMQ	✓	✓	✓	✓	✓	✓+			✓	✓	✓	×
CFQ-Oth		✓		✓		✓				✓		✓
PMQ-LT		✓		✓		×		×		×		×
PMQ-ST		×		×		×		×				
	×		×		×		×		×		×	
PMQ-IC		✓		✓		✓		✓		✓		✓
PMQ-Strat		×										

Key: ✓ = significant effect
× = no significant effect

Indices of Drug Use

Inspection of Table 11.4 reveals that while the use of other drugs among the ecstasy-polydrug users was commonplace, among the nonusers, it was limited mainly to the use of cannabis. The ecstasy-polydrug users had a lifetime dose of cannabis more than three times that of the non-users (4088 joints to 1228 joints), in addition to using it more frequently (2.90 times a week, compared to 0.84 times a week), having smoked more in the last 30 days (48.25 joints compared to 8.26 joints), and having a larger average weekly dose (13.91 joints compared to 5.84 joints). In relation to the cannabis measures, t-test revealed that all of the group difference were statistically significant $t(36.75) = 2.74$, $p<.01$ for total lifetime dose; $t(39.21) = 3.93$, $p<.01$ for frequency of use; $t(30.93) = 2.80$, $p<.01$ for amount used in the last 30 days; and $t(45.89) = 2.14$, $p<.05$ for average dose (As Levene's test was significant, degrees of freedom have been adjusted accordingly).

Table 11.4: Indicators of Drug Use Among Ecstasy Users and Non Ecstasy Users

	Ecstasy Users			Non Ecstasy Users		
	Mean	S.D.	n	Mean	S.D.	N
Total Use						
Ecstasy (Tablets)	346.50	379.32	43	-	-	-
Amphetamine (grams)	77.29	172.74	12	4	-	1
Cannabis (joints)	4087.89	5484.74	31	1277.76	1453.19	18
Cocaine (grams)	37.83	61.96	20	-	-	-
Frequency of Use (times per week)						
Ecstasy	0.45	0.38	41	-	-	-
Amphetamine	0.09	0.11	4	-	-	-
Cannabis	2.90	2.70	31	0.84	0.85	18
Cocaine	0.54	0.48	20	-	-	-
Amount Used During Previous 30 Days						
Ecstasy (tablets)	4.67	6.45	42	-	-	-
Amphetamine (grams)	1.20	2.68	5	-	-	-
Cannabis (joints)	48.25	77.02	30	8.26	10.65	17
Cocaine (grams)	2.54	2.38	18	-	-	-
Average Weekly Dose						
Ecstasy (tablets)	2.31	3.04	43	-	-	-
Amphetamine (grams)	0.39	0.54	10	1	0.09	1
Cannabis (joints)	13.91	16.08	30	5.84	10.03	18
Cocaine (grams)	0.34	0.43	20	-	-	-
Number Ever Used						
Amphetamine	21	-	-	2	-	-
Cannabis	40	-	-	26	-	-
Cocaine	34	-	-	5	-	-

Correlations with Indices of Drug Use.

Due to the small number of illicit drug users among the non ecstasy-polydrug user group it was not possible to control statistically for the effects of other drugs through the use of ANCOVA. Therefore it is possible that some or all of the ecstasy-related effects might have been attributable to the effects of other drugs. To address

this possibility, correlations were performed with different measures of ecstasy, amphetamine, cannabis and cocaine use. Measures of drug use were included as in Chapter 6[18].

A partial Bonferroni correction was applied as in Chapter 6. The results, set out in Table 11.5, show that ecstasy use was significantly correlated with a number of the performance measures. Having ever used ecstasy was significantly correlated with EMQ, CFQ, and CFQ-for-others scores, while total lifetime dose of ecstasy was significantly correlated with CFQ-for-others scores. Average weekly ecstasy dose was also significantly correlated with EMQ, CFQ and PM-internally cued scores.

In relation to other drugs, cannabis appears to be an especially important predictor of everyday memory deficits. Indeed, being a cannabis user, total lifetime dose of cannabis, and average weekly dose of cannabis were significantly correlated with all measures of everyday memory (at $p<.01$). Frequency of cannabis use was significantly correlated with EMQ, CFQ, CFQ-for-others, PM-internally cued and PM-strategies scores, while amount used in the last 30 days was significantly correlated with PM-internally cued. Ever having used cocaine was significantly correlated with CFQ-for others and PM-internally cued scores. Indices of amphetamine use were also significantly correlated with memory scores; Ever having used amphetamine with CFQ, CFQ-for-others and PM-internally cued, total lifetime dose with CFQ and CFQ-for-others scores and average dose with CFQ scores.

The focus of this Chapter was intended to be ecstasy use, but given the strength of correlations with cannabis use rather than ecstasy, main analyses were repeated with having ever used cannabis as the sole independent variable. This enabled us to compare effect sizes for the ecstasy and cannabis analyses.

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[18] Those in the nonuser group who had used amphetamine and cocaine (n=2 and 5) felt unable to accurately estimate patterns of use.

Cannabis, EMQ and CFQ (63 cannabis users, 28 nonusers): There was a main effect of cannabis use, $F(2,88) = 8.47$, $p<.001$ on EMQ and CFQ (with a partial Eta squared of 0.161 compared to 0.095 for ecstasy use). This was owing to cannabis users scoring higher on both the EMQ, $F(1,89) = 10.19$, $p<.01$ and the CFQ, $F(1,89) = 16.75$, $p<.001$. With respect to effects sizes, those for cannabis were larger for both the EMQ (partial Eta squared of 0.103 compared to 0.092) and CFQ (partial Eta squared of 0.158 compared to 0.064) scores.

Cannabis and CFQ-for-others (40 cannabis user, 17 nonusers): Again, there was a significant main effect of cannabis use, $F(1,55) = 7.15$, $p<.01$, although in this case effect sizes were larger for ecstasy than for cannabis use (partial Eta squared of 0.115 for cannabis and 0.133 for ecstasy).

Cannabis and Prospective Memory (44 cannabis users, 19 nonusers): There was a significant main effect of cannabis use, $F(3,59) = 5.89$, $p<.001$, and once again the effect size was larger for cannabis use than for ecstasy use (partial Eta squared of 0.230 compared to 0.092). Cannabis users also scored significantly higher on the three memory scales of the PMQ: $F(1,161) = 7.98$, $p<.01$ for LT episodic; 8.63, $p<.01$ for ST habitual; and 12.30, $p<.001$ for internally cued PM. Effect sizes for the three scales were larger for cannabis than for ecstasy in all cases (partial Eta squared of 0.116, 0.124, 0.168 compared to 0.052, 0.010, 0.087). Contrary to expectations, the cannabis users also used significantly more strategies to aid remembering, $F(1,61) = 14.46$, $p<.001$ with a larger effect size for cannabis than for ecstasy (partial Eta squared of 0.192 compared to 0.022). ANCOVA to control for differences in the strategies scale slightly attenuated the main effect, $F(3,58) = 3.87$, $p<.05$. Although somewhat attenuated, the differences in PMQ subscales remained significant, $F(1,60)$

= 3.42, p<.05 (one-tailed) for LT episodic; 3.26, p<.05 (one-tailed) for ST habitual; and 10.60, p<.01 for internally cued PM.

Cannabis and CFQ/CFQ-for-others interaction (40 cannabis users and 17 nonusers): As with ecstasy use, the interaction between the CFQ and CFQ-for-others was non-significant, F(1,55) = 0.56, p>.05.

Cannabis, Everyday Memory and Executive Function: As with ecstasy use, all main effects for cannabis were attenuated after control for updating. However, most cannabis-related group differences remained statistically significant with the exception of the CFQ-for-others which was reduced to below statistical significance, p>.05. The multivariate main effect on PM scales was reduced to F(3,58) = 4.77, p<.01; with the univariate effect in the LT episodic, ST habitual and internally cued subscales being reduced to F(1,60) = 6.08; 6.29; 10.78, p<.05, .05 and .01 respectively. Strategies used to remember was reduced to F(1,60) = 11.31, p<.001. The multivariate main effect on EMQ and CFQ was reduced to F(2,87) = 5.79, p<.01; with EMQ and CFQ being reduced to F(1,88) = 7.00; 11.43, p<.01 and .001 respectively. With reference to access, the multivariate main effect on PM scales was reduced to F(3,55) = 4.68, p<.01; with LT episodic, ST habitual and internally cued subscales being reduced to F(1,57) = 5.39; 6.02; 11.27, p<.05, .05 and .001 respectively. Strategies used to remember was reduced to F(1,57) = 13.15, p<.001. The main effect on EMQ and CFQ was reduced to F(2,60) = 6.87, p<.01; with EMQ and CFQ being reduced to F(1,61) = 6.29; 13.97, p<.05 and .001 respectively.

So to summarise, cannabis appears to be a more important predictor of everyday memory deficits than ecstasy use, although on one scale (the CFQ-for-others) ecstasy emerged as a more significant predictor.

Table 11.4: Correlations With Indices of Drug Use

	Ecstasy	Cannabis	Cocaine	Amphetamine
Ever Used				
EMQ	-.283*	-.328*	-.165	-.159
CFQ	-.272*	-.380*	-.170	-.225*
CFQ-others	-.333*	-.329*	-.441*	-.515*
PM-LT episodic	-.159	-.368*	-.142	-.158
PM-ST habitual	-.111	-.394*	-.190	-.186
PM-internally cued	-.276	-.465*	-.307*	-.323*
PM-strategies	-.130	-.479*	-.013	-.076
Total Lifetime Use				
EMQ	.242	.305*	.202	.214
CFQ	.215	.361*	.158	.267*
CFQ-others	.312*	.440*	.329	.389*
PM-LT episodic	.116	.416*	.122	.201
PM-ST habitual	.065	.366*	.304	.097
PM-internally cued	.224	.515*	.258	.330
PM-strategies	.053	.452*	-.017	.072
Frequency of Use				
EMQ	.213	.291*	.213	.026
CFQ	.194	.335*	.182	.197
CFQ-others	.224	.467*	.298	.001
PM-LT episodic	.093	.301	.047	.295
PM-ST habitual	.034	.161	.182	-.112
PM-internally cued	.251	.424*	.243	.199
PM-strategies	.071	.346*	.027	-.011
Use in Last 30 days				
EMQ	.139	.197	.061	.120
CFQ	.034	.165	.015	.064
CFQ-others	.105	.301	.044	-
PM-LT episodic	.045	.213	-.051	.161
PM-ST habitual	.004	.068	.034	-.116
PM-internally cued	.153	.380*	.095	.077
PM-strategies	-.008	.208	-.169	-.154
Average Dose				
EMQ	.279*	.314*	.222	.195
CFQ	.277*	.358*	.185	.264*
CFQ-others	.252	.441*	.348	.326
PM-LT episodic	.166	.418*	.127	.145
PM-ST habitual	.095	.329*	.312	.151
PM-internally cued	.297*	.486*	.261	.280
PM-strategies	.111	.452*	.009	.111

* Correlation significant at p<.01, one-tailed

The results also suggest that aspects of executive functioning (access and updating) are important factors in everyday memory slips in both ecstasy and cannabis users.

Implications of Chapter 11

In this chapter ecstasy-polydrug users performed significantly worse than nonusers on a number of everyday memory measures, and on measures of updating and access to long-term memory: the CFQ, EMQ, two subscales of the PMQ (long-term episodic and internally cued PM), computation span and the Chicago Word Fluency Test. Compared to non-ecstasy users, ecstasy-polydrug users were also rated significantly worse by friends on the CFQ-for-others scale. The interaction between CFQ and CFQ-for-others scores and ecstasy-polydrug use was non-significant, indicating that ecstasy users are as aware of their cognitive slips as non-ecstasy users. However, cannabis emerged as a more significant predictor than ecstasy use on all everyday memory measures used, and effect sizes for all analyses incorporating having ever used cannabis as the sole IV were larger for cannabis use than for ecstasy use (except for the CFQ-for-others). Taken as a whole, the results of this chapter suggest that slips in everyday memory are more related to cannabis use than ecstasy use. In all analyses, the updating and access deficits observed in Chapter 6 were important predictors of performance, attenuating all significant results. The results and implications of Chapters 6-11 are discussed in detail in the following Chapter.

Chapter 12 General Discussion

The aim of this thesis was to examine the separability of four executive functions (with reference recent theoretical models of executive functioning, Fisk & Sharp 2004; Miyake et al. 2000) in recreational ecstasy users, and to ascertain the contributions of these executive processes to performance of other cognitive functions (namely reasoning, associative learning and lapses in everyday memory). To summarise the results briefly ecstasy users exhibited impairments in tasks that tap the updating executive component process (letter updating - Chapter 6; Computation span – Chapters 8, 9, 11) and also access to long-term memory (Chicago Word Fluency Test – Chapter 8). No between group differences were observed in task switching (plus-minus task and number-letter task – Chapter 7), and the ecstasy users actually performed better than nonusers on a task of response inhibition by giving more letters (random letter generation – Chapter 7). Three chapters also assessed the contribution of executive processes to reasoning, associative learning, and everyday memory deficits in ecstasy users. While associative learning (verbal paired associates task – Chapter 10) deficits in ecstasy users were not mediated by reduced working memory capacity, the same was not true for syllogistic reasoning and everyday memory. Ecstasy-related group differences in syllogistic reasoning performance were reduced to below statistical significance following control for working memory updating, but not access. The occurrence of everyday memory slips was related to the use of cannabis rather than ecstasy use, and once again, deficits were attenuated following control for working memory updating and not access. This thesis is the first, to the author's knowledge, to study the separability of four executive processes in a sample of recreational ecstasy users.

The first section of the discussion will focus on the results of Chapters 6, 7, and 8 i.e. the four specific executive functions. It was expected that ecstasy users would exhibit deficits on the letter updating task and the access tasks, but given previous research we were unsure if the same would be true for the switching and inhibition tasks. Chapter 6 showed that ecstasy users were impaired on a pure measure of memory updating. The mean scores showed that ecstasy users recalled fewer correct letters at all four list lengths, although contrary to expectations the list length by user group interaction was non significant indicating that ecstasy users did not perform worse at the longer list lengths as originally predicted. There was however a main effect of ecstasy use on chain length 8 and 10 letters. Focusing initially on the list length analysis, bivariate correlations revealed a clear dissociation between the effects of ecstasy, cannabis and cocaine on aspects of letter updating with indices of ecstasy use being related to performance on list length 10, cannabis with list length 8, and cocaine with list length 6. Indeed all ecstasy use variables (with the exception of amount used in the last 30 days) were significantly correlated with updating at list length 10, all cannabis use variables (with the exception of amount used in the last 30 days) with updating at list length 8, and two cocaine use variables (amount used in the last 30 days, total lifetime dose) with updating at list length 6. These effects were quite robust for each drug and only one drug was significantly correlated with each aspect. What may the reason be for this dissociation? One reason (as mentioned in the introduction to Chapter 6) is the possibility that this reflects a difference in strategies adopted to update the contents of working memory. Research on running memory and serial position of updated items suggests that many participants do not adopt an updating strategy, relying instead on a phonological recency strategy. Ruiz et al.

(2005) analysed serial position data from a letter-updating task and found a clear recency effect. Moreover, the recency effect increased sharply with increasing list length indicating that a recency strategy was more likely to be adopted for the longer list lengths.

In terms of the results of Chapter 6 this has a few possible interpretations. One such interpretation is that while deficits in the shorter list lengths (6 and 8 items) may reflect a genuine updating deficit, deficits in longer list lengths (10 and 12 items) may be related to impairments in recency strategies. In Chapter 6 correlations revealed that while chain length 6 and 8 performance were related to indices of cocaine and cannabis use respectively, chain length 10 performance was related to indices of ecstasy use. As mentioned above Ruiz et al. (2005) found that the use of recency strategies increased with increasing list length, which raises the possibility that while the use of cannabis may impair memory updating, and cocaine may impair performance on span measures, the use of ecstasy impairs effective utilisation of recency strategies which are related to rehearsal and in the case of verbal information (as in Chapter 6) the phonological loop (although if this were the case, it would be expected that ecstasy users would be impaired in simple span tasks. Such deficits are not typically observed). This would be in line with studies reporting verbal working memory deficits in ecstasy users (e.g. Parrott et al. 1998; Thomasius et al. 2003). This poses the question as to why ecstasy users in particular may be impaired in this aspect of memory. All participants were instructed to use an updating strategy as per Morris and Jones' (1990) procedure: "dropping the "oldest" item and adding the most recent to the string" (page 113). As it was particularly ecstasy use that was related to chain length 10 performance (which is supposedly more likely to recruit a

recency strategy) it may be that ecstasy users were either unable to follow the updating instructions adequately, or found the procedure too difficult to follow. Although admittedly this is a tenuous link, previous research in ecstasy users provides some support. For example, Rodgers et al. (2001) showed that errors made while completing a questionnaire were predicted by ecstasy use (not cannabis) indicating that the ecstasy users were unable to follow the instructions adequately. Similarly, Fox et al. (2002) found that ecstasy users performed worse on more difficult aspects of some tasks indicating that they found these parts harder than the nonusers did.

If all users of ecstasy adopted an updating strategy (and we have no reason to believe that they did not) then there are a number of inferences that can be made. As cocaine use was associated with performance at 6 items, cannabis at 8 items and ecstasy at 10 items, it may be that cannabis use gives rise to impairment in memory updating prior to ecstasy use. However we cannot rule out the possibility that the significant correlations are a function of polydrug use with drug use in general being associated with deficits. More research is needed to ascertain the precise nature of memory updating in each group of drug users. If Ruiz's account of updating memory is to be followed then it is possible that no participants adopted an updating strategy and while cocaine mildly impairs phonological rehearsal, and cannabis moderately impairs rehearsal, the use of ecstasy has severe effects on rehearsal. Ruiz et al. maintain that their pattern of results from letter and word updating tasks indicate that participants do not generally adopt an updating strategy even when instructed to do so. Furthermore when list length is uncertain as in Chapter 6, it has been postulated that no updating may occur at all. Hockey and co-workers (Hamilton & Hockey 1974; Hockey 1973) postulate that

updating strategies cannot be started retrospectively. In the case of the running memory task used in this thesis, the cue for a participant to start updating is the appearance of a new item (letter) on the screen after the sixth item has been presented. Thus the updating would have to be self-initiated retrospectively after presentation of letter 7. However it does not necessarily follow that individuals would wait until their span was reached to initiate updating. As most of the sequences in the updating task used in this thesis require updating, the participants is likely to approach the test with the expectation that updating will be required rather than initiating the process retrospectively. However, this interpretation would depend on Ruiz's account of memory updating and recency being accurate; Baddeley and Hitch (1993) maintain that recency is a phenomenon of short-term memory which would suggest that the executive process of updating would not be subject to recency effects.

Although the preceding two paragraphs suggest that aspects of ecstasy use may not be associated with updating function deficits at shorter sequence lengths, Chapters 8, 9 and 11 found that ecstasy users performed worse than nonusers on the computation span task, an established measure of memory updating (Fisk & Sharp 2004; Miyake et al. 2000). While this implies that ecstasy users are impaired in memory updating, the results of Chapter 6 may reflect the relative difficulty of the letter-updating task. All participants were required to remember the last 6 letters of each chain, regardless of their letter span, and after control for letter span the main effect of ecstasy use on memory updating was reduced to below statistical significance. Nevertheless ecstasy-related differences in chain length 8 and 10 updating remained significant after control for letter span suggesting that

simple span was not an important factor in ecstasy-related performance decrements on this task.

To summarise, it appears that ecstasy users are impaired on a memory-updating task either due to inappropriate strategy use, inability to follow instructions, or a genuine updating function deficit.

Moving the focus to task switching, mean scores showed that ecstasy users and nonusers had similar switch costs on the plus-minus and number-letter tasks. This was reflected by non-significant multivariate and univariate analyses. It was predicted in Chapter 7 that users and nonusers would perform comparably on these tasks, inline with previous research (e.g. McCardle et al. 2004). Two established tasks were used to assess task switching. The plus-minus task is a key indicator of Miyake et al's conceptual framework and requires participants to switch between adding 3 and subtracting 3 from a list of two digit numbers. It has been suggested that ecstasy users may have exhibited deficits in arithmetic processing rather than a deficit in task switching: Wareing et al. (2004b) found that ecstasy users were impaired on the computation span task but not the reading span task. However no between group differences were observed on the plus minus task in Chapter 7. This could mean one of two things. Firstly, it could be that ecstasy users are not actually impaired in arithmetic processing or task switching, and therefore the results of Chapters 8, 9, and 11 reflect an actual working memory updating deficit indexed by lower computation span scores. This is quite plausible considering that Chapter 6 revealed that ecstasy users were impaired on a memory-updating task that did not require arithmetic processing. Secondly, the plus-minus task may not recruit executive switching resources to the extent that an ecstasy-related deficit would be

evident i.e. the function of adding/subtracting three from a two digit number is not cognitively demanding enough. Previous research also supports this proposal. In a more complex serial add and subtract task that additionally required participants to identify the least significant digit (lowest number) of an arithmetic problem, and if negative add 10 to it, McCann et al. (1999) found that ecstasy users performed worse than nonusers. Fox et al. (2002) also found that on the 3D-IDED switching task, the user group by task difficulty interaction approached significance indicating that the ecstasy users performed worse on the more difficult task switches.

The number-letter task requires participants to switch between making letter judgements (is the letter a vowel or a consonant?) and number judgements (is the number odd or even?) and is also a key indicator of Miyake et al's conceptualisation of executive processes. As with the plus-minus task, ecstasy users and nonusers performed comparably. This task incorporates both numerical and verbal components and hence provides further support for the absence of specific numerical processing deficits in ecstasy users. Both switching tasks required mental set switches to be internally driven. Research has shown that switch cost latencies are higher when switches are internally driven as opposed to when they are cued. For example using the plus-minus task Spector and Biederman (1976) found that switch costs were high when participants had to generate switches internally, but when cues were given (e.g. 51 + 3, 76 – 3) switch costs were reduced. It is possible that inline with the data in Chapter 7, both the ecstasy users and nonusers found it equally difficult to generate internal set switches as both groups had similar switch cost latencies.

In Chapter 7, subsequent stimuli were presented immediately after the previous one had been responded to (in the plus-minus task, all stimuli were printed in a list, and in the number-letter task stimuli appeared on a computer screen immediately after response to the preceding stimulus). Rogers and Monsell (1995) suggest that in the task-switching paradigm, more time is needed for participants to reconfigure task set. In their study Rogers and Monsell found that when response-stimulus latency was increased, the switch cost latency dissipated somewhat (although importantly a large amount of switch cost latency, the "residual switch cost", did not dissipate). It may also be that if longer time was allowed before presentation of the next stimulus in the present study, the residual switch cost would become apparent as task difficulty for both groups had been reduced. Previous research in ecstasy users has shown that ecstasy users give more perseverations on the Wisconsin Card Sort Task (e.g. Alting von Geusau et al. 2004; Thomasius et al. 2003), which can also be interpreted as an inability to reconfigure task set before responding to subsequent stimuli.

Contrary to the results of Chapter 7, Chapter 10 found that ecstasy users gave more perseverative responses on an associative learning task indicating an inability to reconfigure task set as in Alting von Geusau et al. (2004) and Thomasius et al. (2003). Verdejo-Garcia et al. (2005) provided support for the proposal that recreational drugs differentially affect aspects of executive functioning, with cannabis use being related to task switching (termed "cognitive flexibility" in Verdejo-Garcia's study). In agreement with the separable effects of drugs on switching, Morgan et al. (2002) found that although ecstasy users performed worse on the TMT-B task, performance was more related to the use of LSD and Psilocybin mushrooms. The ecstasy users in this thesis did not report

frequent use of psilocybin or mushrooms, although they did report use of cannabis, cocaine and amphetamine. Unlike Morgan's study no indices of drug use were significantly correlated with switch cost latencies on either task, somewhat curious considering previous research. Perseverative errors on the associative learning task (Chapter 10) were related to indices of ecstasy and cocaine use. In view of this it is possible that deficits in task switching in the present sample are related to ecstasy and/or cocaine use. With the exception of the categorical cocaine user/nonuser variable, correlations with perseverative errors were generally higher for ecstasy use than for cocaine use, although all cocaine users on whom these analyses were based were also ecstasy users. Thus perseverative responses in ecstasy users may be related to some aspect of ecstasy-cocaine polydrug use.

To summarise, this thesis found that ecstasy users did not display longer switch cost latencies on two switching tasks, although they did give more perseverative errors on an associative learning task.

Moving on to the next target function of response inhibition, it was predicted that ecstasy users would perform comparably to nonusers. A random letter generation task was used in which participants had to generate 100 letters at three production rates, one letter every 4-seconds, 2-seconds, and 1-second. Contrary to expectations there was a main effect of ecstasy use on inhibition due to the ecstasy users generating more letters than nonusers. There were no group differences on the alphabetical sequences, repeat sequences or redundancy scores indicating that ecstasy users were not impaired in these aspects of random letter generation. In an early study by Wareing et al. (2000) in which participants were instructed only to generate consonants, the ecstasy users performed

worse than nonusers on this task. However Fisk et al. (2004) found that ecstasy users did not perform worse than nonusers on this task when required (as in Chapter 7) to select any letter from the alphabet (vowels and consonants). The lack of consensus between these two studies may reflect the increased task difficulty of constraints in the consonant only generation and the much larger lifetime ecstasy dose in Wareing et al's study. While it is likely that these three measures on which no deficits were found load solely on the inhibition component (Fisk & Sharp, 2005), this may not be the case for number of letters generated. The surplus evident on the number of letters produced may reflect increased impulsivity on the part of the ecstasy users: while nonusers try and concentrate on using the correct generation strategies, ecstasy users try and concentrate on using non-random strategies such as spelling out words (which would not show up in performance measures) to try and attain the maximum possible. As mentioned in Chapter 2, poor performance (through increases in errors) in some tasks has been related to heightened impulsivity. For example Morgan et al. 2002 found that errors on the MFF20 were associated with ecstasy use (interpreted as heighten impulsivity), and Parrott found that ecstasy users had increased impulsivity (SCL-90). It is noteworthy that other tasks that supposedly load on to Miyake et al's conceptual framework e.g. the Stroop test appear not to be affected by ecstasy use (e.g. Croft et al. 2001a; Morgan et al. 2002). Likewise, according to Miyake et al. the Tower of Hanoi/Tower of London tasks load on the inhibition component, and these also appear to be unaffected by ecstasy use. For example Fox et al. (2002) found that only one aspect of TOL performance was adversely affected by ecstasy use while Morgan (1998) found no evidence of ecstasy-related impairment on the TOL task. Since Chapter 7 failed to find between group differences on the three

established random generation measures, the available evidence suggests that ecstasy may not be associated with any substantial impairment in this aspect of executive processing.

Number of alphabetical sequences, repeat sequences and redundancy were not related to any indices of drug illicit drug use. Number of letters produced was significantly correlated with frequency of ecstasy use, average ecstasy dose and amount used in the last 30 days suggesting that the increased number of letters generated is actually a function of ecstasy use and not merely a coincidence.

To sum up, ecstasy users actually performed better than nonusers on the task of response inhibition, which may reflect heightened impulsivity or the adoption of other non random generation strategies which do not show up in the traditional measures of task performance. This should however be treated with some caution as it is not supported by previous research.

Moving on to the fourth executive function, it was expected that ecstasy users would perform worse on all three measures of access, but that deficits would be most pronounced on the harder aspects i.e. ecstasy users would be worst on the constrained "C" letter category, then the "S" letter category, then the semantic fluency task. It was also possible that deficits in word fluency were mediated by the group differences evident in Chapters 6 and 7 in updating and inhibition. Mean scores showed that the ecstasy users performed worse on all three access measures although this was only significant for "S" and "C" letter fluency. This remained significant after control for verbal IQ scores and years spent in education, as it was possible that both of these aspects may have influenced available word knowledge. This supports previous research showing that ecstasy users

retrieved fewer words than nonusers (e.g. Bhattachary & Powel 2001; Fox et al. 2002; Heffernan et al. 2001a).

One aim of this thesis was to study the separability of ecstasy-related deficits in access. Earlier Chapters (6 & 7) show that ecstasy users are impaired in the updating aspect of executive functioning and perform better than nonusers on the inhibition component, although no differences were observed in switch cost latencies. Accordingly, it was possible that differences in access might be mediated by group differences in these two aspects of executive functioning. Control for differences in random letter generation did little to modify the deficits in word fluency. After control for differences in memory updating via computation span, the main effect of ecstasy use on access and the effects on "S" and "C" letter fluency were slightly attenuated but remained significant. Firstly this indicates that updating is related to access as control for updating attenuated deficits in access. Secondly as deficits in access remained significant after removal of the variance due to updating, it suggests that access is a clearly separable executive function, and provides further support for Fisk and Sharp (2004).

It has also been suggested that attention may affect performance on this task. In Chapter 9, attention was assessed via the digit span task (digit span has been used as an indicator of attention in other studies in ecstasy users e.g. Semple et al. 1999). Attention exhibited a suppressor effect on access performance with both the main effect and "C" letter performance being intensified. Cohen and Stanczak (2000) found that performance on the Chicago Word Fluency Test loaded on the same factors as working memory capacity and attention. In the introduction of Chapter 9, it was postulated that ecstasy users may exhibit deficits on the CWFT due to decreased working memory capacity or

attention, as this word fluency task is longer than those previously used in research in ecstasy users. In support of Cohen and Stanczak's work, the results of Chapter 9 suggest that performance on access, working memory, and attention tasks are all interrelated (the former attenuated and the latter intensified ecstasy-related deficits in access), although clearly separable. This raises the possibility that maybe those studies that did not find a deficit in access did not use a long enough version of the task. With reference to which task ecstasy users may have found most difficult, the group differences were most pronounced on the constrained "C" letter category, supporting Heffernan et al. (2001a) where ecstasy users retrieved fewer household items beginning with "T", while group differences on the "S" letter task were also significant. Contrary to expectations, ecstasy users did not perform worse on the semantic fluency task (as in Heffernan et al. 2001a). One possible reason for this could be the specific semantic category chosen. As mentioned in the introduction to Chapter 9, Baldo and Shimamura (1998) found that "animals" is one of the most easily retrieved semantic categories (in their study normal participants retrieved 23 animal names in a minute, and those with frontal lobe damage only 14 animals in a minute). In light of this it would be expected that as ecstasy use may also cause lesions in the frontal lobes (See Chapter 3 for review) ecstasy users would also retrieve fewer words than nonusers. Obviously ecstasy use does not impair frontal lobe function to the same extent as the lesions in Baldo and Shimamura's study. Having said this, Cohen and Stanczak (2000) performed a meta-analysis of studies utilising the CFWT to assess frontal lobe damage. It was found that though the CWFT was ineffective at discriminating left vs. right, and anterior vs. posterior regions of damage, and global vs. diffuse lesions, it was very effective at discriminating brain damaged vs. normal

participants. Thus the results of Chapter 9 provide further support for the idea that ecstasy use damages the brain, giving rise to potential problems that are unrelated to working memory capacity, attentional deficits, or verbal IQ.

Moving on to indices of drug use, a number of ecstasy use variables were significantly correlated with performance on "C" and "S" letter fluency. More specifically total lifetime dose, average dose, and having ever used ecstasy with "S" letter fluency, and total lifetime dose, average dose, frequency of use, amount used in the last 30 days and having ever used ecstasy were all significantly correlated with "C" letter fluency. Indices of cocaine use also emerged as particularly important predictors of performance, with frequency of use being significantly correlated with semantic fluency; total use, frequency of use, average dose, and having ever used cocaine with "S" letter fluency; and total use, frequency of use, average dose, amount used in the last 30 days, and having ever used cocaine with "C" letter fluency. In order to compare the relative magnitude of ecstasy and cocaine effects on access, further analyses were performed with cocaine user/nonuser as the sole independent variable. Effect sizes for the multivariate and semantic analyses were larger for cocaine than for ecstasy. However, effect sizes for "C" and "S" letter fluency were larger for ecstasy suggesting that these two aspects of access tasks are more related to ecstasy use. Referring back to the literature review chapters (Chapter 2 and 4) it appears from previous research that while ecstasy users may be impaired in access tasks (e.g. Bhattachary & Powel, 2001; Fox et al. 2002; Heffernan et al. 2001a) the same is not true for cocaine use (e.g. Berry et al. 1993; Butler & Frank, 2000; Goldstein et al. 2004). Indeed studies in cocaine abusers indicate that even chronic cocaine-only users (using for an average of 5.83 years) are not impaired on this task

(Butler & Frank, 2000). What may this mean in terms of the results of the present study? As all the participants who felt that they were able to accurately estimate patterns of cocaine use were also ecstasy users, one possible explanation is that the strong correlations with indices of cocaine use actually reflect some aspect of ecstasy use. Part correlations between ecstasy use and fluency scores were calculated following control for indices of cocaine use. A number of these were reduced to marginal non-significance following control for cocaine use. However many remained significant (mostly those between ecstasy use and "C" letter fluency) reflecting hat it is likely that the use of ecstasy is related to this aspect of performance. Another explanation could be that concomitant use of cocaine along with ecstasy may increase the neurotoxic potential of ecstasy (see Chapter 4), and thus correlations with both ecstasy and cocaine are strong.

To summarise the discussion thus far, it is evident that ecstasy users are impaired in the executive functions of updating and access, although the use of other recreational drugs also emerged as important contributors. Outside the field of psychopharmacology, this provides further support for Miyake et al's conceptualisation of executive processes and highlights the importance of studying the central executive as a divergent structure.

The first part of this discussion has shown that ecstasy users are impaired in some executive tasks. The second part will discuss the contribution of executive tasks to performance in syllogistic reasoning (Chapter 9), associative learning (Chapter 10), and everyday memory (Chapter 11) tasks. Taking Chapter 9 first, previous research had shown that ecstasy users are impaired in logical thinking (e.g. Alting von Geusau et al. 2004; McCann et al. 1999) and planning (e.g. Fox et al. 2001; Schifano et al. 1998). It was expected that ecstasy users would be impaired on a syllogistic reasoning task, and

that the deficit would be most evident on the harder three-model/No-Valid-Conclusion (3-m/NVC) syllogisms. Mean scores showed that ecstasy users performed worse than nonusers on both levels of difficulty, although this was only significant for the one-model problems. The user group by difficulty interaction was significant, however this reflected the absence of group differences on the more difficult syllogisms where both groups generally performed at around chance. Therefore as previous research has suggested (e.g. Gouzoulis-Mayfrank et al. 2000; McCann et al. 1999) ecstasy users are impaired on a "pure" reasoning task. Updating and access were identified as executive functions that may have contributed to performance on a syllogistic reasoning task. After control for memory updating (computation span) via ANCOVA, the main effect of ecstasy use and the user group by difficulty interaction were both reduced to below statistical significance. When the three access measures were incorporated into ANCOVA, the user group by difficulty interaction was again reduced to below statistical significance, although the main effect of ecstasy use remained significant. In terms of which aspects of executive functioning may affect performance, updating and access deficits in ecstasy users both appear to be particularly important. In the case of updating, this is supported in previous literature where working memory performance slightly attenuates syllogistic reasoning deficits (e.g. Fisk and Sharp, 2002) and provides further support for syllogistic reasoning being reliant on working memory capacity. Although comparisons have been drawn between the effects of ecstasy and the effects of cognitive ageing on the brain (Morgan 1998), this may not be the case for reasoning deficits. Fisk and Sharp (2002) found that control for reading and computation span (both indicators of updating function) did little to attenuate age-related differences in syllogistic reasoning implying

that in ageing, unlike in ecstasy use, updating is not an important contributor to changing performance on reasoning tasks. This is not to minimise the implications of the group differences observed in reasoning in Chapter 9. Even if it is the case that underlying reasoning competence remains intact in ecstasy users, given that they lack the executive resources to make full use of this capacity, they are still likely to exhibit impairments in the capacity for rational thought. With reference to access, it is possible that word knowledge and linguistic abilities may differentially affect performance on syllogisms. Beyond working memory, syllogistic reasoning is also believed to utilise other resources, for example relations between linguistic concepts such as 'all', 'some' and the logical operator 'not', as well as spatial representations of class inclusion relationships (e.g. Ford, 1995). As a result access may mediate syllogistic reasoning deficits via linguistic competence in ecstasy users.

It was predicted in Chapter 9 that the performance deficit between ecstasy users and nonusers would be most pronounced on the more difficult syllogisms, consistent with Johnson-Laird's (1983) mental models theory. However, the absence of group differences on the NVC and three-model syllogisms is difficult to reconcile with Johnson-Laird's (1983) account of mental models theory. While Johnson-Laird (1983) postulates that individuals construct a number of mental models to solve syllogisms, testing each new model against the conclusion that they have formed, Evans and co-workers (Evans, , Handley, Harper & Johnson-Laird 1999; Handley, Dennis, Evans & Capon 2000; Newstead, Handley and Buck 1999; Newstead, Thompson & Handley 2002) maintain that individuals generally only construct one mental model and fail to search for alternatives. In both Evans' and Johnson-Laird's perspectives, for complex and simple

syllogisms the premises need to be retained so that alternative possible conclusions can be accepted or rejected in the context of the initial mental model and the contents of working memory can be updated as necessary. In Chapter 9 the ecstasy-related group differences evident on the one-model syllogisms appear to be consistent with some degree of impairment in this process. On three-model/NVC syllogisms, in which according to Evans et al's theory only a single mental model is constructed, this single model does not itself constitute an exhaustive representation of the premises, and thus conclusions derived from this model (for users and nonusers) are likely to be erroneous. Consistent with the findings of Chapter 9, group differences would not be expected on the three-model/NVC syllogisms. This suggests that nonusers were better able to construct a single mental model than ecstasy users, but that both groups performed equally poorly on the three-model/NVC problems. Consistent with this, a recent paper from our laboratory (Fisk, Montgomery, Wareing & Murphy, 2005) observed that ecstasy users made more non-responses (i.e. did not indicate a response) than nonusers on the easier one-model syllogisms. In addition the nonusers made more erroneous responses on the three model and NVC syllogisms. These findings suggest that ecstasy users with their reduced executive functioning are less able to retain the premises in working memory and as a consequence experience difficulty in forming the initial model necessary to draw a conclusion.

Unlike chapters 6, 7, and 8, indices of cocaine and cannabis use were not significantly correlated with performance on either type of syllogism (although having ever used amphetamine was significantly correlated with performance on one-model syllogisms). Having ever used ecstasy, total lifetime dose and average dose were all

significantly correlated with performance on one-model syllogisms, which may in turn reflect some aspect of memory updating performance, as ecstasy-related differences in one-model syllogisms were reduced to below statistical significance following control for updating. By way of summary, the results of Chapter 9 suggest that ecstasy-related deficits are most apparent in the aspect of executive functioning captured by computation span (updating) and that these deficits in turn produce secondary deficits in reasoning performance.

Chapter 10 assessed the contribution of executive processes to a paired associate learning task, and examined the processes underpinning associative learning deficits in ecstasy users. While previous research suggested that ecstasy users might exhibit impairments in learning, this thesis used a number of different measures of associative learning performance, notably initial learning, trials to completion, perseverative responses, and indices of forgetting well-learned and less well-learned responses. It was expected that ecstasy users would perform worse than nonusers on all these measures. Ecstasy users had lower mean scores on all indices of associative learning, and both the main effect and all univariate analyses were significant (with the exception of forgetting at levels 2 and 4). After control for memory updating and access all significant group differences remained significant, although slightly attenuated in most cases (with the exception of group differences in forgetting at level 4 which were intensified after control for updating). Like syllogistic reasoning, associative learning seems to be related to deficits in executive functions. However, unlike syllogistic reasoning the group differences in associative learning remained significant after control for executive functions. Thus it appears that ecstasy related deficits in associative learning are

relatively independent of deficits in executive processes and that the two functions are at least in part reliant on distinct cognitive systems that are susceptible to different sources of impairment.

As with updating, inhibition and access (in chapters 6, 8 and 8 respectively) there appears to be a dissociation between the effects of recreational drugs on aspects of associative learning performance. While ecstasy use was significantly correlated with trials to completion and perseverative errors, indices of cannabis use were significantly correlated with the number of correct responses on trial one, and indices of cocaine use with forgetting. Implications with reference to perseverative errors have been discussed previously in this chapter. The significant correlations between indices of ecstasy use and trials to completion indicated that as severity of ecstasy use increased (indexed by total lifetime dose, average dose, frequency of use, amount used in the last 30 days) trials taken to learn all the associations also increased. Deficits of the same nature have been observed in ecstasy users in list learning tasks (e.g. Gouzoulis-Mayfrank et al. 2000), although this is the first study on drug use to find that ecstasy users take longer on a paired associates learning task. With reference to cannabis, indices of cannabis use were significantly negatively correlated with the number of correct responses on trial one indicating that as severity of cannabis use increased, number correctly recalled decreased. Deficits in short-term memory have been observed in cannabis users (e.g. Solowij et al. 1992) so it could be that the significant correlations reflect some aspect of cannabis-related impairment in immediate recall. However, Rodgers (2000) and Croft et al. (2001a) both found that cannabis users did not differ from controls on this task (although in Rodger's study, the ecstasy users were worse than the cannabis users on the delayed

recall of word pairs). Indices of cocaine use were significantly positively correlated with forgetting at level 1 indicating that as cocaine use increased, there was a tendency to forget responses that were not well learned.

With reference to the structure of associative learning processes in ecstasy users, it was revealed that ecstasy-user group accounted for ~22% of the total variance in trials to completion. In the regression analysis all of the component measures of learning performance substantially reduced the ecstasy-group related variance in trials to completion. The greatest degree of attenuation was achieved by the level of initial learning (correct responses on trial one). The various measures of forgetting each reduced the ecstasy-group related variance by about one half while for perseverative responses the degree of attenuation was around 40%. Thus the ecstasy-group related effect appears to be mediated through all of the learning sub-processes. Taken together with the results of the MANOVA and correlations, this is consistent with an ecstasy-mediated effect in trials to completion.

Chapter 11 assessed the contribution of executive processes to self-reported incidences of everyday memory failures. Ecstasy users scored significantly higher than nonusers on a number of everyday memory measures: the CFQ, EMQ, two subscales of the PMQ (long-term episodic and internally cued PM) and significantly lower on a measure of memory updating and a measure of access. Ecstasy users were also rated significantly higher by friends on the CFQ-for-others. The interaction between CFQ and CFQ-for-others scores and ecstasy use was non-significant, indicating that ecstasy users do realise their cognitive slips. Surprisingly, although there was a main effect of ecstasy

use on most of the measures, cannabis use variables emerged as the most significant predictors of everyday memory scores.

The findings of Chapter 11 support and extend previous research. Firstly, we found that ecstasy users rated themselves higher on the CFQ, indicating increased incidence of cognitive slips. This provides further support for Fox et al. (2001), who reported a higher incidence of cognitive slips in ecstasy users than in nonusers. However, Rodgers (2000) and Heffernan et al. (2001a) did not find any ecstasy-related differences on this version of the questionnaire. This may be due to differences in lifetime drug consumption. While both studies report that the ecstasy user group had used ecstasy 20 times over a 5-year period, Heffernan et al. (2001a) also report that the average dose was one tablet per session. As the average dose in the present study was 346.5 tablets, this raises the possibility that the types of slip assessed by the cognitive failures questionnaire are relatively preserved until a certain threshold of ecstasy use is reached.

Ecstasy users were also rated higher by friends on the CFQ-for-others. The percentages of reported slips for the CFQ and CFQ-for-others were relatively similar (45.42 and 45.79 for ecstasy users; 38.58 and 33.47 for nonusers). The interaction between ecstasy use and self- and other-reported slips was non-significant. It has been suggested that the absence of a deficit on this task in previous research may reflect a metacognitive deficit in ecstasy users, which renders them unable to monitor their cognitive state accurately. However, the results of the present study suggest that ecstasy users do realise their cognitive slips, which is consistent with Heffernan et al's findings (2005) that self-reported PM and objective PM slips in ecstasy users were similar.

Ecstasy users also scored significantly higher on the EMQ indicating increased incidences of slips in everyday memory. Rodgers et al. (2003) found that frequency of cannabis use was the most important predictor of everyday memory scores (discussed below).

Ecstasy-related differences were also observed on two sub-scales of the PMQ: long-term episodic PM and internally cued PM. This provides some support for Heffernan et al. (2001b) in which ecstasy users reported a greater number of prospective memory slips on the internally cued subscale than the long-term subscale (however, the main effect and short-term PM in the present study were non-significant). Heffernan et al. (2001a) also found evidence for prospective memory deficits in ecstasy users: Short-term, long-term and internally cued PM were all related to ecstasy use. In Rodgers et al's (2001b) study, LT-PM was also negatively associated with ecstasy use. The effects of ecstasy on LT-PM may be due to similar mechanisms as those associated with deficits in recall, where ecstasy users generally perform worst on recall tasks in the delayed condition (as suggested by Rodgers et al. 2001).

Control for access and updating attenuated or reduced the everyday memory deficits to below statistical significance. Heffernan et al. (2001a) suggested a link between executive functioning and prospective memory deficits in ecstasy users (as ecstasy users performed worse on both a word fluency task and PM task in their study), although they did not investigate such an interaction. Thus the present study provides further support for the mediating role of executive functioning in prospective memory deficits in ecstasy users. This is also seen in older adults, who perform worse on PM tasks partly due to decreased working memory capacity (e.g. Martin & Schuman-Hengsteler,

2001); thus unlike the syllogistic reasoning deficits observed in Chapter 9, the nature of everyday memory deficits in ecstasy users is similar to that of older individuals and further supports the notion that ecstasy-polydrug use may facilitate premature ageing of the brain (Morgan 1998).

The focus of Chapter 11 was intended to be ecstasy use. There was a main effect of ecstasy use on most of the everyday memory measures, and indices of ecstasy use were associated with EMQ scores (ever used, average dose), CFQ scores (ever used, average dose), and CFQ-for-others scores (ever used, total lifetime dose). However, a number of other illicit drugs consumed by the participants tested here appear to have produced effects on the measures that were administered. Indices of cannabis use seem to be particularly important predictors of everyday memory deficits. Indeed, having ever used cannabis, total lifetime dose and average weekly dose were significantly correlated with all everyday memory measures. Given that 40 (maximum 43) of the ecstasy users and 26 (maximum 51) of the nonusers had ever tried cannabis, with 30 and 18 respectively being able to estimate lifetime consumption, it is entirely possible that the ecstasy-related group differences in ratings of everyday memory reflect some aspect of ecstasy-cannabis use, or cannabis only use (e.g. Schwartz et al. 1989). Studies which have attempted to adequately control for cannabis use via ANCOVA and regression analysis have found a dissociation between the two drugs in terms of their impact on aspects of everyday memory functioning, suggesting that the effects observed in the present study on prospective memory at least may be accurate. Rodgers et al. (2003) found that while cannabis use predicts self-reports of failures in everyday memory, long-term prospective memory deficits were related to ecstasy use. Rodgers et al. (2001) also

found that cannabis use was related to self-reports of "here and now" (ST and internally cued PM) memory deficits, while ecstasy use was associated with long-term PM deficits. Heffernan et al. (2001a; 2001b) also found that ecstasy-related deficits in PM remained significant after control for alcohol, cannabis and cocaine, and a cannabis only group did not report more cognitive failures compared to ecstasy users and controls (2001a).

Cannabis use thus appears to be a particularly important contributor to everyday memory deficits. In addition to the many significant correlations between cannabis use and everyday memory, separate analyses were performed with cannabis user (two levels: user/nonuser) as the independent variable. Effect sizes were larger in all cases (with the exception of the CFQ-for-others) for cannabis use than ecstasy use indicating that deficits in everyday memory are more related to the use of cannabis. Unlike the analyses with ecstasy use, all cannabis use analyses remained significant following control for updating and access. In terms of the components of everyday memory, this may imply that decrements in users of ecstasy and users of cannabis are apparent for different reasons. It may be that while cannabis users exhibit genuine everyday memory deficits which may or may not dissipate somewhat with prolonged abstinence, ecstasy users exhibit deficits in aspects of executive functioning (access and updating in this thesis) which render them unable to efficiently utilise their everyday memory skills. Hence the everyday memory deficits in ecstasy users are not as strong as those in cannabis users and are reduced to below statistical significance following control for working memory capacity.

To recapitulate, it appears that while associative learning deficits in ecstasy users are relatively independent of updating and access, the same is not true for everyday memory and syllogistic reasoning deficits. Ecstasy-related group deficits in reasoning and

everyday memory were reduced to below statistical significance following control for memory updating, and in some cases for access also. Additionally cannabis emerged as a more important predictor of everyday memory performance than ecstasy use.

The next section of this discussion will focus on the results of this thesis in terms of the neural areas that may be associated with such deficits. Focusing primarily on updating, Salmon, van der Linden, Collette and Delfiore (1996) used a letter-updating task adapted from Morris and Jones (1990) requiring participants to recall the most recent six items from strings of eight, nine and ten consonants. Brain activation during the updating task was compared to that during a phonological short-term memory task. For the updating task only, an increase in activation was seen in the mid-dorsal prefrontal cortex (BA 9), left middle frontal regions (BA 46 and BA 10) and in the right frontal pole (BA 10). In a more recent study using PET imaging Van der Linden et al. (1999) required participants to remember the most recent 4 items in letter strings of varying length and it was found that the most significant increases in activation occurred in the left frontopolar cortex (BA 10) spreading to the left middle frontal area (BA 46). Utilising ERP and neural imaging techniques, Postle and co-workers provide further support for the role of the dorsolateral prefrontal cortex in updating tasks (e.g., Postle, Berger, Goldstein, Curtis, & D'Esposito, 2001). Thus it appears that these areas of the prefrontal cortex may be especially sensitive to the effects of ecstasy use. Ecstasy users were also impaired in access to long-term memory. Similarly, it appears that access[19] also recruits resources in the DLPFC: Lesion studies have implicated the left dorsolateral prefrontal cortex in impaired letter and category-based fluency (Stuss et al. 1998) and also in impaired

[19] The Chicago Word Fluency Task, as mentioned earlier in the discussion, is very effective at identifying brain damaged individuals compared to non brain damaged, although it is not believed to be as effective at identifying the site of damage. Such studies refer to other access tasks.

fluency among children (Levine et al. 2001). In a PET study of word finding, also using a word fluency task (Frith, Friston, Liddle & Frackowiak, 1991), performance was associated with an increase in left dorsolateral prefrontal cortical activity specifically BA46. Taken together these results suggest that ecstasy use may adversely affect the DLPFC. In this thesis ecstasy users were not impaired in switching tasks or inhibition tasks. Given that performance on both of these tasks has also been linked to functioning in the left prefrontal lobes (e.g. Petrides. Alivastos, Evans, & Meyer, 1993a and b; Rogers et al.1998; Stuss & Benson, 1998) the lack of group differences on these tasks is surprising. It may be that ecstasy-related deficits in updating and access do not reflect degradation of the serotonin system in the prefrontal cortex, although this seems unlikely (see below). Moving on to syllogistic reasoning the pattern of neural correlates is rather more diverse, indeed syllogistic reasoning even in its abstract form is very complex and relies on numerous cognitive capabilities including executive functioning. Such capacities are likely to be distributed in different areas of the brain: the process of integrating premises is associated with increased activation in the DLPFC (BA46 bilateral, BA8 left hemisphere), the left inferior prefrontal cortex (BA10 and 44) and the right inferior/medial prefrontal cortex (BA46). The key aspect of syllogistic reasoning (i.e. evaluating the conclusion) is associate with increased activation in the inferior frontal lobe (BA45 bilaterally, left BA44), bilateral cerebellum and basal ganglia, bilateral fusiform gyrus (BA18), and the left superior parietal lobe (BA7, Goel, Buchel, Frith & Dolan, 2000).

What support is there for the proposition that the deficits observed in this thesis may be related to decrements in the serotonin system caused by ecstasy use? Evidence

suggests that the prefrontal cortex in general and the DLPFC in particular are especially sensitive to the effects of ecstasy (See Chapter 3 for a review of the human ecstasy neuroimaging literature). In terms of neurotransmitters, Robbins (2000) highlights the contrasting roles of dopamine and serotonin in underpinning different aspects of cognitive functioning, especially the role of dopamine in spatial working memory functioning. To further support this Dopamine is also involved in modulating DLPFC activity (BA46) in non-human primates (Henze, Gonzalez-Burgos, Urban, Lewis & Barrionuevo, 2000). In terms of serotonergic functioning Luciana, Collins, and Depue (1998) found that fenfluramine (a serotonin agonist) impaired visuo spatial working memory performance while bromocriptine (a dopamine agonist) generally facilitated performance.

There are a number of important implications of this thesis outside the area of Psychopharmacology. Firstly, one aim of this thesis was to study the separability of four executive processes in ecstasy users. Until recently it was believed that the central executive of working memory was a unified structure. However recent theoretical models postulate that although some executive functions are inter-correlated, they are also clearly separable (Fisk & Sharp, 2004; Miyake et al. 2000). This thesis therefore provides further support for the fractionation of executive processes into four sub categories: updating, shifting, inhibition and access. Secondly this thesis provides further support for Evans et al's (1999) theory of syllogistic reasoning. In Chapter 9 both groups performed comparably on the three-model/NVC syllogisms suggesting that individuals generally only construct a single mental model of premises and fail to search for alternatives. This is consistent with cognitive ageing literature (e.g. Fisk & Sharp, 2002). Thirdly this thesis

provides a framework for the nature of associative learning processes which may apply to non-ecstasy users as well as the ecstasy-using group in the present study. Fourthly it is also suggested that syllogistic reasoning and everyday memory functioning may be reliant on working memory resources (providing further support for e.g. Gilhooly et al. 1993). Although deficits in syllogistic reasoning performance appear unrelated to working memory performance in older populations (e.g. Fisk & Sharp 2002) this was not true of ecstasy users. Equally it appears that everyday memory performance is related to executive and working memory functioning in a number of populations (e.g. Marsh & Hicks, 1998).

There were a number of limitations with the research in this thesis. While the results of Chapters 6-10 emphasize the importance of ecstasy use in accounting for the observed deficits (and in the case of Chapter 11, cannabis use), the possibility that the use of other recreational drugs may have contributed to such deficits cannot be entirely ruled out. The use of ANCOVA was not deemed appropriate as it would not have been possible to test for homogeneity of regression in the case of cocaine use, which would have rendered the ANCOVA result difficult to interpret. Accordingly correlations and where appropriate part correlations were used to try and ascertain relationships between drug use and performance. In the case of updating, ecstasy generally emerged as the most significant source of variance, although it is possible that for word fluency cocaine or ecstasy/cocaine polydrug use were important contributors. Likewise, cannabis emerged as the most significant predictor everyday memory deficits. Even where statistical controls were implemented, the reliance on self-report data can be potentially problematic. The indices of drug use that were calculated for each chapter were based on the individual

being able and willing to provide an accurate indication of their drug use. Additionally, there is no guarantee that the substances that were consumed always contained the drug in question, although a recent review of the contents of amnesty bin contents from nightclubs suggests that ecstasy tablets mostly contain MDMA (Parrott, 2004a). Due to limitations in available resources, it was not possible to use urine, saliva or hair samples to confirm recent patterns of drug use. However, this thesis is not alone in this respect. Most published studies assessing cognitive deficits in ecstasy users (e.g. Fox et al. 2002; Heffernan et al. 2001a and b; Morgan 1998; Parrott and Lasky, 1998; Rodgers 2000; Rodgers et al. 2001) have not resorted to these objective measures of drug use.

While subjective measures of prospective and everyday memory have been used in ecstasy research investigating this area to date (e.g. Heffernan et al. 2001a; Heffernan et al. 2001b; Rodgers et al. 2001; Rodgers et al. 2003), such subjective measures are not without their limitations. Although the everyday memory measures such as the PMQ seem to correlate well with more objective measures of PM (Hannon et al. 1995; Heffernan et al. 2005), there are obvious benefits to the use of objective PM tasks (not least that they are not reliant on subjective perceptions of memory, in a group of supposedly memory impaired individuals). Therefore perhaps future research should aim to use more objective measures of PM for example the Cambridge Prospective Memory Test (CAMPROMT) which contains 4-event based and 4-time based situations, and can be used in a laboratory setting (Wilson, Emslie, Foley, Shiel et al. 2005). In addition, Heffernan et al. (2001b) note that subjective memory ratings can be affected by depression. Research in clinical populations has shown that both objective and subjective cognitive deficits are heavily related to depression (in one study differences between

groups were reduced to below statistical significance following control for depression-Chamelian & Feinstein, 2006). Some studies in ecstasy users show that users of the drug report higher levels of depression (Curran & Travill, 1997; Parrott and Lasky, 1998) and consequently it remains a possibility that the group deficits in prospective and everyday memory observed in this thesis may reflect increased depressed mood in ecstasy users. However, a recent meta-analysis concluded that there is little evidence for ecstasy-related depression, and incidences of such are not likely to be clinically relevant (Sumnall & Cole, 2006). To summarise, the research in this thesis may be limited by the use of some subjective measures and future research should seek to use more objective measures and investigate the link between subjective reports of memory slips and depressed mood in ecstasy users.

While established and validated tests have been used in every chapter, the results of such laboratory measures may have limited generalisability to the real world. This is not however to minimise the implications of this thesis. Tests such as the PMQ, EMQ and CFQ could have very serious real-world implications for ecstasy users. These tests contained items such as "I forgot an important appointment"; "I forgot what I went in to a room for". Such lapses in memory could have serious implications for users of the drug (especially for example in a university setting, or an occupational setting where individuals are required to keep appointments). More worryingly, the results showed that ecstasy users did not implement more strategies than nonusers although they did exhibit more slips in prospective memory. Therefore the results of this thesis could be used to educate individuals who have used/consider using ecstasy, and make them aware of strategies that can aid memory.

It was also possible that the groups differed in some aspect other than their use of illicit drugs. In each Chapter data were collected on indices of sleep quality, alcohol consumption, premorbid and fluid intelligence, age, gender and other lifestyle variables. In a number of Chapters the groups did not differ significantly on background variables (Chapters 7 and 10). In those chapters where there were significant group differences on background measures, such differences mainly acted to intensify ecstasy-related effects. In Chapter 6 (updating) where alcohol use, ESS scores and gender were entered into ANCOVA both the main effect and the univariate analyses were intensified, and the previously non-significant 12-letter list length difference became significant. In Chapter 8 (access) after Raven's Progressive Matrices scores, Alcohol use and ESS scores were entered into ANCOVA, the main effect and the univariate effects for all three-word fluency scores were intensified, with the previously non-significant Semantic category now becoming significant. In Chapter 9 (syllogistic reasoning), although control for alcohol use reduced the interaction between ecstasy use and problem type to below statistical significance, the main effect was once again intensified. The results of these ANCOVAs suggest that although ecstasy users and nonusers may differ on some lifestyle variables, these are not responsible for the ecstasy-related deficits observed in this thesis. Indeed after removing the variance due to background variables the ecstasy-related deficits were actually intensified. Nonetheless, it is possible that the groups differed on some other pre-existing factors that we have not controlled for.

Finally there are a number of suggestions for future research arising from this thesis. Chapters 6 and 10 revealed that ecstasy users exhibit deficits in memory updating and associative learning respectively. In Chapter 2 section 2.11.3 a number of studies

show that ecstasy users are impaired is aspects of visuo-spatial working memory (e.g. Wareing et al. 2004a). Both of the tasks used in Chapters 6 and 10 were verbally based, and it would therefore be interesting to see if ecstasy users are also impaired in visuo-spatial memory updating and visuo-spatial associative learning. Although some studies have already looked at the updating of visuo-spatial information (e.g. Alting von Geusau et al. 2004) it would be of great benefit to use an established memory updating paradigm such as that Fisk & Sharp (2003). Similarly visuo-spatial associative learning has also been assessed in ecstasy users (e.g. Croft et al. 2001a; Fox et al. 2002). However, once again it would probably be beneficial to look at other measures of learning similar to those used in Chapter 10, for example, trials to completion, initial learning, perseverations, forgetting at various levels, and to further explore the relationship between them in the context of ecstasy-related effects. Chapter 8 revealed that ecstasy users were impaired in access to long-term memory. Research so far in ecstasy users has mainly assessed this executive function via word fluency tasks (see Chapter 2, section 2.3.2). It would be interesting to see if this deficit in access to long-term memory is restricted to performance on word fluency or if other tasks that are also supposedly reliant on access (e.g. verb generation) are also susceptible to the effects of ecstasy. Finally, one obvious limitation is the reliance on opportunity sampling. Due to the method of recruitment and the nature of the sample it was not possible to recruit a group that solely used ecstasy, a group that solely used cannabis and a group that solely used cocaine. Thus it is possible that some of the observed deficits were attributable to the concomitant use of other recreational drugs. Future research should focus on trying to recruit such groups, although most published studies in this area contain an ecstasy-polydrug using group.

There is alarming evidence that suggests that individuals are starting to use ecstasy at a younger age now (e.g. British Crime Survey 2004-05). Therefore future research could focus on possible deficits in such age groups. While it would also be useful to perform a longitudinal study with such age groups, securing funding for such projects remains potentially problematic. This thesis attempted to control for possible lifestyle/background factors that may have affected the results (e.g. sleep quality, intelligence). Nonetheless it still remains a possibility that the groups differed in some other factor than their ecstasy use, such as diet (e.g. Curran & Robjant, 2006), lifestyle (e.g. dancing for long periods of time in crowded clubs e.g. Parrott, 2004b). Thus future research could perhaps focus on protective factors such as adequate diet, the importance of regular rest breaks, and possible functional differences between groups of ecstasy users with/without adequate diets and with/without regular rest breaks. As well as drug-taking situations such as dancing and hyperthermia, other drug-taking factors may also be important in functional differences. It has long been reported that higher dosage groups of ecstasy users exhibit more severe cognitive deficits than low dosage groups (e.g. Halpern et al. 2004). In addition to this, it is likely that those who ingest a higher number of tablets per occasion ("bingeing") are more likely to be subject to possible neurotoxicity. Thus it would be expected that such individuals would present worse psychological profiles. This would be an interesting area for future research.

Thesis Summary

This thesis sought to evaluate executive function deficits in a sample of recreational ecstasy users using recent theoretical models of executive functioning. It was found that ecstasy use differentially impairs executive functions with updating and access

to long-term memory being affected and inhibition and switching being relatively preserved. Access and updating were then evaluated as potential mediators of syllogistic reasoning, associative learning and everyday memory in ecstasy users. It was found that reasoning and everyday memory deficits are dependent on executive resources (particularly updating) while ecstasy-related differences in associative learning are relatively independent of these processes. In most cases deficits appear to be related to the use of ecstasy. However cocaine emerged as an important predictor of access deficits and cannabis of everyday memory deficits. Outside the area of psychopharmacology this thesis has important implications for the structure of executive processes, the nature of associative learning and syllogistic reasoning processes.

In conclusion, the results of this thesis raise a number of important issues concerning future research, and recommendations are made. The results suggest that the use of ecstasy may be harmful to the human brain, possibly through degradation of the serotonergic system, and thus the results should be used in the education of individuals considering using the drug.

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Appendices

Appendix 1

The table below shows the overlap of participants in Chapters 6-11.

	Ch 6	Ch 7	Ch 9	Ch 8	Ch 10	Ch 11
Chapter 6 (updating)	-	-	-	-	-	-
Chapter 7 (Switching & Inhibition)	8 U 11 NU	-	-	-	-	-
Chapter 9 (Syllogisms)	27 U 35 NU	15 U 35 NU	-	-	-	-
Chapter 8 (Access)	11 U 19 NU	15 U 18 NU	17 U 39 NU	-	-	-
Chapter 10 (Associative Learning)	27 U 35 NU	14 U 34 NU	17 U 38 NU	33 U 62 NU	-	-
Chapter 11 (Everyday Memory)	29 U 35 NU	8 U 11 NU	24 U 32 NU	28 U 39 NU	27 U 39 NU	-

U = Ecstasy Users

NU = Nonusers.

Appendix 2: Drug Use Qusetionnaire

Participant Number _____

Height _____

Weight _____

Gender _____

Age _____

1. Have you ever used the drug ecstasy? Yes/No*

(If 'No' please move on to Question 16)

2. How long have you been taking ecstasy? _____ Months _____ Years

3. How aware are you that using the drug ecstasy may have harmful long term effects on your health?

(Please tick relevant answer)

Very aware ____

Quite aware ____

Unsure ____

Quite unaware ____

Very unaware ____

Can you explain below what these harmful effects may be?

4. Are you concerned about the possible dangers of using ecstasy?

(Please tick relevant answer)

Extremely Concerned ____

Very Concerned ____

Concerned ____

Slightly Concerned ____

Not Concerned ____

5. How do you find out information about ecstasy?
(Please tick all relevant answers)

TV-News		Radio	
TV-Specialist Programes\Debate		Drug Agencies	
Daily Newspaper		Drug Leaflets	
Music Magazines		Friends	
Magazine		Clubs	
Other			

6. Where do you usually take ecstasy?
(Please tick relevant boxes)

Pubs/Bars	
Night-clubs	
Rave Events	
Private House/Flat	
Parties	
Own Home	
Friends Home	
Other	

7. What activities do you participate in when under the influence of ecstasy?
(Please tick relevant boxes)

Dancing	
Listen to Music	
Talking	
Driving	
Sexual Behaviour	
Drinking	
Smoking	
Other	

8. Do you take any sort of precautions when using ecstasy? (E.G. Vitamins) Yes\No

If yes please give details

9. Are you aware that medical advice suggests that you should take precautions when using ecstasy? Yes___ No____

If yes can you explain below what precautions should be taken and why

10. When under the influence of ecstasy:

(a) Do you take regular rest-breaks when dancing Yes— No—

(b) Do you monitor your fluid intake Yes— No—

(c) Is there anything else you do Yes— No—

*If **yes** please give details*

11. Is there a maximum number of ecstasy tablets you will take in one session? Yes— No—

If **Yes**, what is the maximum number _____

12. What factors decide when you have taken enough ecstasy tablets in one session? (***Please give details below***)

13. Do you believe that since using ecstasy you have changed in any way?

Please look at the following list very carefully

(For example, if you believe that since using ecstasy you have become more caring then tick caring under the heading MORE. If however you feel that you have become less caring then tick caring under the heading LESS. If you feel that you have not become any more or less caring the tick caring under the heading NO CHANGE)

	MUCH MORE	MORE	NO CHANGE	LESS	MUCH LESS
CARING					
PARANOID					
ALERT					
DEPRESSED					
SOCIABLE					
AGGRESSIVE					
HAPPY					
HEALTHY					
MOODY					
PATIENT					
IRRITABLE					
CONFIDENT					
SAD					
LOVING					
CONFUSED					

Any other changes _____

14. What has stopped you taking ecstasy in the past?
(Please tick relevant boxes)

Bad Experience (You)	
Bad Experience (Other)	
Work/College	
Parents	
Short Term Health (Physical)	
Long Term Health (Physical)	
Death	
Responsibilities	
Prison	
Psychological Problems (Short Term - in the last 1 month)	
Anxiety	
Depression	
Flashbacks	
Panic Attacks	
Paranoia	
Psychological Problems (Long Term - continuing after 1 month)	
Anxiety	
Depression	
Flashbacks	
Panic Attacks	
Paranoia	
Other (please specify)	

15. From the following list, please indicate what type of other drugs you use **at the same time** as ecstasy and the frequency of use.

(Please tick all relevant boxes)

Drug	Always	Frequently	Occasionally	Never
Alcohol				
Amphetamine				
Cannabis				
Cocaine				
Crack				
DMT				
GHB				
Herbal E				
Heroin				
Ketamine				
LSD (Acid\Blotters)				
LCB				
Mushrooms				
Poppers				
Prozac				
Salvia Divindrum				
Tranquillisers				
Tobacco				
Viagra				
Other				

16. From the following list, please indicate what type of other drugs you **have used in the last three months** use and the frequency of use.

(Please tick all relevant boxes)

Drug	Always	Frequently	Occasionally	Never
Alcohol				
Amphetamine				
Cannabis				
Cocaine				
Crack				
DMT				
GHB				
Herbal E				
Heroin				
Ketamine				
LSD (Acid\Blotters)				
LCB				
Mushrooms				
Poppers				
Prozac				
Salvia Divindrum				
Tranquillisers				
Tobacco				
Viagra				
Other				

17. From the following list, please indicate which types of drugs you have used in the past. Please indicate when you **first began using** and when you **last used** the drug.

Drug	When did you first use?	When did you last use? (Please circle one only)				
	mm/yr.	Hours Previous	Days Previous	Weeks Previous	Months Previous	Years Previous
Ecstasy (MDMA)			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Alcohol			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Amphetamine			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Cannabis			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Cocaine			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Crack			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
DMT			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
GHB			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Herbal E			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Heroin			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Ketamine			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
LSD (Acid\Blotters)			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
LCB			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Mushrooms			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Poppers			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Prozac			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Salvia Divindrum			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Tranquillisers			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Tobacco			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Viagra			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10
Other			0 1 2 3 4 5 6	1 2 3	1 2 3 4 5 6 7 8 9 10 11	1 2 3 4 5 6 7 8 9 10

If less than a day, indicate hours previous

18. Please list any <u>controlled substances</u>, prescription <u>medications</u>, and <u>alcohol</u> you have consumed **in the last 10 days?** Please list ALL occasions during the last 10 days.

Substance	Days/hours previous	Amount taken			
		Grams	Cost	Units *e.g. bags/wraps*	Dose *e.g. joints, line*

19. How would you describe you current pattern of **ecstasy** use?

_____ times per week OR

_____ times per month OR

_____ times per year OR

_____ previous user (more than 6 months since last used)

Please estimate your pattern of use from the first year of taking the drug to present use

- Fill in the year you began taking ecstasy
- Select an average month of use within that year
- Estimate the total number of ecstasy tablets you would normally have taken during one session
- Indicate frequency of use, e.g., number of times per week/month/year

Continue to fill in each consecutive year regardless of whether you used ecstasy or not. If you have not used for a particular year, continue to enter the year and specify a month, and then enter zero in the space provided for the total number of tablets taken.

Year	Month	Total number of tablets taken in one session	Frequency of use	Route of Administration
e.g. Year 1 1993	June	1	One a Week	e.g. swallow, sniff, inject
This year	Last 30 days		How many times?	

20. How would you describe you current pattern of **Amphetamine** use?

_____ times per week OR

_____ times per month OR

_____ times per year OR

_____ previous user (more than 6 months since last used)

In what form do you take amphetamine?
Powder (amphetamine sulphate) _____

Tablets (please indicate type) _____

Other _____

Please estimate your pattern of use from the first year of taking the drug to present use

- Fill in the year you began taking amphetamine
- Select an average month of use within that year
- Estimate the total number of amount of powder you would normally have taken during one session
- Indicate frequency of use, e.g., number of times per week/month/year

Year	Month	Total amount taken in one session	Frequency of use	Route of administration
e.g. Year 1 1993	June	e.g. 1	One a Week	e.g. swallow, sniff, inject
This year	Last 30 days		How many times?	

21. How would you describe you current pattern of **Cannabis** use?

_____ times per week OR

_____ times per month OR

_____ times per year OR

_____ previous user (more than 6 months since last used)

In what form do you take Cannabis?

Joints _____

Other _____

Please estimate your pattern of use from the first year of taking the drug to present use

- Fill in the year you began taking Cannabis
- Select an average month of use within that year
- Estimate the total number of joints you would normally have taken during one session
- Indicate frequency of use, e.g., number of times per week/month/year

Year	Month	Total number of joints in one session	Frequency of use	Route of administration
e.g. Year 1 1993	June	e.g. 1	One a Week	e.g. Smoke, Swallow,
This year	Last 30 days		How many times?	

22a. **Other drug regularly used:** Please estimate your pattern of use from the first year of taking the drug to present use.

_____ times per week OR

_____ times per month OR

_____ times per year OR

_____ previous user (more than 6 months since last used)

Which Drug? _____

In what form? _____

Please estimate your pattern of use from the first year of taking the drug to present use

- Fill in the year you began taking the drug
- Select an average month of use within that year
- Estimate the total amount you would normally have taken during one session
- Indicate frequency of use, e.g., number of times per week/month/year

Year	Month	Total amount in one session	Frequency of use	Route of administration
e.g. Year 1 1993	June	e.g. 1	One a Week	e.g. Smoke, Swallow, Inject, Snort
This year	Last 30 days		How many times?	

22b. **Other drug regularly used:** Please estimate your pattern of use from the first year of taking the drug to present use.

_____ times per week OR

_____ times per month OR

_____ times per year OR

_____ previous user (more than 6 months since last used)

Which Drug? _____

In what form? _____

Please estimate your pattern of use from the first year of taking the drug to present use

- Fill in the year you began taking the drug
- Select an average month of use within that year
- Estimate the total amount you would normally have taken during one session
- Indicate frequency of use, e.g., number of times per week/month/year

Year	Month	Total amount in one session	Frequency of use	Route of administration
e.g. Year 1 1993	June	e.g. 1	One a Week	e.g. Smoke, Swallow, Inject, Snort
This year	Last 30 days		How many times?	

23. How many years of full time education have you completed from primary school to date?

_____Years

24. From the following list, please indicate if you have obtained any of the following educational qualifications?

Qualification	Y\N	Details
CSE		
GCE		
GCSE		
A LEVEL		
NVQ		
GOV. EMPLOYMENT TRAINING SCHEME		
CRAFT\TRADE (EG CITY & GUILD)		
HND		
DEGREE		
OTHER		
NONE		

25. Do you have any convictions for drugs Yes— No—
If yes, would you please give details below?
E.g. year of conviction, type of drug, type of offence

26. Do you have any other convictions Yes— No—
If yes, would you please give detail below?
E.g. year of conviction, type of offence

Appendix 3

Adjusted Means for Chapter 6 following ANCOVA.

Below is a table showing the adjusted means for the letter updating task following ANCOVA for Epworth Sleepiness Scale, Alcohol consumption and gender. The means show that the scores are in the direction predicted in the original hypothesis.

	Ecstasy Users	Nonusers
Length 6	2.54	2.87
Length 8	1.99	2.51
Length 10	1.86	2.46
Length 12	1.96	2.35

Appendix 4

Supplementary analyses for Chapter 8

The data for Chapter 8 were analysed via MANOVA. However, it was suggested that semantic fluency may be the easier part of the task, with the "S" letter fluency being intermediate in difficulty and the constrained "C" letter fluency being the hardest category. If this were the case, we would expect ecstasy users and nonusers to perform comparably on the semantic fluency task, with performance differences increasing with increasing task difficulty. To see if word fluency deficits were qualified by a ecstasy-user group by difficulty interaction, the data were analysed via profile analysis. Ecstasy user group was the sole independent variable and level of difficulty (three levels: semantic fluency → "S" letter fluency → "C" letter fluency) was the dependent variable. The interaction between user group and difficulty was non-significant, $F(2,95) = 0.90$, $p>.05$ for Pillai's trace.

APPENDIX NOT COPIED

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Syllogistic Reasoning Performance in MDMA (Ecstasy) Users

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Previous research has demonstrated working memory and executive deficits in recreational users of MDMA (3,4-methylenedioxymethamphetamine; Ecstasy). In turn, both of these constructs have been implicated in syllogistic reasoning performance. Twenty-two MDMA users (mean age = 21.36) and 26 MDMA nonuser controls (mean age = 21.31) were tested on syllogisms of varying difficulty and on measures of working memory and executive functioning. MDMA users were significantly impaired in aspects of syllogistic reasoning, and the effect remained significant after the authors controlled for the use of other drugs. However, the MDMA-related variance was reduced to below statistical significance following control for group differences in working memory span. The results are consistent with the possibility that MDMA-related deficits in aspects of executive functioning result in impaired reasoning performance among MDMA users.

Syllogistic reasoning performance in populations of those not using drugs has been shown to rely on working memory and executive resources (Fisk & Sharp, 2002; Gilinsky & Judd, 1994). The purpose of the present study was to establish whether MDMA-related deficits in these aspects of cognitive functioning (Curran & Travill, 1997; Morgan, McFie, Fleetwood, & Robinson, 2002) might give rise to syllogistic reasoning deficits. Because syllogistic reasoning is generally regarded as an indicator of the capacity for rational thought, MDMA-related deficits on this measure raise the possibility that extensive use of MDMA might be associated with impaired rational thinking.

A key construct in cognitive psychology is Baddeley's (1986) model of working memory. The model consists of phonological and visuospatial components and an executive system that coordinates these and is responsible for managing goal-directed behavior and reconciling processing conflicts. The working memory system is believed to underpin a wide range of key cognitive processes, for example, learning to read (Hitch, Towse, & Hutton, 2001), the development of arithmetic competence (Hitch et al., 2001; Trbovich & LeFevre, 2003), knowledge and skill acquisition (Head, Raz, Gunning-Dixon, Williamson, & Acker, 2002), and thinking and reasoning (Stanovich & West, 2000). Previous and current MDMA users have been found to exhibit impairments in working memory functioning. For example, Wareing, Fisk, Murphy, and Montgomery (2004) found that MDMA users were impaired on the computation span measure. Computation span is an established indicator of working memory functioning loading on both the phonological and executive components (Salthouse & Babcock, 1991). Wareing, Fisk, et al. (2004) observed that MDMA users were impaired specifically on the executive component of the task. MDMA-related deficits have also been found in other aspects of executive functioning, for example, the subtracting serial sevens task (Curran & Travill, 1997) and the Tower of London task (Fox et al., 2002).

An important area of cognitive functioning that has not been directly addressed with regard to MDMA users is reasoning. Of the broad range of intellectual abilities that has been investigated, reasoning is perhaps the most cognitively demanding. There is cause to believe that among the many illicit drugs commonly in use, MDMA in particular has the potential to disrupt reasoning processes. The drug is believed to have long-term adverse effects on the serotonin system (Morgan, 2000). In turn, the serotonin system is believed to underpin the operation of working memory processes through its modulation of the dopaminergic systems that support prefrontal executive processes (Luciana, Collins, & Depue, 1998; Robbins, 2000). Indeed, in his review of the literature, Morgan (2000) noted that "it has been proposed that it [serotonin] may play an orchestrating role in cognition" (p. 234). However, the possibility that MDMA users might be impaired in reasoning, and more specifically in syllogistic reasoning, has not yet been investigated.

Syllogistic reasoning requires a participant to draw valid inferences from a set of premises. For example,

Given that:	Some A are B, and No B are C
It follows that:	Some A are not C.

Johnson-Laird (1983) maintained that reasoning involves constructing mental models of the premises and testing conclusions against these models. Constructing a single model may solve some problems, but other problems may

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require up to three models.[1] The more complex the problem, the greater number of models required and the greater the load on working memory and executive resources. Syllogistic reasoning is also believed to utilize resources outside of working memory, for example, relations between linguistic concepts such as "all," "some," and the logical operator "not," as well as spatial representations of class inclusion relationships (see, e.g., Ford, 1995).

Among the different measures of reasoning competence, syllogistic reasoning is perhaps one of the best known. It was central in the development of Johnson-Laird's mental models theory (Evans, Handley, Harper, & Johnson-Laird, 1999; Johnson-Laird, 1983). Within a developmental context, it has been used as a key indicator of reasoning competence in early childhood (Lourenço & Machado, 1996) and over the adult life span (Fisk & Sharp, 2002; Gilinsky & Judd, 1994). Syllogisms have also featured prominently in the debate on human rationality (e.g., Stanovich & West, 2000). Given that MDMA use has been associated with impaired working memory and executive functioning and that these cognitive constructs are believed to underpin syllogistic reasoning performance (e.g., see Fisk & Sharp, 2002; Gilhooly, Logie & Wynn, 1999), it seems reasonable to expect MDMA users might be impaired on this measure of reasoning ability.

In evaluating the potential effects of MDMA, controls for the effects of other drugs, especially cannabis, are necessary. Cannabis has been found to adversely affect several aspects of executive functioning, including the organization and integration of information (Hall & Solowij, 1998), verbal fluency performance (Croft, Mackay, Mills, & Gruzelier, 2001; Klugman, Hardy, Baldeweg, & Gruzelier, 1999), and among heavy users, perseveration errors on the Wisconsin Card Sorting Test (Pope & Yurgelun-Todd, 1996). Although there is no direct evidence that cannabis affects syllogistic reasoning, because the drug appears to impair certain executive processes, it is possible that reasoning might be affected as a consequence. In the present study, we therefore attempt to control for the effects of cannabis and other drugs.

In summary, we expected MDMA users to perform worse compared with controls in a syllogistic reasoning task and the MDMA-related deficit to be most pronounced on the two- and three-model syllogisms because these load most heavily on working memory and executive resources. Analysis of covariance (ANCOVA) was used to investigate the extent to which MDMA-related differences in syllogistic reasoning are related to group differences in working memory capacity and executive functioning. Working memory and executive functioning were assessed through a computation span task and through random letter generation.

Method

Participants

Twenty-two MDMA users (11 men, 11 women) and 26 MDMA nonuser controls (10 men, 16 women) between the ages of 18 and 25 were recruited. Participants were initially recruited through direct approach to Liverpool John Moores University undergraduate students, including psychology majors and psychology–biology joint students. Subsequently, word-of-mouth referral was used, with most participants being recruited by this means. Participants were requested to refrain from MDMA use for at least 7 days and ideally 10 days prior to testing (the mean period of abstinence was actually 4.61 weeks). Participants were also requested not to use any other illicit drugs for at least 24 hr and ideally for 7 days prior to testing.[2] Participants were paid U.K.£15 (U.S.$27) in store vouchers for their participation.

Materials

Fluid intelligence was measured through Raven's progressive matrices (Raven, Raven, & Court, 1998). Premorbid intelligence was assessed through the National Adult Reading Test (NART, Nelson, 1982). A background questionnaire used by Montgomery, Fisk, and Newcombe (2004) assessed the use of MDMA and other drugs as well as age, years of education, general health, and other lifestyle variables. In relation to other drugs, among other things, participants were asked to indicate their frequency of use and the last time that they had used each drug. Cigarettes smoked per day and units of alcohol consumed each week were also assessed. Participants were also questioned concerning their history of drug use. Using a procedure developed by Montgomery et al. (2004), we used these data to estimate total lifetime use for each drug.

Syllogistic reasoning. The syllogisms were presented in abstract form as in the example set out above. Participants attempted to generate solutions for 4 one-model syllogisms, 4 three-model syllogisms, and 4 syllogisms for which there was no valid conclusion (NVC). The syllogisms were the same as those used by Fisk and Sharp (2002). Scores were based on the number of correct solutions, or in the case of the NVC syllogisms, a response was deemed correct when the participant indicated that no valid conclusions were possible. According to Johnson-Laird (1983), NVC syllogisms require either two or three mental models in order to derive the correct solution. In the present study, 2 of the NVC syllogisms were two-model and 2 were three-model. Therefore, in terms of the number of models required, three-model and NVC syllogisms were the hardest, and one-model syllogisms were the easiest. The syllogisms used in the study were presented in random order. The test was administered following the procedure outlined by Fisk and Sharp (2002).

Working memory and executive functioning. The computation span measure and random letter generation were used to assess these aspects of cognitive functioning. Computation span has been used as an indicator of working memory functioning in the cognitive aging literature (Fisk & Warr, 1996; Salthouse & Babcock, 1991), and it is similar to the operation span measure used by Miyake et al. (2000) in their investigation of executive processes. Participants were required to solve a number of arithmetic problems (e.g., 4 + 7 = ?) by circling one of three multiple-choice answers as each problem was presented. They were also required to simultaneously remember the second digit of each presented problem. At the end of each set of problems the second digits had to be recalled in the order in which they were presented. The number of arithmetic problems that the participant had to solve while remembering each second digit gradually increased as the

[1] Although a full description of the distinction between one-, two-, and three-model syllogisms is beyond the scope of the present article, such a description can be found in Fisk and Sharp (2002, pp. 1274–1275) and Johnson-Laird (1983, pp. 98–100).

[2] For those persons using other illicit drugs, the mean period of abstinence in weeks was 62.24 for amphetamine, 4.55 for cannabis, 6.47 for cocaine, 62.98 for magic mushrooms, and 17.71 for poppers.

test proceeded. For each of the first three trials only a single problem was presented. For the next three trials, two problems were presented. Subsequently, the number of problems presented per trial increased by one every third trial. In order to proceed, the participant was required to be correct in at least two of the three trials at the current level. Computation span was defined as the maximum number of end digits recalled in serial order, with the added requirement that the corresponding arithmetic problems had been solved correctly. Because computation span is reliant on both phonological and executive processing resources, a simple digit span task (Fisk & Warr, 1996) was also administered so that it could be ascertained that any observed MDMA-related deficits were not simply a result of lower level nonexecutive impairments (i.e., the phonological loop).

Random generation is an established measure of executive functioning. For example it features prominently in both Baddeley's (1996) and Miyake et al.'s (2000) accounts of executive processes, and by use of the dual task methodology, it has been studied directly in relation to syllogistic reasoning performance (Gilhooly et al., 1999). We used the procedure developed by Baddeley (1966). However, a computer display and concurrent auditory signal were used to pace responses. Participants were asked to speak aloud a letter every time the signal was presented. They were told to avoid repeating the same sequence of letters, to avoid producing alphabetical sequences, and to try to speak each letter with the same overall frequency. Individuals attempted to produce three sets of 100 letters: one set at a rate of 1 letter every 4 s, a second set at 1 letter every 2 s, and a third set at 1 letter every 1 s. The order in which the sets were generated was randomized. The experimenter recorded the responses on an answer sheet. The test yields four scores: first, the number of alphabetically ordered pairs; second, a repeat sequences score, corresponding to the number of times that the same letter pair is repeated; third, a redundancy score, which measures the extent to which all 26 letters of the alphabet are produced equally often (0% being truly random); and fourth, the number of letters produced. In the first three cases, higher scores indicate poor performance; in the fourth the opposite is the case. The scores for each separate variable at each of the three generation rates were standardized. A single random generation score for each participant was produced by averaging the standardized scores and reversing the sign for the number of letters generated so that for the overall measure a positive score was indicative of poor performance.

Sleep quality. Research has shown that MDMA users exhibit altered sleep patterns, with less total sleep time and qualitative changes in the characteristics of Stage II sleep (Allen, McCann, & Ricaurte, 1993). It has been suggested that apparent MDMA-related cognitive deficits might simply be due to the fact that MDMA users get less sleep (Cole, Sumnall, & Grob, 2002). To assess this possibility, we used a screening questionnaire and the Epworth Sleepiness Scale (Johns, 1991) to investigate any group differences in sleep quality and wakefulness. The Epworth Sleepiness Scale measures subjective daytime sleepiness. It contains eight items, which a participant has to score on a scale of 0 (*would never doze off in this situation*) to 3 (*high chance of dozing off in this situation*). Summing the responses to all eight items produced an overall total score. The screening questionnaire contained a number of questions on sleep quality, as detailed in Table 1.

Procedure

Informed consent was obtained. The tests were administered under controlled laboratory conditions. A computer using MS-DOS was used for the digit span, computation span, and random letter generation tests. Tasks were administered in the following order: health–education questionnaire, MDMA background questionnaire and sleep questionnaire, random letter generation, digit span test, computation span test, syllogistic reasoning test, NART, and Raven's progressive matrices. The order of the random gen-

Table 1
Performance of MDMA Users (n = 22) and Nonusers (n = 26) on Background Variables

Variable	MDMA user				MDMA nonuser			
	M	*SD*	*Mdn.*	%	*M*	*SD*	*Mdn.*	%
Age (years)	21.36	1.67			21.31	1.69		
Education (years)	15.05	2.84			15.96	1.89		
Raven's total score[a]	47.43	6.53			48.28	5.52		
NART	27.95	7.60			30.19	6.07		
Digit span	6.52	1.21			6.88	1.21		
Computation span	3.00	1.58			4.88	1.63***		
Random generation	0.05	0.38			−0.09	0.28		
Self-report health			4				4	
Epworth Sleepiness Scale (total score)[b]	5.33	2.67			6.50	2.53		
Screening questionnaire								
Sleep (hours per night)	8.09	1.49			8.10	0.85		
Sleep refreshed[c]			2				2	
Sleep quality[d]			2				2	
Sleep morning/evening type (neutral/morning type)[e]				23				46*
Sometimes miss out a night's sleep				86				73

Note. *t* tests were used to analyze age, education, Raven's total score, digit span, computation span, and random generation. Mann-Whitney *U* tests were used to analyze self-report health, sleep refreshed, sleep quality, and sleep morning/evening type. Chi-square tests were used to analyze sometimes miss out a night's sleep. NART = National Adult Reading Test (Nelson, 1982).
[a] Raven et al. (1998). [b] Johns (1991). [c] Sleep refreshed represents "How refreshed do you feel in the morning?" Response options are 1 = *very alert*, 2 = *fairly alert*, 3 = *fairly tired*, and 4 = *very tired*. [d] Sleep quality represents "How well do you normally sleep at nights?" Response options are 1 = *very well*, 2 = *satisfactory*, 3 = *not very well*, and 4 = *very badly*. [e] Sleep morning/evening type represents "We hear about people who feel better in the morning or who feel better in the evening. Which of these two types do you think you are?" Response options are 1 = *definitely a morning type*, 2 = *more morning than evening*, 3 = *neither one nor the other*, 4 = *more evening than morning*, and 5 = *definitely an evening type*.
* $p < .05$. *** $p < .001$.

eration, computation span, and syllogistic reasoning tests was rotated to eliminate order effects. Overall, testing took between 2 hr and 3 hr, at the end of which the participant was debriefed and provided with drug education leaflets. The study was approved by the Ethics Committee of Liverpool John Moores University and was administered in accordance with the ethical guidelines of the British Psychological Society.

Design

A mixed design was used with MDMA user group (with two levels, user and nonuser) as the between-participants variable and level of difficulty of the syllogism (again with two levels, low and high) as the within-participants variable. Level of difficulty was based on the number of models required to derive a solution. Thus, one-model syllogisms were low in difficulty. Because the NVC and three-model syllogisms require a similar number of models to produce a solution, responses for these types were combined to form the high difficulty level. The dependent variable was the number of correct solutions for the low and high difficulty syllogisms (maximum score was eight in both cases). We also sought to determine whether the main effect of user group was qualified by a User × Difficulty interaction. In common with established practice, ANCOVA was used to statistically control for group differences in potentially confounding or moderating variables (e.g., see Fisk & Sharp, 2002; Morgan, 1999; Verkes et al., 2001; Wareing, Murphy, & Fisk, 2004). Thus, where appropriate, indices of other drug use, sleep quality, and working memory measures were included as covariates.

Results

Background Variables

Average age, years of education, fluid intelligence, premorbid intelligence, and other background variables for the two groups are set out in Table 1. Statistical tests (analysis of variance, *t* test, Mann–Whitney U, and chi-square) revealed that there were some significant group differences among the background variables. MDMA users performed worse than did nonusers on the computation span test, $F(1, 45) = 15.92$, $p < .001$. With regard to wakefulness, most users considered themselves to be evening types, whereas nonusers made neutral responses or stated that they were morning types (Mann–Whitney $U = 181.50$, $p < .05$).

Inspection of Table 2 reveals that the use of other drugs was commonplace among MDMA users, whereas among MDMA nonusers, drug use was mainly limited to alcohol, cannabis, and tobacco. There were large differences between MDMA users and MDMA nonusers in the total number of cannabis joints smoked, the mean period of abstinence from cannabis, and the frequency of cannabis use. For total number of joints smoked and period of abstinence these differences were nonsignificant, $t(20) = 0.92$, and $t(11) = -1.53$, respectively, $p > .05$ in both cases. In both cases standard deviations were large and Levene's test was significant in relation to period of abstinence. Clearly, these nonsignificant results need to be treated with caution given the relatively small number of cannabis users among the MDMA nonuser group. The group difference was significant for frequency of cannabis use, $t(14.98) = 2.94$, $p < .05$.

Syllogistic Reasoning: Main Analysis

Table 3 reveals that MDMA users performed worse than did nonusers on both the one-model and three-model/NVC syllogisms, although in the latter case the group difference was less pronounced. Mixed analysis of variance yielded a significant Models × User interaction, $F(1, 46) = 5.56$, $p < .05$, with an effect size of 10.8% (i.e., partial $\eta^2 = .108$). Subsequent analyses revealed that MDMA users performed significantly worse on the one-model syllogisms, $F(1, 46) = 11.24$, $p < .01$, but there was little difference between the groups on the three-model/NVC problems ($F < 1$).

Covariate Analyses

Working memory and executive functioning. It is possible that the observed MDMA-related deficit in syllogistic reasoning might be mediated by working memory components. MDMA users performed significantly worse than did nonusers on the computation span measure. ANCOVA with computation span as a covariate generated a significant result with respect to computation span, $F(1, 44) = 7.23$, $p < .05$. Consistent with this, the interaction effect between MDMA user group and models on syllogistic reasoning was reduced to below statistical significance after we controlled for differences in computation span,[3] $F(1, 44) = 2.41$, $p > .05$, and the effect size was reduced to 5.2%, approximately half its original magnitude. The main effect of user group was also reduced to below statistical significance[4] ($F < 1$). By way of contrast, ANCOVA with random letter generation as a covariate generated a nonsignificant result with respect to random generation ($F < 1$). The interaction effect between group and models on syllogistic reasoning remained significant after we controlled for random generation, $F(1, 45) = 4.59$, $p < .05$, and at 9.3% the effect size was barely reduced at all. In both analyses the Group × Covariate interactions were nonsignificant ($F < 1$), indicating that homogeneity of regression was obtained.

Sleep quality. As noted above, with regard to whether individuals viewed themselves as morning or evening types, relative to nonusers MDMA users were more likely to see themselves as evening types. To establish whether this outcome had any effect on group differences in reasoning performance, we entered each participant's ordinal response for the sleep type variable (ranging from 1 = *definitely a morning type* to 5 = *definitely an evening type*) as a covariate, and the main analysis was repeated. This produced a nonsignificant result with respect to the covariate ($F < 1$), and the Groups × Models interaction effect on syllogistic reasoning remained significant, $F(1, 45) = 4.52$, $p < .05$.

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[3] Control for digit span produced no substantial degree of attenuation. The interaction between group and models remained significant, $F(1, 44) = 6.03$, $p < .05$, with the effect size 12.0%.

[4] Prior to the inclusion of computation span as a covariate, the main effect of user group yielded $F(1, 46) = 6.41$, $p < .05$.

Table 2
History of Drug Use

History	MDMA user *M*	MDMA user *SD*	MDMA user *n*	MDMA nonuser *M*	MDMA nonuser *SD*	MDMA nonuser *n*	*p*
MDMA							
Lifetime use							
Tablets consumed	303.30	374.04	22				
Length of use (weeks)	164.82	99.58	22				
Current use							
Weeks since last use	4.61	6.82	22				
Frequency of use (times/week)	0.47	0.40	22				
Other drugs							
Lifetime use							
Amphetamine (g)	102.20	220.14	5	—	—	—	—
Cannabis (joints)	4,700.44	7,040.93	16	1,986.00	1,883.40	6	*ns*
Cocaine (g)	56.84	79.26	11	—	—	—	—
Current use							
Cigarettes (number/day)	9.62	4.19	13	11.50	4.87	5	*ns*
Alcohol (units/week)	21.82	11.14	22	11.83	8.19	26	***
Cannabis (times/week)	2.58	2.54	15	0.63	0.31	6	*
Cocaine (times/week)	0.76	0.54	11	—	—	—	—
Weeks since last use							
Amphetamine	62.24	92.89	10	—	—	—	—
Cannabis	1.68	4.64	18	9.23	15.99	11	*ns*
Cocaine (times/week)	6.75	15.53	16	2.00		1	
Mushrooms	62.98	66.75	7	—	—	—	—
Poppers	15.91	18.17	19	52.00		1	

History	% of MDMA users	% of MDMA nonusers
Other drugs used during 3 months prior to testing		
Alcohol	100	100
Amphetamine	14	0
Cannabis	86	46
Cocaine	50	4
Mushrooms	9	0
Poppers	46	4
Tobacco	55	23

Note. Means and standard deviations relate only to those individuals taking the drug in question. Dashes indicate either cases in which individuals were only occasional users and were unable to provide an accurate estimate of their lifetime use or cases in which there were no users of the illicit drug in question.
* $p < .05$. *** $p < .001$.

Homogeneity of regression was obtained ($F < 1$) for the Group × Covariate interaction. Thus, it appears that group differences in aspects of sleep quality were not responsible for the MDMA-related impairments in syllogistic reasoning performance.[5]

Other drugs. It was necessary to establish whether the prevalence of polydrug use, especially among the MDMA user group (see Table 2), contributed to the MDMA-related differences in reasoning performance. ANCOVA with frequency of cannabis use as a covariate[6] reduced the interaction between group and models to below statistical significance, $F(1, 45) = 2.15$, $p > .05$. The main effect of user group was also reduced to below statistical significance, $F(1, 45) = 2.57$, $p > .05$. Homogeneity of regression was obtained ($F < 1$) for the Group × Covariate interaction. However, subsequent ANCOVA with the number of correct one-model syllogisms as the sole dependent variable, user group as the between-participants independent variable, and frequency of cannabis use as the covariate left the main effect of group statistically significant, $F(1, 45) = 4.64$, $p < .05$, and homogeneity of regression was obtained, $F(1, 44) = 1.75$, $p > .05$, for the Group × Covariate interaction.

The possibility that prolonged cannabis use might produce a cumulative decrement in syllogistic reasoning performance was also evaluated. An estimate of lifetime can-

[5] It is possible that MDMA-related differences in the morning or evening type ratings may have played some role in producing the computation span group differences, thereby indirectly accounting for some of the syllogistic reasoning deficits. However, ANCOVA with computation span as the dependent variable, MDMA user group as the independent variable, and the sleep measure as a covariate left the group difference in computation span and the corresponding effect size intact, $F(1, 44) = 17.05$, $p < .001$. Thus, it appears that the sleep measure plays no role, either direct or indirect, in accounting for the syllogistic reasoning deficit.

[6] A value of zero was entered for those persons who had never consumed cannabis.

Table 3
Average Number of Correct Responses for One-Model Syllogisms and Three-Model/NVC Syllogisms for MDMA Users (n = 22) and Nonusers (n = 26)

	MDMA Users		MDMA nonusers	
Syllogisms	*M*	*SD*	*M*	*SD*
One model	3.45	2.13	5.27	1.61**
Three model/NVC	1.45	1.99	1.81	1.58
Overall % correct	30.62		44.25	

Note. For the 4 one-model problems (for which there were two valid conclusions per syllogism) and the 8 three-model/NVC syllogisms (for which there was one valid conclusion per syllogism), the maximum possible score was eight. NVC = no valid conclusion.
** $p < .01$.

nabis use was included as a covariate,[7] and the main analysis was repeated. The interaction between groups and models was reduced to just below significance, $F(1, 45) = 3.71$, $p = .061$. However, the main effect of user group remained significant, $F(1, 45) = 3.77$, $p < .05$, one-tailed. Homogeneity of regression was obtained ($F < 1$) for the Group × Covariate interaction. Again, subsequent ANCOVA with the number of correct one-model syllogisms as the sole dependent variable, user group as the between-participants independent variable, and lifetime cannabis use as the covariate left the main effect of group statistically significant, $F(1, 45) = 7.15$, $p < .05$, and homogeneity of regression was obtained ($F < 1$) for the Group × Covariate interaction.

In view of the fact that some of the participants, both MDMA users and nonusers, had smoked cannabis during the week prior to testing, for all cannabis users, time since last use of cannabis was correlated with performance on the syllogisms. This yielded nonsignificant correlation coefficients of .05 and .07 for the one-model and three-model/NVC syllogisms, respectively ($p > .05$, $n = 29$, in both cases).

Thus, on balance it appears that the MDMA-related deficits in syllogistic reasoning remain significant following statistical controls for various measures of cannabis use. Nonetheless, the possibility that cannabis exerts an influence cannot be entirely excluded. The correlation coefficient between lifetime use of cannabis and performance on the one-model syllogisms was −0.36 ($p < .05$). This compares with a correlation of −0.40 ($p < .01$) between lifetime use of MDMA and performance on the one-model syllogisms (for the three-model/NVC syllogisms neither of the equivalent correlations were statistically significant).

Whereas 55% of MDMA users smoked cigarettes, only 23% of nonusers were smokers. Therefore it is possible that users might have been more susceptible to nicotine deprivation during testing. Furthermore, whereas both groups consumed alcohol regularly, MDMA users consumed almost twice as many units per week compared with nonusers. To evaluate the potentially confounding effects of these variables, the number of cigarettes consumed per day and the units of alcohol per week were entered as covariates. The interaction between groups and models was reduced to just below significance, $F(1, 44) = 3.54$, $p = .067$. However, the main effect of user group remained significant, $F(1, 44) = 7.45$, $p < .01$, and homogeneity of regression was obtained ($F < 1$) for the two Group × Covariate interactions.

With regard to the use of other illicit drugs, Table 2 reveals that MDMA users had previously consumed amphetamine and "mushrooms." In addition, they were currently also consuming "poppers" and cocaine. It would have been desirable to statistically control for the effects of these other drugs; however, there were insufficient users of them among the MDMA nonuser group to perform ANCOVA because it was not possible to properly test for homogeneity of regression. To try to distinguish the effects of the individual drugs, we conducted multiple regression analysis. Two separate regressions were run, the first with the number of correct responses on the one-model syllogisms as the dependent variable and the second with the number of correct responses on the three-model/NVC syllogisms as the dependent variable. For both regressions, independent variables were estimates of lifetime consumption of amphetamine, cannabis, cocaine, and MDMA.[8] For the one-model syllogisms the regression model accounted for a significant proportion of the variance, $R^2 = .243$, $F(4, 43) = 3.45$, $p < .05$. However, the regression model failed to reach significance for the three-model/NVC syllogisms ($R^2 = .063$, $F < 1$). Examination of Table 4 reveals that for the one-model syllogisms, total lifetime use of MDMA was the only significant predictor, uniquely accounting for around 7% of the variance. With the exception of total use of cannabis, the standardized beta coefficients were negative for all of the predictors, indicating that performance on the one-model syllogisms declines as lifetime consumption of each of the predictors increases.

In situations in which ANCOVA cannot be used and as an alternative to regression analysis, a further method to control for the potentially confounding effects of these other drugs is to exclude all users of each drug in turn and reanalyze the data. Although this technique has its limitations in that it ignores the likelihood that there are correlations between the use of these other drugs, nonetheless it does provide at least some degree of control for their use. Therefore the main analysis, with user group as the between-participants variable and models as the within-participant variable, was repeated, excluding all those who had used a particular substance during the last 3 months. This was done with respect to amphetamine, cocaine, mushrooms, poppers, and tobacco.

In all but one case this reduced the Group × Models interaction to below statistical significance. Specifically, F values for the models by user group interaction were as follows: $F(1, 43) = 3.46$, $p = .07$, excluding amphetamine users; $F < 1$, excluding cocaine users; $F(1, 44) = 6.69$, $p <$

[7] A value of zero was entered for those persons who had never consumed cannabis.

[8] It is difficult to meaningfully quantify lifetime consumption of poppers; so this substance was not included in the regression analyses.

Table 4
Results From Regression Analysis With Number of Correct Syllogism Responses as Dependent Variables and Measures of Lifetime Use of Other Drugs as Independent Variables

Independent variable	Standardized beta weight	$t(47)$	Squared semipartial correlation coefficient
Correct one-model syllogisms			
Total lifetime use			
Amphetamine	−.260	−0.65	.007
Cannabis	.197	0.66	.008
Cocaine	−.175	−0.55	.005
MDMA	−.408	−2.03*	.072
Correct three-model/NVC syllogisms			
Total lifetime use			
Amphetamine	−.639	−1.43	.045
Cannabis	.179	0.54	.006
Cocaine	.445	1.25	.034
MDMA	−.246	−1.10	.026

Note. NVC = no valid conclusion.
* $p < .05$.

.05, excluding mushroom users; $F(1, 35) = 1.75$, $p > .05$, excluding poppers users; and $F < 1$, excluding tobacco users. However, in each of the analyses the main effect of MDMA user group remained statistically significant, with MDMA users obtaining fewer correct responses compared with nonusers. F values were as follows: $F(1, 43) = 4.39$, $p < .05$, excluding amphetamine users; $F(1, 34) = 12.31$, $p < .01$, excluding cocaine users; $F(1, 44) = 5.31$, $p < .05$, excluding mushroom users; $F(1, 35) = 10.29$, $p < .01$, excluding poppers users; and $F(1, 28) = 4.92$, $p < .05$, excluding tobacco users. For MDMA users and MDMA nonusers sample sizes were 19 and 26, respectively, excluding amphetamine users; 11 and 25 excluding cocaine users; 20 and 26 excluding mushroom users; 12 and 25 excluding poppers users; and 10 and 20 excluding tobacco users.

Thus, by way of summary, in relation to the possible confounding effects of these other drugs, the main effect of MDMA user group remained significant when the analyses were rerun excluding users of each of the other drugs in question. Furthermore, in the regression analyses, among the total use variables that were included as independent variables, only MDMA proved to be significant as a predictor of performance on the one-model syllogisms.

Discussion

As expected, the present results demonstrate an MDMA-related deficit in syllogistic reasoning. Furthermore, because the average reported period of abstinence was 4.61 weeks, the results observed are unlikely to be a short-term consequence of using the drug. Contrary to expectations, there was no group difference between the NVC and three-model syllogisms. MDMA users did, however, perform significantly worse than did nonusers on the one-model syllogisms. The absence of group differences on the NVC and three-model syllogisms is difficult to reconcile with Johnson-Laird's (1983) account of mental models theory. It does however provide further support for Evans et al. (1999), who maintained that individuals generally construct only a single mental model of the premises and fail to search for alternatives. From either perspective, for both one-model and more complex syllogisms, the premises need to be retained so that alternative possible conclusions can be accepted or rejected in the context of the initial mental model and the contents of working memory can be updated as necessary. The MDMA-related deficit evident in the one-model context appears to be consistent with some degree of impairment in this process. In the three-model/NVC situation, in which according to Evans et al. (1999) only a single model is constructed, this model does not itself constitute an exhaustive representation of the implications of the premises, and for both users and nonusers, most inferences derived from it are therefore likely to be erroneous. Therefore, consistent with the findings reported here, group differences would not be expected on the three-model/NVC problems. Apart from the present findings, other evidence has been obtained consistent with Evans et al.'s (1999) conceptualization of reasoning processes. For example, Newstead, Thompson, and Handley (2002) have demonstrated that many individuals do not proceed beyond the initial model of the premises, relying solely on it when constructing their inference (Newstead, Handley, & Buck, 1999; Newstead et al., 2002). Similar findings have been reported also by Handley, Dennis, Evans, and Capon (2000).

It is possible that any group differences in syllogistic reasoning were due to reduced working memory and executive resources rather than a specific deficit in underlying reasoning competence. Computation span was significantly lower in MDMA users, and when included as a covariate, this measure accounted for half of the MDMA-related variance in syllogistic reasoning. This suggests that the MDMA-related deficit in syllogistic reasoning might be attributable to executive impairment rather than a consequence of some fundamental deficit in underlying reasoning competence. However, this is not to minimize the implications of the present findings. Even if it is the case that underlying reasoning competence remains intact in MDMA users, given that they lack the executive resources to make full use of this capacity, they are still likely to exhibit impairments in the capacity for rational thought.

It is worthy of note that although there were MDMA-related differences in computation span, no such trend was evident in the random letter generation scores, and inclusion of the latter as a covariate did not attenuate the group differences in reasoning performance. In fact, previous research has shown that performance on the two working memory executive measures is not invariably correlated (Lehto, 1996; Miyake et al., 2000), and it has been argued that each measure loads on a qualitatively different aspect of executive functioning (Fisk & Sharp, 2004; Miyake et al., 2000). Thus, the present results suggest that MDMA-related deficits are most apparent in those aspects of executive functioning captured by the computation span measure and that these deficits produce secondary effects on reasoning performance.

A number of background variables were considered in the present study, including various measures of sleep and wakefulness. These appear to play no part in the group differences in syllogistic reasoning that were obtained. However, the measures that were used were largely self-reported, and it remains possible that more physiologically based measures might have produced a different outcome. Therefore the possibility that sleep impairment mediates some or all of the MDMA-related effects cannot be totally excluded.

An important aspect that was addressed in the present study was the potentially confounding effect of other drugs. The use of other drugs was much more common among the MDMA user group, and with a few exceptions, the use of other drugs among the MDMA nonuser group was limited to alcohol, tobacco, and cannabis. ANCOVA with various measures of alcohol, tobacco, and cannabis use as covariates were conducted, and in all cases, at least in relation to the one-model syllogisms, MDMA users remained significantly impaired. Furthermore, regression analysis revealed that measures of total use of cocaine and amphetamine were not significant predictors of performance on the one-model syllogisms; indeed, total use of MDMA was the only significant predictor. Although these results highlight the importance of MDMA in accounting for the results obtained, the possibility that other drugs might exert some impact cannot be totally excluded. For example, total cannabis use among the whole sample was significantly and negatively correlated with performance on the one-model syllogisms.

It remains unclear whether this potential cannabis-related effect is mediated through executive or nonexecutive processes. We find it interesting that in the population of those not using drugs, Fisk and Sharp (2002) found that syllogistic reasoning performance was positively correlated with word fluency scores. In turn, it has been suggested that word fluency taps an important aspect of executive functioning: access to semantic memory (Fisk & Sharp, 2004). Although there is little evidence to link MDMA with impaired word fluency performance, cannabis use has been found to produce such an effect (e.g., Croft et al., 2001; Klugman et al., 1999). Thus, it is possible that cannabis impairs this aspect of executive functioning, thereby producing a detrimental effect on syllogistic reasoning. However, it must be acknowledged that this possibility is speculative and requires further investigation.

A number of limitations were evident in the present study; for example, we were reliant on individuals being willing and able to provide an accurate account of their previous drug use. Furthermore, it was not possible to quantify the amounts of each psychoactive drug present within the tablets or joints consumed; in addition, because of limited resources, we were unable to use urine, saliva, or hair samples to confirm recent patterns of drug use. However, the drug use questionnaire was designed to check the internal consistency of the information provided. It is equally worthy of note that most of the published studies that have probed cognitive deficits among MDMA users have not resorted to urine, hair, or saliva testing (e.g., Fox et al., 2002; Morgan, 1999; Parrott & Lasky, 1998; Rodgers, 2000).

Aside from the issue of drug testing, other limitations of the present study need to be acknowledged. For example, lifestyle differences and premorbid factors cannot be excluded as possible sources of group differences in studies of this nature. MDMA users may neglect their diet and physical health. Studies have reported that they suffer from a range of subclinical conditions, including depression, anxiety, paranoia, and phobias (Morgan et al., 2002). Depression and anxiety have been shown to impair cognitive functioning (Eysenck & Calvo, 1992; Murphy, Michael, Robbins, & Sahakian, 2003), and so it is possible that these aspects of psychological affect may have mediated some of the effects observed in the present study. This is clearly a possibility that needs to be addressed in future research. Furthermore, it has also been suggested that MDMA users are subject to a heightened state of impulsivity (Morgan, 1998). In the present study, this may have resulted in responses being produced before their logical necessity had been thoroughly probed. It is also important not to over generalize from the present findings. For example, given that word-of-mouth referral was used as the primary means of recruiting participants, our MDMA user group may not be entirely representative of all MDMA users, especially those who consume the drug in settings that are unlike those frequented by those individuals constituting the present sample.

In conclusion, the results of the present study show that syllogistic reasoning is impaired among MDMA users. This impairment may be a consequence of an MDMA-related decline in aspects of working memory and executive functioning. Furthermore, although the impairment appears to be associated with MDMA use, it remains possible that other drugs, including cannabis, may also exert an influence either independently or in conjunction with MDMA.

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Appendix 7

Peer-reviewed publication for Associative Learning

Some text bound close to the spine.

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ORIGINAL INVESTIGATION

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The nature of ecstasy-group related deficits in associative learning

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Abstract *Rationale/objectives:* Research has revealed associative learning deficits among users of ecstasy; the present study explored the component processes underlying these deficits. *Methods:* Thirty-five ecstasy users and 62 non-ecstasy users completed a computer-based, verbal paired-associates learning task. Participants attempted to learn eight sequentially presented word pairs. After all eight had been presented, the first member of each pair was displayed and participants attempted to recall the second. Eight trials were administered. Correct responses on each trial, forgetting at various levels of learning, perseveration errors and the rate at which the associations were learned (trials to completion) were all recorded. *Results:* MANOVA revealed that ecstasy users performed worse overall and subsequent ANOVAs showed that users performed significantly worse on virtually all measures. Regression analysis revealed that over half of the ecstasy-group related variance in trials to completion was attributable to group differences in initial learning and forgetting. In relation to forgetting, it appears that cannabis use may be an important determinant. In relation to rate of learning (trials to completion) and initial learning, both ecstasy and cannabis may be implicated. *Conclusions:* There appears to be abundant evidence of associative learning deficits among ecstasy users. However, it appears that a range of illicit drugs including cannabis and ecstasy may contribute to these deficits.

Keywords Ecstasy · MDMA · Learning · Paired associate learning · Cannabis

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Introduction

Developing an understanding of relationships between concepts is a fundamental aspect of human learning. One key aspect of this is associative learning, which involves forming appropriate links between previously unrelated phenomena. The working memory system in general, and the executive in particular are essential components in learning new skills before they become automatic, so that learning and the acquisition of knowledge is dependent on working memory (Tanji and Hoshi 2001). The term associative learning describes the process by which an organism develops or reinforces connections between stimulus representations (Rose et al. 2001). Ecstasy users have been shown to exhibit deficits in aspects of working memory functioning (e.g. Fisk et al. 2004; Wareing et al. 2004) and in view of the role of working memory and executive processes in supporting associative learning it is possible that users might also experience impairments in learning processes.

Much of the research in this domain has focussed on animal learning and to date the results have been equivocal. While some studies have found MDMA-related deficits in aspects of learning (Broening et al. 2001; Frederick et al. 1995; Taylor and Jentsch 2001; Williams et al. 2003) others have not (Frederick and Paule 1997; Ricaurte et al. 1993; Romano and Harvey 1993; Winsaeur et al. 2002). In a study examining learning in rats, Robinson et al. (1993) found that the extent of 5-HT denervation (72.6%) was not sufficient to produce marked deficits (this may be a sign of neurocompensatory changes). More generally, it is possible that the apparent lack of MDMA-related deficits in some animal studies is because the tasks are too simple, and they do not mirror learning in humans.

Although some studies in humans have investigated associative learning, this is an area that is still under investigated as a number of tasks used relate more to immediate and delayed recall, rather than the learning of associations. Gouzoulis-Mayfrank et al. (2003) used the word-pair learning test of the LGT-3 test battery, which

requires participants to memorise 20 word pairs consisting of a Turkish word and it's German translation. In the retrieval phase, participants had to identify the correct Turkish word corresponding to each German word (out of five possible answers). Heavy ecstasy users performed worse than non-users in the delayed recall of the word pairs, but not the immediate recall component. However, the effect was reduced to below statistical significance after control for general knowledge scores.

Croft et al. (2001) studied the relative contributions of ecstasy and cannabis to spatial and non-spatial Paired Associates Learning (PAL). Participants were required to learn associations between six spatial pairs (spatial) and six colour pairs (non-spatial). The task began with the participant guessing, then learning the prompted association through feedback from the experimenter (yes/no). The task finished when the participant correctly reported 18 consecutive associations, and the number of guesses required to get to this point was the score (maximum allowed was 180). No significant differences were observed between the ecstasy/cannabis group and the cannabis only group. A combined drug-user group performed significantly worse than controls on the non-spatial PAL. ANCOVA revealed that this effect was more due to cannabis than ecstasy. However, the average cannabis abstinence period was only 17 h so it was possible that participants were still intoxicated. Also, Croft et al.'s participants only had a modest lifetime dose of ecstasy.

Fox et al. (2002) also used a spatial PAL task in which participants were required to learn the spatial locations of abstract patterns. In the test trials, participants were first required to learn six pattern-location pairs and then in the next trial eight pairings. No significant group differences were observed in the number of errors, the number of presentations required per trial, or the memory score (total number of patterns successfully located on initial presentation). The group by trial interaction approached significance, and post-hoc tests revealed that the ecstasy group made a greater number of errors on the eight pair trials. Rodgers (2000) found that ecstasy users were unimpaired during the initial learning phase of the verbal and visual paired associates sub-tasks of the Wechsler Memory Scale. However, subsequent deficits in the delayed recall of the verbal and visual paired associates were apparent among ecstasy users but not among cannabis-only users.

In addition to deficits in associative learning, basic verbal learning deficits have also been observed using the Rey Auditory Verbal Learning Test (RAVLT). During trials 1–5, a list of 15 words is read to participants, and they are then required to recall as many words as possible in any order; in trial 6 this is repeated with a new list of words (interference). Trial 7 requires participants to again recall the original list. Finally, participants are given a list of words containing those from the first list with phonemic and semantic distractors, and required to circle words that appeared in the first list. McCardle et al. (2004) found that ecstasy users performed significantly worse than non-users on delayed recall (trial 7), and Reneman et al. (2000) found that ecstasy users recalled significantly fewer words than non-users. Ecstasy-related deficits were also observed on trial 1, the total number of words recalled and trials 6 and 8 in ex-ecstasy users compared to drug-naïve controls (Thomasius et al. 2003).

A problem with research in this area is that the ecstasy-related deficits observed may be, at least in part, attributable to cannabis or the concomitant use of other drugs. Croft et al. (2001) used a battery of neuropsychological tests to compare a group of cannabis only users, a combined ecstasy and cannabis group, and a control group. No significant differences were observed between the ecstasy/cannabis and the cannabis only groups. However, a combined drug-using group (merging the cannabis only and ecstasy/cannabis group) performed worse than controls on working memory (forward and backward digit span), information processing, and learning and recognition memory. The authors concluded that cannabis, not ecstasy, was responsible for the deficits. However, the lifetime ecstasy dose of Croft et al.'s participants was only 41.9 tablets, which is relatively modest compared to other studies (e.g. Morgan et al. 2002 study in which users consumed over 500 tablets). While Croft et al.'s results appear to implicate cannabis use, Gouzoulis-Mayfrank et al. (2000) found an ecstasy/cannabis group (with an average lifetime dose of 93.4 tablets) to be impaired relative to a cannabis-only and a non-user group in selective attention, a verbal learning task, immediate visual recall, logical thinking and general knowledge. However, more recently Dafters et al. (2004) found that combined ecstasy–cannabis users, although worse than drug free controls on various measures of episodic memory (free recall and story recall), did not differ significantly from cannabis only users on any of the measures that were administered. Furthermore, unlike Croft et al.'s study, Dafters et al. included both a heavy and light ecstasy user group, both of which performed similarly and did not differ from the cannabis-only users. This being the case, Dafters et al. (2004) maintain that the memory impairments obtained were due to cannabis rather than ecstasy. In relation to the present study, it is important therefore to consider the extent to which cannabis and other drugs might contribute to any apparent ecstasy-group related deficit in associative learning.

Thus the aim of the present study is to determine if users of ecstasy exhibit deficits in associative learning while attempting to control for the potentially confounding effects of other elicit drugs. In addition to the measures used by other researchers (mainly immediate and delayed recall of words), the test used in the present study assesses various measures of forgetting, perseverative errors, and the speed with which all associations are learned (trials to completion) that have not yet been systematically investigated in ecstasy research. The number of pairs repeated correctly on trial one gives a measure of initial learning, and the number of trials required for a participant to learn all associations ("trials to completion") gives an overall indication of speed of learning. Forgetting at each level will also be recorded, whereby forgetting a response that had previously been recalled correctly once would indicate

Table 1 Age, years of education, intelligence, and sleep quality for ecstasy users and non ecstasy users

	Ecstasy users		Non-ecstasy users	
	Mean	SD	Mean	SD
Age (years)	21.66	1.64	21.30	1.79
Years of education	15.77	1.88	15.36	2.12
Ravens progressive matrices (maximum 60)	49.94	4.55	48.13	5.27
NART (maximum 50)	28.91	5.98	29.76	5.80
Hours sleep per night	8.11	1.56	8.01	1.27
Epworth Sleep Scale (maximum 24)	6.38	3.38	5.97	3.03
Self-report health[a]	3.74	0.74	3.84	0.81

[a]The self-report health measure scores range from 1 (very poor) to 5 (very good)

After each presentation, the participant was prompted with the first member of each pair and required to recall the second member. Eight such trials were administered. The order of presentation was randomised and changed for each trial. Measures included the number of correct responses in trial 1 (a measure of initial learning), forgetting at various levels, the number of trials required to learn all associations, and the number of perseverative errors (giving the same incorrect answer consecutively).

Sleep quality A screening questionnaire and the Epworth Sleepiness Scale (ESS; Johns 1991) were used to investigate any group differences in sleep quality. The ESS is a measure of subjective daytime sleepiness and contains eight items, which a participant has to score on a scale of 0 (would never doze off in this situation) to 3 (high chance of dozing off in this situation). A total score of all eight items was used in the analysis. The screening questionnaire contained a number of questions on sleep quality, e.g. hours per night, "how refreshed do you feel in the morning", in addition to relevant lifestyle questions relating to cigarette and alcohol consumption.

Procedure

The tests were administered under controlled laboratory conditions. A computer running on MS-DOS was used for the associative learning task. Tasks were administered in the following order: health/education questionnaire, ecsta sy and drug use background questionnaire, sleep qu tionnaires, associative learning, NART and finally Rav Progressive Matrices. Overall, testing took 2–3 h pe person. The study was approved by the Ethics Committee of Liverpool John Moores University, and was administered in accordance with the ethical guidelines of the British Psychological Society.

Table 2 Indicators of drug use among ecstasy users and non-ecstasy users

	Ecstasy users			Non-ecstasy users		
	Mean	SD	Number	Mean	SD	Number
Total use						
Ecstasy (tablets)	315.30	330.10	35			
Amphetamine (g)	4.00	3.86	8	4.00	–	1
Cannabis (joints)	2,128.71	2,401.96	26	1,082.54	1,439.33	18
Cocaine (g)	18.96	22.03	15	–	–	
Frequency of use (times per week)						
Ecstasy	0.40	0.34	35			
Amphetamine	0.04	0.04	5	–	–	
Cannabis	2.45	2.40	25	0.77	0.90	18
Cocaine	0.26	0.23	15	–	–	
Amount used during previous 30 days						
Ecstasy (tablets)	3.38	3.58	34			
Amphetamine (g)	1.20	2.68	5	–	–	
Cannabis (joints)	17.52	18.26	24	7.91	11.03	16
Cocaine (g)	1.23	1.77	13	–	–	
Average weekly dose						
Ecstasy (tablets)	1.67	1.31	35			
Amphetamine (g)	0.10	0.20	8	0.01	–	1
Cannabis (joints)	7.75	8.73	25	5.11	9.94	18
Cocaine (g)	0.14	0.24	15	–	–	

Table 3 Performance on associative learning measures for ecstasy users and non-ecstasy users

	Ecstasy users		Non-ecstasy users		$F_{1,91}$
	Mean	SD	Mean	SD	
Trials to completion	6.11	1.94	4.32	1.46	26.54***
Number of correct responses in trial 1	2.97	2.01	4.32	2.01	10.14**
Number of perseverative responses	0.69	1.16	0.16	0.66	8.13**
Number forgotten at					
Level 1	0.86	1.03	0.39	0.75	6.61*
Level 2	0.26	0.66	0.10	0.35	2.47
Level 3	0.14	0.36	0.00	0.00	10.12**
Level 4	0.06	0.24	0.00	0.00	3.68

*p<0.001
**p<0.01
*p<0.05

Results

Average age, years of education, fluid intelligence, premorbid intelligence and other background variables for the two groups are set out in Table 1. Statistical tests (ANOVA, t test) revealed that there were no significant differences between the groups regarding these variables, so they are not discussed further.

Inspection of Table 2 reveals that the use of other drugs was commonplace among the ecstasy group, but was restricted mainly to the use of cannabis among the control group. The Ecstasy users had a lifetime dose of cannabis nearly twice that of the controls (2,128 joints compared to 1,082 joints), in addition to using it more frequently (1.45 times per week, compared to 0.77 times), and was smoking more in the last 30 days (17.52 joints compared to 7.91 joints). There were significant group differences in the amount smoked in the last 30 days $t_{41.24}$=2.07, and the frequency of use $t_{32.56}$=3.20, p<0.05 in both cases. However, the difference in lifetime use was not statistically significant: $t_{41.31}$=1.80, p>0.05. (As Levene's test was significant, degrees of freedom have been adjusted accordingly.) The ecstasy group reported an average total lifetime dose of ecstasy of 315 tablets; of amphetamine, 4 g (n=8); and of cocaine, 18.96 g (n=15). The average frequency of use for ecstasy was 0.4 times per week, and for cocaine, 0.26 times per week (n=15).

Ecstasy users performed worse on all measures of associative learning. Users required more trials to learn the pairings; they scored lower on the measure of initial learning (the number of correct responses on Trial 1); and they made more perseverative responses. However, Table 3 reveals that the group differences were less pronounced for the measures of forgetting. Indeed, the means reported in the table indicate that once the material had been learned to a moderate degree, forgetting was a rare event among both users and non-users. Thus, for example, once a response had been successfully learned for four or more consecutive trials, there was no occurrence of forgetting in the non-user group and only seven of the 35 users forgot a previously learned response. MANOVA revealed that the ecstasy-related group difference on the measures of associative learning was statistically significant, $F_{7,89}$=4.64, p<0.001. Furthermore, subsequent uni-

Table 4 Ecstasy user group effect (F values) on measures of associative learning following statistical controls for various measures of amphetamine, cannabis, and cocaine use

	Covariate measures				
	Total use	Times used per week	Amount consumed in the previous 30 days	Average weekly dose	Ever used[a]
Multivariate effect (df=7,85)	3.16*	4.16***	5.20***	4.10***	3.64**
Trials to completion	18.71***	18.06***	21.78***	23.76***	15.45***
Number of correct responses in trial 1	6.21*	2.65	4.27*	7.70*	0.73
Number of perseverative responses	4.17*	7.54**	12.26***	8.13**	4.52*
Forgetting: number forgotten at level 1	2.30	5.80*	6.95**	3.75	7.23**
Forgetting: number forgotten at level 2	2.26	5.98*	4.94*	2.74	6.05*
Forgetting: number forgotten at level 3	5.53*	16.76***	18.83***	7.28**	7.72**
Forgetting: number forgotten at level 4	3.39	0.73	0.53	3.82	6.84*

[a] Covariate measures relating to the use of each of the three drugs were entered as covariates in each analysis. For all univariate analyses, df=1,91. Unless otherwise noted, the units were as follows: cannabis, number of joints; amphetamine and cocaine, grams. Non-users of the drug in question were coded as zero on the particular measure concerned
[b] Categorical variable coded: *0* user, *1* non-user
*p<0.001
**p<0.01
*p<0.05

Table 5 Correlations between various measures of learning performance and measures of illicit drug use

	Trials to completion	Initial learning	Perseverative responses	Forgetting level 1	Forgeting levels 2–7
Total use					
Ecstasy	0.193	−0.226	0.162	0.146	−0.045
Cannabis	0.281*	−0.242*	−0.039	0.309*	0.360*
Cocaine	0.092	−0.155	0.274	0.047	−0.012
Amphetamine	0.085	0.058	0.172	0.093	0.074
Frequency					
Ecstasy	0.218	−0.173	0.004	0.189	0.066
Cannabis	0.165	−0.320*	−0.102	−0.016	0.057
Cocaine	0.169	−0.248*	0.139	0.148	−0.014
Amphetamine	0.143	0.107	0.331*	0.085	−0.058
Use in last 30 days					
Ecstasy	0.226	−0.127	0.075	0.154	0.082
Cannabis	0.198	−0.279*	−0.052	−0.037	0.000
Cocaine	0.092	−0.154	0.036	0.109	−0.038
Amphetamine	−0.054	0.106	−0.040	0.051	−0.035
Average weekly dose					
Ecstasy	0.234	−0.260*	0.149	0.100	−0.038
Cannabis	0.235	−0.230	−0.032	0.266*	0.305*
Cocaine	0.042	−0.107	0.113	0.005	0.014
Amphetamine	−0.033	0.103	−0.002	0.057	−0.025
User/non-user					
Ecstasy	−0.466**	0.310*	−0.281*	−0.259*	−0.281*
Cannabis	−0.221	0.245*	0.013	−0.075	−0.100
Cocaine	−0.302*	0.345*	−0.202	−0.075	−0.078
Amphetamine	−0.167	0.184	−0.072	−0.078	−0.143

N=97. A Bonferroni corrected significance level of α=0.01 was used
*p<0.01, one-tailed
**p<0.001, one-tailed

variate analyses revealed significant group differences on each of the measures with the exception of forgetting at levels 2 and 4 (see Table 3).

It is possible that some or all of these effects might have been attributable to the effects of other drugs. To address this possibility, the preceding analysis was repeated *five* times with different measures of amphetamine, cannabis, and cocaine use as covariates. In the first analysis, measures of lifetime use of each of these other drugs were included; in the second, the number of times each drug was consumed each week; in the third, the amount of each drug consumed within the last 30 days; in the fourth, the average weekly dose (i.e. total amount consumed divided by the length of use in weeks); and in the fifth, categorical variables in which users and non-users of each individual drug were coded as 0 or 1, respectively. Thus *each* of the analyses contained specific measures of amphetamine, cannabis, and cocaine use as covariates. This was done for the multivariate data yielding five multivariate outcomes and for each of the *seven* measures of associative learning yielding *35* univariate analyses in total. The results are set out in Table 4. In the analyses, the multivariate effect of ecstasy user group and the univariate ecstasy user group effects on trials to completion and perseverative errors remained statistically significant. The same was true in relation to forgetting at level three although this result needs to be treated with caution as all non-ecstasy users scored zero on this

Table 6 Performance on associative learning measures for ecstasy users with high and low lifetime dose and non-ecstasy users

	High lifetime ecstasy dose >200 tablets[a]		Low lifetime ecstasy dose ≤200 tablets[b]		Non-ecstasy user		$F_{1,95}$
	Mean	SD	Mean	SD	Mean	SD	
Trials to completion	5.67	1.28	6.59	2.40	4.32	1.46	14.92***
Number of correct responses in trial 1	2.67	1.81	3.29	2.20	4.32	2.01	5.49**
Number of perseverative responses	0.67	1.28	0.71	1.05	0.16	0.66	4.03*
Number forgotten at							
Level 1	0.72	0.83	1.00	1.22	0.39	0.75	3.75*
Level 2	0.06	0.24	0.47	0.87	0.10	0.35	4.75*
Level 3	0.00	0.00	0.29	0.47	0.00	0.00	16.15***
Level 4	0.00	0.00	0.12	0.33	0.00	0.00	5.17**

***p<0.001
**p<0.01
*p<0.05
[a]n=18; mean lifetime number of tablets consumed, 520; range 219–1,682
[b]n=17; mean lifetime number of tablets consumed, 98; range 15–192

Table 7 Variance in associative learning uniquely associated with ecstasy user group following statistical controls for the effects of other independent variables

Regression model	Independent variables in the model prior to the inclusion of ecstasy user group	Total R^2	R squared increment associated with Ecstasy user group
0	None	0.218	0.218***
1	Number of correct responses in Trial 1	0.454	0.086***
2	Number of perseverative responses	0.304	0.134***
3	Number forgotten at level 1	0.445	0.109***
4	Number forgotten at levels 2, 3 and 4	0.405	0.091***

***$p<0.001$

measure. Somewhat less reliable were the group differences in initial learning where measures of the frequency of other drug use and the categorical other drug use/non-use covariates reduced the ecstasy-related group differences to below statistical significance. Similarly, ecstasy-group related differences in forgetting were reduced to below statistical significance following control for total lifetime use and average weekly dose of the other drugs.

In relation to the cannabis measures that were included in each of the 35 ANCOVA analyses referred to in the previous paragraph, homogeneity of regression was obtained in 31 out of 35 cases, $p>0.05$ for the covariate by ecstasy user group interaction. The exceptions were: (1) in relation to the cannabis user group covariate, for the initial learning measure; (2) again in relation to the cannabis user group covariate, for the forgetting at level 4 measure; (3) regarding the average weekly dose of cannabis covariate, for the forgetting at level 3 measure; and (4) in relation to the frequency of cannabis use covariate, for the forgetting at level 1 measure. For these exceptional cases, the covariate by ecstasy user group interactions were all statistically significant; $p<0.05$ in all cases.

Since the number of cocaine and amphetamine users among the non-ecstasy user group was small, it was not possible to properly test for homogeneity of regression in relation to the cocaine and amphetamine measures. Given these limitations, we cannot entirely rule out the possibility that other drugs may have played a part in accounting for the results obtained here. Indeed the correlations set out in Table 5 reveal that various aspects of other drug use were correlated with associative learning processes. Assuming a value of $\alpha=0.01$, forgetting, both for well-learned and for less well-learned material, was significantly correlated with total lifetime dose and average weekly dose of cannabis. Perseverative responses were significantly correlated with the frequency of amphetamine use. Initial learning was significantly correlated with lifetime cannabis use, the frequency of cannabis and cocaine use, cannabis use during the previous 30 days, and the average weekly dose of ecstasy. Consistent with the results of the MANOVA, the ecstasy user group variable was significantly correlated with all measures of learning performance.

In relation to possible ecstasy dosage effects, Table 6 reveals that for the most part while both ecstasy user groups performed worse than non-users, there is little difference between the high lifetime ecstasy dose and the low lifetime ecstasy dose user groups. MANOVA with level of ecstasy use as the independent variable (high lifetime dose $n=18$, low lifetime dose $n=17$, non-user $n=62$) and the seven measures of learning performance as dependent variables yielded a significant multivariate effect of level of ecstasy use $F_{14,178}=5.19$, $p<0.001$. Table 6 reveals that significant differences were also obtained for each of the component learning measures. Pairwise comparisons revealed that non-users performed significantly better than both user groups in trials to completion, $p<0.05$ via Tukey's test. Equally non-users were significantly better than heavy users on the initial learning measure, $p<0.05$. Non-users were also significantly better than light users on all of the forgetting measures, $p<0.05$. The only significant differences between the two ecstasy user groups were for forgetting at levels 2, 3, and 4 where paradoxically light users performed significantly worse then heavy users, $p<0.05$, via Tukey's test.

Regarding the ecstasy-group related variance in trials to completion, it is important to emphasise that the ecstasy-group related variance potentially arises from a range of sources. In addition to using ecstasy, a range of other drugs was also used and there may also be pre-morbid differences between the two groups, as well as differences in psychological affect. Thus the ecstasy-group related variance might have arisen from any one of these sources. The focus here is to establish which sub-processes were responsible for the difference in overall learning performance among this group of poly-substance abusers.

Table 7 reveals that the ecstasy-group related variance amounted to 21.8% of the total variance in associative learning (as indicated by the R^2 increment of 0.218). In subsequent analyses, ecstasy use was entered in the regression equation following the inclusion of each specific learning sub-process. This makes it possible to establish how much of the ecstasy-group related variance was accounted for by each of the learning sub-processes. Inspection of Table 7 reveals that following statistical control for group differences in initial learning (as measured by the number of correct responses in Trial 1), the residual ecstasy-group related variance amounts to 8.6%. Thus over half of the ecstasy-group related variance is accounted for by individual differences in the level of initial learning. Three other regression models were evaluated. Prior control for group differences in perseverative responses reduced the ecstasy-related variance from 21.8 to 13.4%. Inclusion of forgetting at level one and at higher levels in the first stage of the hierarchy removed at least half of the ecstasy-group related variance in both cases.

Discussion

As expected, the results demonstrated an ecstasy-group related deficit in associative learning. The ecstasy user group performed worse on all measures of associative learning, they required more trials to learn the associations, achieved fewer correct responses on trial one, produced more perseverative responses, and demonstrated a greater propensity to forget previously learned responses, especially those that were not well learned. Furthermore, when indices of cannabis, cocaine, and amphetamine use (lifetime dose, frequency of use, average weekly dose, amount consumed in the last 30 days, and a categorical variable of user/non-user) were included as covariates, the ecstasy-group related deficits in trials to completion and perseverations remained significant. However, differences in initial learning fell to below statistical significance with control for other drug use (frequency of use, user/non-user). In addition, group differences in forgetting were reduced to below statistical significance following control for lifetime, and average weekly dose of other drugs.

As some of the apparent ecstasy-group related effects were reduced to below statistical significance following controls for the use of other drugs and since homogeneity of regression was not obtained in all cases or could not be tested, the possibility that other drugs might affect associative learning performance cannot be excluded. Indeed, the correlations obtained in the present study suggest that cannabis use may affect a number of aspects of learning performance. However, the correlations set out in Table 5 do need to be treated with caution. Most of them were modest in scale so that the variables in question shared only a relatively small amount of variance with the learning measures. Furthermore, the Bonferroni correction that was used is based on the assumption that it is appropriate to consider expectations for each illicit drug separately; hence the procedure is based on a total of 25 comparisons where both the outcome variables and the predictor variables were intercorrelated. If a more conservative Bonferroni correction procedure was employed, then with 100 independent correlations, a value for α=0.0005 would be appropriate. At this level only two of the correlations would be statistically significant, specifically, perseverative responses with the frequency of amphetamine use and the ecstasy user/non-user variable with trials to completion.

It was noteworthy that the apparent ecstasy-group effect does not appear to be directly related to the level of lifetime ecstasy use, since MANOVA revealed that, relative to non-users, heavy ecstasy users were no more impaired than light ecstasy users. This outcome is not readily explained. It may be that no straightforward relationship exists between the total number of tablets taken and the risk of a neurotoxic dose (O'Shea et al. 1998). Rather the likelihood of MDMA related impairment is associated with the co-occurrence of a number of factors, which are not necessarily related to the total number of tablets consumed such as the number of tablets ingested on a single occasion and the conditions (ambient temperature, level of hydration, background sound level) prevailing at the time (O'Shea et al. 1998). Thus an individual who typically consumes a modest dose, relatively infrequently but over a long period of time may have a high lifetime dose but not demonstrate any substantial learning deficits.

Turning to the results of the regression analysis, it was revealed that ecstasy user group accounted for ~22% of the total variance in trials to completion. All of the component measures of learning performance substantially reduced the ecstasy-group related variance. The greatest degree of attenuation was achieved by the level of initial learning (number correct in trial 1). The various measures of forgetting each reduced the ecstasy group related variance by about one half while for perseverative responses the degree of attenuation was around 40%. Thus the ecstasy-group related effect appears to be mediated through all of the learning sub-processes. Taken together with the results of the MANOVA, the robustness of the group difference in trials to completion following the various ANCOVA analyses is consistent with an ecstasy-mediated effect in relation to this aspect of learning. However, it is at least possible that some of the attenuation produced by the level of initial learning and by forgetting may have been due to other drugs such as cannabis. Such a possibility would be consistent with the results of Dafters et (2004) and Croft et al. (2001) linking cognitive deficit cannabis use rather than ecstasy. However, in relation to the other learning measures, statistical controls for group differences in various measures of cannabis consumption did not eliminate the overall ecstasy related group difference.

There are a number of limitations of the present study that need to be acknowledged. In a quasi-experimental design such as that adopted in the present study, it is possible that the groups may have differed on some variable other than ecstasy. Some possibilities can be excluded such as intelligence (NART and Raven's) and aspects of sleep quality. However, others such as general health, nutrition, or some pre-morbid condition cannot be ruled out. Furthermore, we relied on self-reports of drug use and so it is possible that there were inaccuracies in this data. There is also no guarantee of the purity of drugs used, and the quantitative amounts per tablet, gram, etc. (Cole et al. 2002). Furthermore, due to limited resources, we were unable to provide an objective measure of recent drug use (e.g. from hair and urine samples). However, most published studies testing cognitive deficits among ecstasy users have not used these techniques (e.g. Fox et al. 2002; Morgan 1998; Morgan 1999; Parrot and Lasky 1998; Rodgers 2000; Wareing et al. 2000). All participants reported being drug free for 24 h, and ecstasy-free for at least 7 days (average abstinence period was actually 12 weeks), and we have no reason to believe this information to be false (participants were not informed that they would be excluded prior to testing).

In conclusion, the present study further supports evidence for cognitive deficits in ecstasy users. Individual differences in initial learning, perseverative responses and forgetting all appear to be important determinants of verbal associative learning deficits in these individuals. How-

ever, while some of these impairments appear to be related to ecstasy use, others may be attributable to other drugs such as cannabis.

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