The acute and long lasting psychological effects of 3, 4-Methylenedioxymethampethamine (MDMA, 'Ecstasy'): A cohort study conducted during the period 2002-2007

Lynn Taurah

PhD thesis

London Metropolitan University

NO CD/DVD ATTACHED

PLEASE APPLY TO UNIVERSITY

PAGE

NUMBERING

AS ORIGINAL

I, Lynn Taurah, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Table of contents

Chapter 5 – Sleep and MDMA   131

Chapter 6 – Memory and MDMA   154

List of tables

List of figures

List of abbreviations

MDMA (3,4-Methylenedioxymethampethamine; Ecstasy)
MDA (3,4-Methylenedioxyamphetamine)
MDE (methylenedioxyethamphetamine)
LSD (Lysergic Acid Diethylamide)
Nicotine (Tobacco)
MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)
SSRIs (Selective serotonin reuptake inhibitors)
TCAs (Tricyclic antidepressants)
Serotonin (5-HT; 5-hydroxytryptamine)
TPH (tryptophan hydroxylase)
5-HTP (5-Hydroxy-L-tryptophan)
5-HIAA (5-hydroxyindole acetic acid)
DA (Dopamine)
GABA (γ-Aminobutyric acid)
CNS (Central Nervous System)
PET (Positron emission tomography)
SPECT (Single photon emission computed tomography)
SERT (Serotonin transporter)
CSF (cerebrospinal fluid)
MRI (Magnetic Resonance Imaging)
BDI-II (Beck depression inventory)
BIS (Barrat Impulsiveness scale)
WSM (Weschler memory test - Revised)
ToL (Tower of London)
WCST (Wisconsin card sorting test)
PSQI (Pittsburgh sleep inventory)
REM (sleep rapid eye movement sleep)

Abstract

Rationale - MDMA is currently an illegally abused recreational drug. Non-human animal studies demonstrate that MDMA causes non-repairable damage to serotonergic neurons. As the acute behavioural effects of MDMA are similar between non-human animals and humans, it is plausible to suggest that the neurotoxic effects of MDMA will be the same in each group. Results from previous human research investigating the psychobiological effects of MDMA have been inconsistent. They have relied on limited sample sizes and lack adequate control groups. The overall aim of the present study was to examine behaviours associated with 5-HT including: sleep, depression, impulsivity, memory, and executive functioning. The study investigated 5-HT related behaviours comparing past and present polydrug MDMA users whilst controlling for other recreational drugs.

Method - The study involved a total of 1399 participants split across 6 groups: non-drug control; nicotine/alcohol control; nicotine/alcohol/cannabis control; non-MDMA polydrug control; current MDMA polydrug and past MDMA polydrug. Participants were required to complete the following: demographic and drug history questionnaire, Becks Depression Inventory (Version II), Pittsburgh Sleep Scale, Barratt Impulsivity Questionnaire, Wechsler Memory Test (Revised), Wisconsin Card Sorting Test, and the Tower of London Test.

Results - The study found that past and present MDMA users suffer from specific deficits in measures of depression (cognitive-affective subscale), sleep, impulsivity (attention and motor subscales) and memory (verbal, visual, delayed). Past and present MDMA users displayed problems in selected executive functions: planning; solution time; and number of errors. Interestingly, statistical regression analysis predicted that these deficits in executive functioning may be due to MDMA, (1) directly affecting other psychological processes: memory, impulsivity, and sleep, which indirectly affects performance on executive functions; or, (2) MDMA directly disrupts executive functions: planning, solution time, and number of errors.

Discussion – The present study is the first and largest study to date to suggest that MDMA causes acute and long lasting changes to specific psychological functioning: depression, sleep, impulsivity, memory, and executive functioning; without recovery even after 5 years of abstinence. Future studies need to control for mood, sleep disturbance, memory deficits, and elevated impulsivity when investigating disruptions to executive functions in past and present polydrug MDMA users.

Chapter 1 - General Introduction

1.1 Timeline of the thesis

The hypothesis and methodology of this thesis were formulated during the period 2000 - 2001. During this time, non-human animal research had indicated +/- 3, 4-methylenedioxyamethamphetamine (MDMA, ecstasy) was a specific neurotoxin to serotonin (5-HT, 5-Hydroxytryptamine). From the mid-1980's, human research had indicated that the frequent use of MDMA and other recreational drugs resulted in short-term psychological deficits (memory, executive functioning, depression, sleep, and impulsivity). During the period of research up to 2007, these studies were heavily criticised for biased samples from frequent drug users and lack of control of other recreational drugs. In addition, the studies reported conflicting results. From the mid 1980s to 2011 there have been no single investigation focussing on the long lasting consequences of MDMA, as the majority of MDMA users were young and it was rare to find people whom had abstained from MDMA. Collection and analysis of the data for the presented thesis was during the period 2002-2007 and the thesis written during the years 2010 and 2011.

1.2 The history and popularity of MDMA

The research interest in MDMA has increased over the past 30 years, as has its popularity as a recreational drug. The history of MDMA clearly demonstrates it is a global recreational drug of abuse.

The history of the compound MDMA commenced in 1912, initially discovered by the German pharmaceutical company Merck as a blood-clotting agent (Green et al. 1995; Haddad et al. 2002; Green et al. 2003; Gudelsky et al. 2003). Merck performed animal experiments using MDMA in 1927. The results from these studies suggested MDMA was similar to adrenaline. At this stage there was no evidence indicating the psychoactive properties of MDMA. It remained dormant until the period 1953-1954, when the US army conducted studies on non-human animals. The findings for these studies were never fully revealed, being documented as 'sensitive'. In 1959, Merck investigated MDMA's pharmacological effects and tested its properties as a 'stimulant'.

In 1972, police in Chicago seized MDMA, suggesting that the use and distribution of MDMA as a recreational drug was commencing. The very first publication concerning MDMA and its psychotropic effects on humans was in 1978 by Shulgin and Nichols, where they described the effects of MDMA. Explaining it was neither a full stimulant nor psychedelic. Their publication cited it as a new drug with novel behavioural effects.

MDMA soon became a therapeutic drug during early 1970s. Word spread that MDMA was a drug that enhanced communication during clinical sessions, allowing patients to reduce their psychological defences and increase their ability for introspection (Green et al. 1995; Haddad et al. 2002; Green et al. 2003; Gudelsky et al. 2003). During the next 10 years, there was a surge in the distribution and popularity of MDMA across the Dallas area, which soon spread to the rest of the USA and to Europe. A few therapists used the drug for therapeutic purposes until it became illegal. During the mid-1980s, a legal battle began concerning the classification of MDMA and its potential harmful effects within the USA. Many doctors, scientists and therapists argued MDMA was a 'safe' drug under medical supervision. They argued it had low potential for addiction. Following a 5-year legal battle on 23rd March 1988, MDMA became a class 1 illegal recreational drug within the USA due to its health concerns (Green et al. 1995; Haddad et al. 2002; Green et al. 2003; Gudelsky et al. 2003). In the United Kingdom, MDMA became a 'class A' scheduled drug under the Misuse of Drugs Act (1971) and it was illegal from 1977.

Worldwide, the possession, manufacture and sale of MDMA is prohibited and can result in prosecution. To date there is still support for the reclassification of MDMA (Curran, 2000; Parrot, 2000; Parrot, 2001; Back-Madrugs et al. 2003; Morton, 2005; Nutt et al. 2010). One publicised debate concerning the reclassification of MDMA in the UK was by Nutt, who argued for the downgrading of MDMA (Nutt et al. 2010). He argued the current 'class A' classification of MDMA did not reflect scientific evidence. Nutt argued that the most powerful and damaging drugs were those that were pleasurable, he debated this did not include MDMA. Nutt noted that MDMA was the least pleasurable illegal drug. Nutt states that MDMA is less toxic in overdose than alcohol. Nutt argues that only a small percentage (15%) of MDMA users inject the drug, which would result in more severe and intense consequences (Nutt et al. 2010). Thus, still today there remains debate concerning the addictive properties and health risks of MDMA (Curran, 2000; Parrot, 2000; Parrot, 2001; Back-Madrugs et al. 2003; Morton, 2005). Robust research such as this study is required in order to identify the long lasting consequences of using MDMA.

Irrespective of its illegalisation, MDMA became a popular recreational drug of abuse across the world (Curran, 2000; Parrot, 2000; Parrot, 2001; Back-Madrugs et al. 2003; Morton, 2005). MDMA first became a recreational drug of abuse during the early 1970s; however, its popularity remained limited. During the 1980s, MDMA became known as 'Adam'. It became popular in nightclubs within the Dallas area, quickly spreading to the UK and the rest of the world. It was associated with the 'gay scene' and popular in clubs across major cities of the world. MDMA was a common drug of abuse amongst 15-35 year olds (Aldridge et al. 1998; Green et al. 1995; Morgan, 2000; Curran, 2000; Landry, 2002; Back-Madruga, 2003; Morton, 2005) and associated with the rave and dance scene as well as electronic music genres (Green et al. 1995; Morgan, 2000; Curran, 2000; Parrot et al. 2000, Landry, 2002; Back-Madruga, 2003; Morton, 2005; Aldridge et al. 2008).

In a survey of British University students, 13% stated they had taken MDMA at least once in their life, whilst 3% stated that they had used it regularly (Parrot, 2000). This recreational use of MDMA seems to be continually increasing in every Westernised country with female use increasing (Parrott et al. 1998, Parrot, 2000; Pope et al. 2001). UK statistics report a lifetime prevalence of 2% for the general population in 1994 (Griffiths et al. 2008). In a UK survey of 15-16 year olds, 9.2% of boys and 7.3% of girls reported taking MDMA (Griffiths et al. 2008). Saunders estimated that at least half a million MDMA tablets each weekend during the 90s in the UK alone were consumed (Saunders, 1995). A report suggested that MDMA within the UK had risen by 100% within the period 1998-2003, increasing by 70% worldwide during this time interval (Office on drugs and Crime, 2003). The United Nations (2003, 2008) report stated that the recreational use of MDMA was widespread, and had continually increased over the last decade.

These figures indicate that MDMA was a popular recreational drug of abuse for all ages, genders, and its use was worldwide during the period 2000-2007.

1.3 The pharmacokinetics, neuropharmacology, neuroanatomy and behavioural effects of MDMA

Before considering the psychological and behavioural effects of MDMA, it is necessary to explain the chemical structure of MDMA, how it works within the brain and the neuroanatomical areas it targets.

1.3.1 Synthesis of MDMA

In 2011, the availability and supply of MDMA worldwide is being limited; due to the lack of safrole, a substance used in the manufacture of MDMA. The oils of several plants are synthesised in order to produce MDMA. These plants include: nutmeg, sassafras, saffron, dill, parsley seed, crocus, vanilla beans, and calamus. The synthesis of MDMA involves four procedures (Green et al. 1995; Haddad et al. 2002; Green et al. 2003; Gudelsky et al. 2003). This suggests that future MDMA abuse might be limited due to the over harvesting of safrole in Southeast Asia (European monitoring centre for Drugs and Drug Addiction, 2008). Even if MDMA is no longer a future recreational drug, there are still a large number of individuals exposed to MDMA during the period up to 2010. These individuals may suffer from potential consequences. Hence, the importance and need for investigating the long lasting consequences of MDMA.

1.3.2 Chemical structure of MDMA

MDMA is a unique drug with similarities and differences to other psychedelics. MDMA is an amphetamine derivative (Green et al. 1995; Haddad et al. 2002; Green et al. 2003; Gudelsky et al. 2003) and is chemically similar to amphetamine. It is similar to other hallucinogenic chemicals, such as mescaline (Green et al. 1995;

Haddad et al. 2002; Green et al. 2003; Gudelsky et al. 2003). Even though MDMA is similar in chemical structure to amphetamine, it is not a potent stimulant like amphetamine. It is chemically different from amphetamine and other hallucinogenic compounds; as MDMA has a secondary amine. Subsitution of the basic nitrogen is with N-methyl (Green et al. 1995; Haddad et al. 2002; Green et al. 2003; Gudelsky et al. 2003; De la Torre et al. 2004). MDMA is the N-methylated form of 3,4-methylenedioxyamphetamine (MDA). This added N-methyl group hinders the psychedelic actions of MDMA; making it less hallucinogenic than MDA. The N-methyl group increases the affinity of MDMA to dopamine/serotonin (DA/5-HT) transporters (Green et al. 1995). This affinity to DA and 5-HT transporters is important for the possible role of MDMA induced long lasting psychological consequences.

1.3.3   Pharmacokinetics of MDMA

As MDMA is illegal, the purity of MDMA is largely unknown to the user. In its purest form MDMA is a white crystalline powder with a musty odour (Green et al. 1995; Haddad et al. 2002; Green et al. 2003; Gudelsky et al. 2003; Cole et al. 2002; De la Torre et al. 2004). MDMA is normally consumed orally; in the form of pills and tablets (Green et al. 1995; Cole et al. 2002; Haddad et al. 2002; Landry, 2002; Green et al. 2003; Gudelsky et al. 2003; Back-Madruga, 2003). MDMA is mixed with other chemicals including: amphetamine, methamphetamine, ephedrine, and caffeine (European monitoring centre for Drugs and Drug Addiction, 2008). The typical UK dose of MDMA, in one tablet, is 75-80mg although it can range from 50 to 250 mg per tablet (Green et al. 1995; Haddad et al. 2002; Cole et al. 2002, Green et al. 2003; Gudelsky et al. 2003; Back-Madruga, 2003; European monitoring centre for Drugs and Drug Addiction, 2008). Onset of action is within 30 minutes after administration; with peak serum levels after 1 to 3 hours and the elimination half-life is 7 hours (Green et al. 1995; Haddad et al. 2002; Green et al. 2003; Gudelsky et al. 2003; De la Torre et al. 2004). These figures can vary amongst individual users and dosage (Landry, 2002). Once swallowed, MDMA reaches the stomach, where it is absorbed into the blood stream. Approximately, 20% of the dose of MDMA will actually reach the brain, where it will exert its psychedelic effects. The kidneys will eliminate around 60% of MDMA via urine. A further 7% will be metabolised into MDE (Green et al. 2004). MDE can have neurotoxic effects, adding to the possible neurotoxic effects of MDMA (Green et al. 2003; 2004). The varying amount of MDMA found in tablets makes this type of research rather problematic in terms of quantifying lifetime exposure and consumption.

1.3.4   Neuropharmacology of MDMA

The neurotoxicity of MDMA occurs within the CNS, thus it is necessary to explain the actions of MDMA within the CNS.

Immediately after MDMA reaches the CNS it is absorbed into the 5-HT neurons (De la Torre et al. 2004). MDMA is able to do this as it has a greater affinity with the reuptake transporters (SERT) than 5-HT, resulting in MDMA being able to enter the axon terminal before 5-HT.

Normal neuronal activity involves the synthesis of 5-HT and its storage in neuronal vesicles. Following neuronal stimulation by an action potential, the presynaptic neuron releases into the synaptic cleft, the stored 5-HT (Iravani et al. 2000; and Pifl et al. 2005). The released 5-HT will attach to a postsynaptic receptor, or, be reclaimed, via a reuptake transporter into the presynaptic neuron.

MDMA is absorbed into the 5-HT neuron by the reuptake transporter via indirect passive diffusion, or directly through the reuptake transporter (Iravani et al. 2000; Green et al. 2003; De la Torre et al. 2004). A single dose of MDMA can release up to 80% of stored 5-HT (Iravani et al. 2000; Green et al. 2003). Once MDMA is in the neuron it will release larger amounts of 5-HT into the synaptic cleft than normal (Iravani et al. 2000). MDMA is able to block the reuptake of 5-HT (Iravani et al. 2000; Green et al. 2003; Pifl et al. 2005). Thus MDMA releases stored 5-HT into the synapse and prevents its reuptake, resulting in increased 5-HT producing a greater response on the postsynaptic neuron. It is able to reverse the reuptake transporter action to allow the 'transporter' to begin pumping 5-HT into the synapse from the cell (Iravani et al. 2000; Green et al. 2003; Pifl et al. 2005). In this way, MDMA re-establishes the functioning of 5-HT. Thus MDMA is generally accepted to be a potent indirect monoaminergic agonist producing carrier-mediated release and reuptake inhibition of 5-HT. MDMA possibly affects dopamine and noradrenaline levels within the CNS (Green et al. 1995; Haddad et al. 2002; Green et al. 2003; Gudelsky et al. 2003; Back-Madruga, 2003; De la Torre et al. 2004). Several hours after ingestion of MDMA, the enzyme monoamine oxidase (MAO) degrades any 5-HT left in the synapse. At this point, the effects of MDMA are minimal. After 7-8 hours, MDMA has released all the synthesised and stored brain 5-HT. During this time interval, if more MDMA was consumed, it would have little or no effect; as the 5-HT now needs to be re-synthesised (Iravani et al. 2000). A period of two/three weeks is required for the replenishment of neuronal 5-HT and for levels to return to normality (Iravani et al. 2000; Green et al. 2003). This two/three week time interval would be dependent on the dosage of MDMA consumed. Large doses of MDMA result in the release of more 5-HT, resulting in more time needed to replenish 5-HT levels (Iravani et al. 2000). Accuracy of dosage in human experiments is therefore essential.

Non-human animal studies suggest the synthesis of tryptophan hydroxylase (TPH) is inhibited by MDMA and reports have suggested that it can take several days before TPH levels return to baseline levels (Iravani et al. 2000; Green et al. 2003). This lack of available TPH can provide an explanation for the time needed for the resynthesis following exposure to MDMA. Ultimately the time interval (2 weeks) is required for the re-synthesis of 5-HT, allowing 5-HT levels to return back to baseline levels (Green et al. 1995; Haddad et al. 2002; Green et al. 2003; Gudelsky et al. 2003; Back-Madruga, 2003; Green et al. 2003; De la Torre et al. 2004). Research investigating the long lasting consequences of MDMA needs to maintain that users abstain

from MDMA for a period of up to 3 weeks before psychological testing, to allow time for the TPH levels and 5-HT to return to baseline.

When MDMA enters the CNS, it triggers a wide range of receptors including: 5HT-1A, 5HT-1B, 5HT1E, 5HT1F, 5HT2A, 5HT2C, 5HT3, 5HT4, 5HT5, 5HT6, and 5HT7 (Green et al. 1995; Iravani et al. 2000; Haddad et al. 2002; Green et al. 2003; Gudelsky et al. 2003; De la Torre et al, 2004). Apart from the 5-HT3 receptor, which is a ligand gated ion channel; all other 5-HT receptors are G protein coupled seven transmembrane receptors that work by activating an intracellular second messenger process (Green et al. 1995; Haddad et al. 2002; Green et al. 2003; Gudelsky et al. 2003; De la Torre et al. 2004). It is through these receptors that MDMA is proposed to have its behavioural and psychoactive effects, which subsequently might be long lasting (Series et al. 1994; Willem et al. 2007; Soar et al. 2001; Montoya et al. 2002).

In brief, MDMA causes the release of stored 5-HT from nerve terminals; prevents the reuptake of 5-HT from the synaptic cleft; and inhibits TPH, consequently preventing new serotonin being synthesised for a time interval lasting up to two weeks (Green et al. 1995; Haddad et al. 2002; Green et al. 2003; Gudelsky et al. 2003; Back-Madruga, 2003). Following this initial release of serotonin, there is a period of 24 hours to two weeks, during which new 5-HT needs to be re-synthesised (Figure 1.1). As MDMA affects a number of receptors and 5-HT is limited following MDMA exposure, it is highly probable that there will be diverse acute behavioural and psychological changes associated with MDMA use.

Figure 1.1   Schematic illustration of proposed 5-HT levels following MDMA consumption.

The diagram demonstrates the proposed 5-HT levels following the use of MDMA. After the consumption of MDMA, stored 5-HT is released from neurons. This releasing of stored 5-HT, can last for up to 3 hours. After this initial 3-hour period, no more 5-HT is released and any available 5-HT in the synapse will attach to post-synaptic receptors and be used up hence the acute effects of MDMA. As all stored 5-HT is released by the neurons, time is needed to synthesis new 5-HT. During this period of 5-HT synthesis, which can last up to 3 weeks, there will be a lack of available 5-HT for the individual. This will result in unwanted side effects. The question remains whether following this 3-week interval, 5-HT levels return to baseline or if future serotonin availability is limited? The present study investigates the possible long lasting psychological problems following MDMA use.
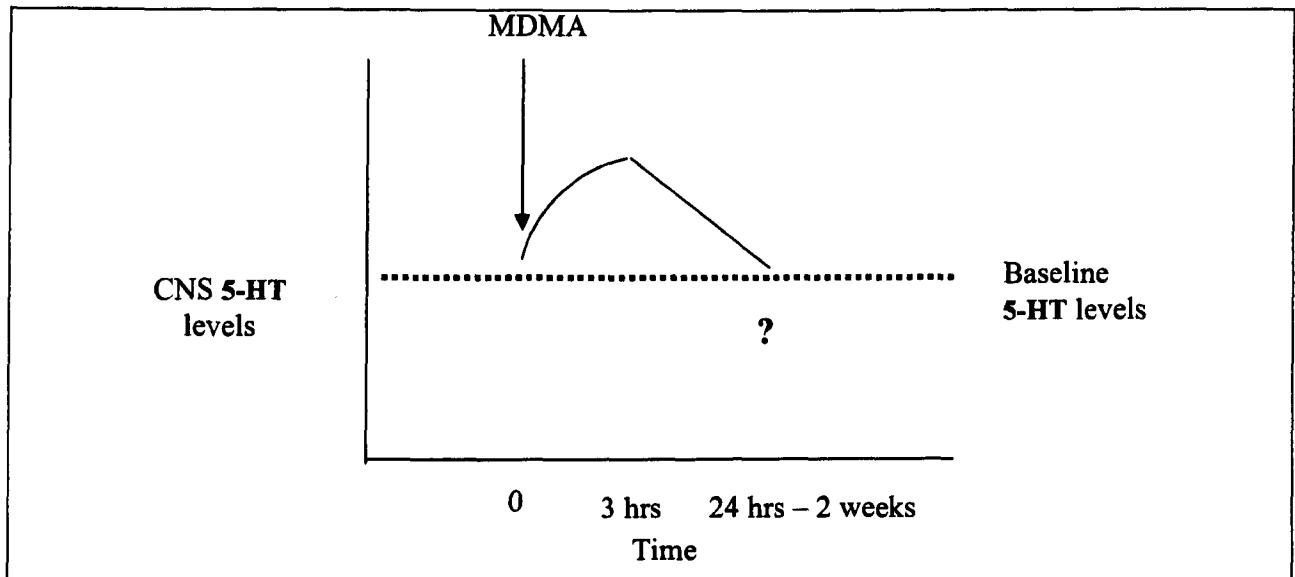
1.3.5   Neuroanatomy of MDMA

In order to understand the possible long lasting consequences of MDMA, it is essential to locate the anatomical areas that MDMA targets. The action of the majority of recreational drugs appears to be the pre-cortical and sub-cortical regions of the brain (Dworkin et al. 1988; Di Ciano et al. 1995; Iravani et al. 2000; Green et al. 2003; Koprich et al. 2003). The site of action for many recreational drugs includes many different pathways: opiate, dopamine (DA), 5-HT, gamma-Aminobutyric acid (GABA), acetylcholine and glutamate. Biological studies have discovered that the majority of recreational drugs work on two main neural pathways i) sertonergic, ii) and dopaminergic (Dworkin et al. 1988; Di Ciano et al. 1995; Iravani et al. 2000; Green et al. 2003; Koprich et al. 2003). There is controversy surrounding the effect of MDMA on other neurotransmitters including dopamine and noradrenaline (Johnson et al. 2000; Parrot et al. 2003; Xie et al. 2004; Fornai et al. 2005; Galineau et al. 2005). Non-human animal studies have demonstrated that MDMA can cause an increase in the level of DA; these results are inconclusive (Iravani et al. 2000; Green et al. 2003; Koprich et al. 2003). It is clear from non-human animal studies that MDMA is a complicated drug affecting many

neurotransmitters. Consequently, the possible long lasting consequences of MDMA may be neuropharmacologically complicated.

1.4 The neuropharmacology and behavioural properties of 5-HT

As MDMA is a 5-HT agonist, it is necessary to explain the vast role of 5-HT within the CNS, including its pharmacology and its behavioural effects.

1.4.1 Neuropharmacology of 5-HT

5-HT is a monoamine neurotransmitter (Green et al. 1995; Haddad et al. 2002; Green et al. 2003; Gudelsky et al. 2003; Back-Madruga, 2003). 5-HT is synthesised in serotonergic neurons within the central nervous system (CNS) and enterochromaffin cells (a type of enteroendocrine cell found in the lining of lumen of the gastrointestinal tract) in both non-human animals and humans. Mushrooms, fruits, plants, vegetables and turkey are high in tryptophan (Green et al. 1995; Haddad et al. 2002; Green et al. 2003; Gudelsky et al. 2003; Elliott et al. 2005).

In humans, 5-HT is synthesised from the natural occurring amino acid tryptophan, via two-steps (Figure 1.2). Two enzymes are involved in this metabolic process, including TPH and the amino acid 'decarboxylase'. TPH is the rate-limiting step in the pathway. TPH comes in two isoforms, known as TPH1 and TPH2. Several tissues contain TPH1 whereas the TPH2 is the brain specific isoform. Tryptophan and TPH can pass the blood-brain barrier readily. The process begins with the conversion tryptophan into a temporary product called 5-HTP (5-Hydroxy-L-tryptophan) by the enzyme TPH. During this initial phase, addition of a hydroxyl group to tryptophan forms 5-HTP. Subsequently, the combination of 5-HTP with the enzyme 'decarboxylase' produces 5-HT. During this second step a carboxyl group is removed from 5-HTP to form 5HT. 5-HT is broken-down by the enzyme monoamine oxidase to produce the inactive metabolite 5-hydroxyindoleacetic acid (5-HIAA) (Green et al. 1995; Haddad et al. 2002; Green et al. 2003; Gudelsky et al. 2003; Elliott et al. 2005). The synthesis of 5-HT is important concerning probable MDMA neurotoxicity and future treatment options.

Figure 1.2   Two step synthesis of serotonin

The synthesis of serotonin is a two-step process. The first step involves tryptophan (natural occurring from the diet) being converted to 5-HTP via the enzyme tryptophan hydroxylase. The second step involves this 5-HTP being converted to 5-HT via the enzyme amino acid decarboxylase.

Step 1   Tryptophan converts to 5-HTP (enzyme tryptophan hydroxylase)
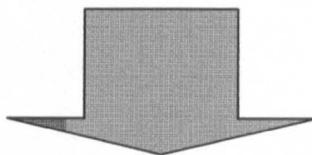
Step 2   5-HTP converts to 5-HT (enzyme amino acid decarboxylase)

Termination of 5-HT is predominantly via the reuptake from the synapse to the presynaptic neuron (Elliott et al, 2005; Pifl et al, 2005). The '5-HT reuptake transporter' or SERT specific monoamine transporter for serotonin is involved (Pifl et al, 2005). The SERT has greater affinity to MDMA. Various other agents inhibit SERT including: amphetamine, cocaine, dextromethorphan, tricyclic antidepressants and selective serotonin reuptake inhibitors (Table 1.1; Green et al. 1995; Haddad et al. 2002; Green et al. 2003; Gudelsky et al. 2003; Back-Madruga, 2003). As other recreational drugs affect 5-HT, their exposure needs to be controlled in future MDMA research, as it may not be MDMA alone causing the proposed damage to the 5-HT (Table 1.1).

Table 1.1   Commonly abused recreational drugs within the UK

The table provides a list of the most commonly abused drugs within the UK, providing details of the effects of the drug, and the CNS mode of action (Di Fort et al. 2007; Yucel and Lubman, 2007; de Wit, 2009; Stalnaker et al. 2009).

Drug name	Drug affect	Method Action
Alcohol (ethanol)	CNS depressant	GABA, NMDA receptor antagonist
Alkyl nitrites (poppers)	Muscle relaxant/vasodilator	Relaxes smooth muscle
Amphetamines (speed/methamphetamine)	Psychostimulant	Increase synaptic dopamine
Barbiturates	CNS depressant	GABA
Marijuana (cannabis)	Relaxant	Cannabinoid receptors
Cocaine and 'crack'-cocaine	Psychostimulant	Increase synaptic dopamine
Gamma hydroxybutyrate (GHB)	Sedative-hypnotic/ CNS depressant	Dopamine, glutamate, acetylcholine
Hallucinogens (Lysergic Acid Diethylamide (LSD) and 'magic mushrooms')	Hallucinogenic or psychedelic	Serotonin
Heroin and morphine	Opioid	Interact with dopamine / opioid receptor
Ketamine	Psychostimulant/ dissociative anesthetic	Inhibits GABA, dopamine, serotonin
MDMA (3,4-Methylenedioxymethamphetamine, Ecstasy)	Psychostimulant/psychedelic	Serotonin/dopamine
Tobacco (nicotine)	Psychostimulant	Dopamine/acetylcholine agonist
Tranquillisers	Sedative	GABA
Androgenic steroids	Cell growth	Androgen receptors
Inhalants (glues, aerosols and solvents)	Psychostimulant, hallucinogenic, depressant	Dopamine

There is a primary anatomical pathway within the CNS for 5-HT (Figure 1.3). This serotonergic pathway includes a narrow band of cell bodies that run along the brain stem to the mid-brain (hippocampus, basal ganglia and amygdala) sending axons to higher regions of the brain (Green et al. 1995; Haddad et al. 2002; Green et al. 2003; Gudelsky et al. 2003). Nerve connections from the hippocampus pass to the suprachiasmatic nucleus; considered the 'master clock', controlling physiological processes like sleep and wakefulness (Balogh et al. 2004). Additional neuroanatomical areas containing serotonergic projections include the septum and the cerebral cortex (Green et al. 1995; Haddad et al. 2002; Green et al. 2003; Gudelsky et al. 2003).

The raphe nuclei is rich in 5-HT. The raphe nuclei are a cluster of nine nuclei found within the brain stem. These nine nuclei project virtually to every part of the brain (Green et al. 1995; Haddad et al. 2002; Green et al. 2003; Gudelsky et al. 2003). In general, the caudal raphe nuclei project towards the spinal cord/brain stem and the rostral nuclei project to the cortex. 5-HT plays a major role within the CNS and if disrupted can result in serious behavioural and psychological problems.

Figure 1.3   The major pathways of 5-HT within the rat CNS (Carlson, 2001)

The figure provides the main 5-HT pathways within the rat CNS including the Raphe nuclei and its projections spanning the length of the brain, towards the cortex and the brain stem.
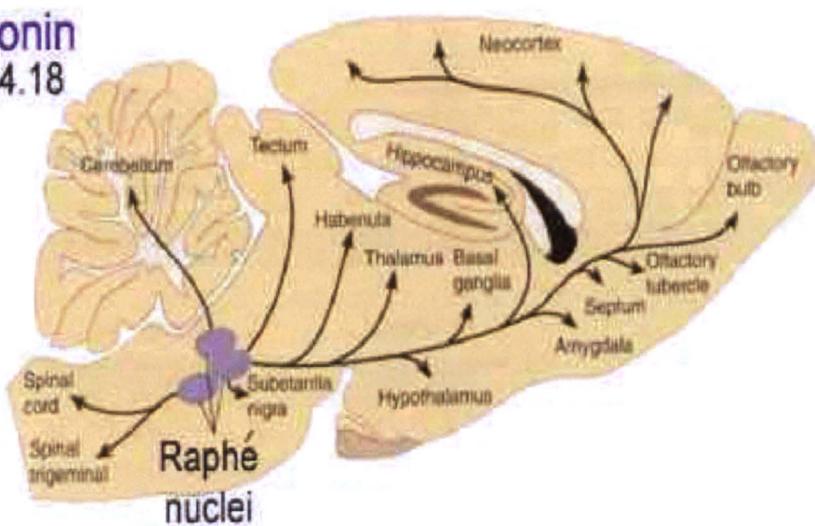
1.4.2 Behavioural aspects of 5-HT

5-HT within the CNS is highly documented in the research literature, forming an important role in a number of central psychological functions (Green et al. 2003; Elliott et al. 2005). 5-HT influences and regulates various processes: mood, anxiety, anger, aggression, impulsiveness, sexual activity, appetite, sleep, pain, circadian and seasonal rhythms, motor activity, metabolism, vomiting and body temperature (Green et al. 1995; Haddad et al. 2002; Green et al. 2003; Gudelsky et al. 2003; Back-Madruga, 2003).

Extremely high doses of 5-HT can be very dangerous; sometimes lethal, in both non-human animals and humans. High doses of 5-HT can led to a condition called the 'serotonin syndrome' (Green et al. 1995; Parrot, 200; Green et al. 2003). The 'serotonin syndrome' occurs due to an over stimulation of the 5-HT2A receptors within the CNS. Symptoms are usually rapid, often occurring within minutes; including cognitive, autonomic and somatic effects (Table 1.2). The symptoms observed in non-human animals after a single dose of MDMA provide evidence that MDMA is a 5-HT agonist (Green et al. 1995; Green et al. 2003). There are similarities in 'serotonin symptoms' between humans and non-human animals (Table 1.2). It could be argued that as the acute effects of excess 5-HT are similar between non-human animals and humans, it is therefore possible that the consequences of limited 5-HT would be the same between species. As MDMA is a 5-HT agonist, it is clear that MDMA could potentially have adverse effects on physiological and psychological functions.

Table 1.2   Symptoms of the 'serotonin syndrome' in humans and animals (Green et al, 1995 and Green et al, 2003).

The table provides details of the physiological and behavioural symptoms following a high dose of 5-HT. The symptoms between non-human animals and humans are compared in the table and it is clear that these acute symptoms are very similar.

Human 'Serotonin Syndrome'	Animal 'Serotonin Syndrome'
Increased heart rate	Increased heart rate
Drowsiness	Drowsiness
Shivering	Shivering
Sweating	Sweating
Dilated pupils	Dilated pupils
Myoclonus	Hyperactivity
Tremor	Tremor
Hyperthermia	Hyperthermia
Mental confusion	
Headache	
Nausea	

1.5   The acute effects of MDMA in non-animals

The acute effects of MDMA in laboratory non-human animals (rats, monkeys, and hamsters) include hyperthermia (related to ambient temperature), hyperactivity, and the 'serotonin syndrome' (Carlin et al. 2000; Bhattacharya et al. 2001; Croft et al. 2001; Cornish et al. 2003; McCardle, 2004). The 'serotonin syndrome' in non-human animals consists of a series of complex behavioural changes including: enhanced locomotor activity, reciprocal forepaw treading, head weaving, piloerection, hind limb abduction, proptosis, ataxia, unawareness, which finally result in convulsions and death (Green et al. 2004). Research indicates that these symptoms are caused by a rapid release of stored 5-HT (Carlin et al. 2000; Bhattachary et al. 2001; Croft et al. 2001; Back-Madruga, 2003; McCardle, 2004). The 'serotonin syndrome' in non-human animals provides further evidence that MDMA is indeed an indirect 5-HT agonist. This initial phase of 5-HT release will discontinue after a period of 24 hours (Green et al. 1995; Back-Madruga, 2003; Fantegrossi et al. 2003; Green et al. 2004).

1.6   The acute behavioural and psychological effects of MDMA in humans

There are similarities in the acute effects of MDMA between non-human animals and humans including: increased temperature, sweating, increased motor activity, tremors, and shivering (Green et al. 2004). In addition, acute adverse effects of MDMA in humans includes: tachycardia, jaw clenching, nystagmus, a nervous desire to be in motion, transient anorexia, panic attacks, nausea and vomiting, ataxia and muscle aches, urinary urgency, diplopia, insomnia and fatigue, tremors, inhibition of ejaculation and rarely transient hallucinations (Green et al. 1995; Cohen, 1998; Morgan, 2000; Curran, 2000; Parrot et al, 2000, Back-Madruga, 2003). There are other physiological side effects of MDMA: lower back pain, blurred vision and headaches. Symptoms can commence approximately 30 minutes after ingestion of MDMA and persist for a further six to eight hours following initial consumption (Green et al. 1995; Cohen, 1998; Morgan, 2000; Curran, 2000; Parrot et al. 2000, Back-Madruga, 2003). Previous studies indicate there is an inverse relationship between the positive and negative effects of MDMA. Thus regular MDMA polydrug users will state that the adverse 'negative' effects increase with successive use whilst the 'positive' mood enhancing effects decrease (Curran et al. 1997; Peroukta et al. 1998; Parrot et al. 1998; Parrot et al. 2002).

In humans, there are acute psychological and cognitive effects caused by MDMA. The literature describes it as 'evoking an altered sense of consciousness with emotional and sensual overtones' (Curran, 2000; Parrot, 2000; Parrot, 2001; Back-Madrugs et al. 2003; Morton, 2005). This state is a pleasant state of introspection, a highly controllable experience that invites intensification of feelings and greatly facilitating interpersonal communication (Boy et al. 2001). This explains why MDMA was used by some psychotherapists to enhance psychotherapeutic processes and promote emotional communication during the 1970s (Curran, 2000; Parrot, 2001; Back-Madrugs et al. 2003; Morton, 2005). The use of MDMA as a therapeutic drug has been withdrawn, despite therapists' persistent arguments for its therapeutic benefits, despite the underlying side effects including increased cardiac disease and potential long lasting neurotoxicity (Curran, 2000; Parrot, 2001). Future research work should investigate the actual possible long lasting consequences of MDMA, as it could be a potential therapeutic drug with many beneficial attributes.

The majority of MDMA users will use the drug in small social gatherings/parties with other drug users (Curran, 2000; Parrot, 2000; Parrot, 2001; Back-Madrugs et al. 2003; Morton, 2005). The suggested reasoning behind this pattern of use is that MDMA users can heighten the positive experience of the drug by using it in this social fashion (Curran, 2000).

The psychological effects of MDMA include a reduction of inhibitions, an increase in openness and empathy (Curran, 2000; Parrot, 2000; Parrot, 2001; Back-Madrugs et al. 2003; Morton, 2005). Drug users under the influence of MDMA will be more energetic, happy, excited and playful (Curran, 2000). MDMA results in a reduction in violent behaviours and aggression (Curran, 2000; Parrot, 2000; Parrot, 2001; Back-Madrugs et al. 2003; Morton, 2005). MDMA will occasionally result in a reduction in libido for some individuals. Users will experience an increase in intimacy, resulting in an increase in kissing and hugging of friends and/or strangers (Curran, 2000). Other psychological experiences include an altered perception of time (Curran, 2000). The majority of MDMA polydrug users fail to report hallucinations, whilst they are under the influence of MDMA; however they report an elevated intensity in visual input (Parrot et al, 2000). MDMA is associated with the dance scene, as MDMA users tend to be completely absorbed by colour and light (Climko et al. 1987; Curran, 2000; Parrot, 2000; Parrot, 2001; Back-Madrugs et al. 2003; Morton, 2005).

In summary, the acute physiological effects of the 'serotonin syndrome' are similar between humans and non-human animals (Greer and Tolbert, 1986; Green et al. 1995; Morgan, 2000; Curran, 2000; Parrott et al. 2000, Back-Madruga, 2003). In addition, favourable psychological effects attributed to human usage include positive mood changes, enhanced communication and intimacy, improved interpersonal relationships, increased self-esteem and elevated mood (Climko et al. 1987; Green et al. 1995; Morgan, 2000; Curran, 2000; Parrot et al. 2000, Back-Madruga, 2003). It is clear that MDMA can have beneficial effects particularly in terms of treatment and counselling. If MDMA is not a selective neurotoxin it could be a positive drug and employed in therapy. Research is required to find the exact nature of this possible neurotoxicity to humans.

1.7   The Neurotoxic effects of MDMA in non-human animals

The remainder of this chapter will be focus on the possible long lasting neurotoxicity of MDMA. Firstly, it is necessary to summarise the evidence for neurotoxicity within non-human animals. Human MDMA users are not suitable for MDMA research, ethics notwithstanding, as they have varying patterns of polydrug use and varying drug histories. Non-human animal studies do not have this problem so it is easier to attribute any neurotoxicity with MDMA alone.

1.7.1 Explanation for the neurotoxicity of MDMA in non-human animals

Following the consumption of MDMA, in both human and non-human animal studies, there is an initial increase in 5-HT levels followed by a significant reduction in 5-HT levels, during the period of 3-6 hours after its use (Green et al, 1995). This reduction in 5-HT could last up to three days after consumption of MDMA (Curran, 2000; Green et al. 2004). Whether this reduction in CNS 5-HT levels is permanent or levels return to baseline is under considerable scientific debate. The recovery of 5-HT neurons during the period of 24 hours and beyond is controversial with the majority of researchers suggesting that it is during this 24 hour period and possibly longer that 5HT neuronal toxicity begins, which is a long lasting and possibly permanent consequence (Green et al. 1995; Morgan, 2000; Curran, 2000; Back-Madruga, 2003).

More than a decade ago, the first evidence emerged that following the initial increase in 5-HT, MDMA and MDA (3,4-Methylenedioxyamphetamine) produced selective toxic effects on brain neurons in almost all non-human species (Frith et al. 1987; Ricaurte et al. 1988; Fisher et al. 1995; Frederick et al. 1997; Scheffel et al. 1998; Ricaurte et al. 2000; Ricaurte et al. 2001; Gurtman et al. 2002; Blessing et al. 2003; Bogan et al. 2003; Bowyer et al. 2003; Buchert et al. 2004; Wang et al. 2004; Garcia Osta et al. 2004; Fornai et al. 2004; Conductier et al. 2005; Escobedo et al. 2005; Galineau et al. 2005; Jones et al. 2005; Mueller et al. 2009; Biezonski and Meyer, 2010; Li IH et al. 2010; Perrine et al. 2010; Mueller et al. 2011). There are several proposed explanations for this MDMA induced selective neurotoxicity as discussed below.

One possible explanation for this MDMA induced toxicity is due to DA. MDMA is an indirect serotonergic agonist, which releases all available CNS 5-HT (Green et al. 1995; Morgan, 2000; Curran, 2000; Parrot et al. 2000, Back-Madruga, 2003). Laboratory studies have shown that MDMA causes DA to release from dopaminergic neurons (Darvesh et al. 2005). Experimental studies indicate that this release of DA can cause neurotoxicity to 5-HT neurons. MDMA initially causes a depletion of 5-HT for a period of up to two weeks. This leaves the SERT empty. Consequently, DA enters the SERT and enters the 5-HT neuron. This DA is neurotoxic to 5-HT neurons and causes damage. Furthermore, DA is broken down by MAO to form hydrogen peroxide. Hydrogen peroxide is highly neurotoxic to neurons and results in oxidation of the 5-HT cell (Darvesh et al. 2005). This oxidation causes the 5-HT axon terminals to degenerate, causing damage and eventual neuronal death. This is important

as recreational MDMA users often co-use MDMA with other recreational drugs that increase DA levels (Hamida et al. 2009; Daza-Losada et al. 2009). This could potentially increase the possible neurotoxicity of MDMA (Table 1.1).

A second possible suggestion for MDMA neurotoxicity includes MDMA-induced hypothermia and free-radical formation (Cadet et al. 1998, Kreth et al. 2000; Boot et al. 2000; Camarero et al. 2002; Zhou et al. 2003; Simic and Malicevic, 2008). Further investigations need to form conclusive answers whether DA is linked with the hyperthermia and free radical theory. Clearly, MDMA users are likely to be consuming MDMA in a manner, which will increase the potential neurotoxic behavioural and psychological effects.

1.7.2   Evidence for neurotoxicity in non-human animals

Over the past 25 years there have been numerous non-human animal studies indicating MDMA is a selective 5-HT neurotoxin (Frith et al. 1987; Ricaurte et al. 1988; Fisher et al. 1995; Frederick et al. 1997; Scheffel et al. 1998; Ricaurte et al. 2000; Gurtman et al. 2002; Ricaurte et al. 2001; Blessing et al. 2003; Bogan et al. 2003; Bowyer et al. 2003; Buchert et al. 2004; Wang et al. 2004; Garcia Osta et al. 2004; Fornai et al. 2004; Galineau et al. 2005; Conductier et al. 2005; Escobedo et al. 2005; Jones et al. 2005; Mueller et al. 2009; Biezonski and Meyer, 2010; Li IH et al. 2010; Perrine et al. 2010; Mueller et al. 2011). Anatomical damage to 5-HT neurons has been demonstrated via the use of immunocytochemical methodologies (Ricaurte et al. 2000) and antibody staining (Ricaurte et al. 2000).

Experimental non-human animal studies demonstrate that MDMA induced neurotoxicity is specific, resulting in a decrease in 5-HT content to selective brain regions, mainly the dorsal raphe nuclei (Mokler, 1987; Ali et al. 1990). The dorsal raphe nuclei projects to the following regions: (i) cortex, (ii) hippocampus, (iii) limbic system, (iv) hypothalamus (Green et al. 2004) and, (v) Striatum (Schnieder 1973; Sachs et al. 1975; Wiklund et al. 1978; Bjorklund et al. 1979; Levitt et al. 1980; Jonsson et al. 1982; Frankfurt et al. 1984; Gustafson et al. 1987; Fritschy et al. 1992; Ricaurte, 2000; Boot et al. 2000; Mueller et al. 2009; Perrine et al. 2010; Biezonski and Meyer, 2010; Li IH et al. 2010; Mueller et al. 2011). This implies that these brain areas are affected by MDMA induced neurotoxicity.

Non-human animal studies clearly demonstrate that MDMA is a 5-HT neurotoxin and is selective to certain regions of the brain; therefore it is likely to result in psychological and behavioural disturbances.

1.7.3   Long lasting evidence in non-human animals

So far, the studies have been limited to acute neuroanatomical damage. There is, however, mounting evidence for possible MDMA induced long lasting damage to 5-HT.

Exposure to MDMA resulting in selective 5-HT neurotoxicity has been demonstrated in a number of species: rats, guinea pigs, squirrel monkeys, cynomolgus monkeys, rhesus monkeys and baboons (McCann et al. 1997; Battaglia et al. 1988; Green et al. 1995; Morgan, 2000; Green et al. 2004). In all the above species, studies have found that MDMA is highly selective, affecting 5-HT containing neurons almost exclusively (Commins et al. 1987). Interestingly, the mouse is the one species that is resistant to MDMA-induced 5-HT injury; however, at high doses it can also develop a persistent loss in brain 5-HT markers (Stone et al. 1986).

Experimental non-human animal studies reveal that 5-HT nerve terminals and axons 'whither away' following exposure to MDMA; reports indicate that if regeneration occurs it fails to return to complete normality (Battaglia et al. 1988; Green et al. 1995; Morgan, 2000).

In one particular study, 4 days of exposure to MDMA resulted in neuronal damage that persisted for 7 years in non-human primates. The recovery of the 5-HT neurons was specific to certain brain regions. Specific brain regions that failed to return to normality including the amygdala and hypothalamus; where regeneration tended to be re-organised and hyperinnervated (Fischer, 1995; Green et al. 1995; Curran, 2000; Morgan, 2000). Other brain regions, predominantly the dorsal neocortex, failed to show any recovery (Insel et al. 1989).

Studies from MDMA treated monkeys showed evidence of reorganisation of ascending 5-HT projections; this is similar to the 'pruning' effect' (Fischer et al. 1995, Ricaurte et al. 2000). The 'pruning effect' is a method of describing a tendency for neurons to conserve the quantity of their axon terminal fields; however, there is a loss of synaptic contacts in distant brain regions, which is associated with increased synaptic contacts in more proximal brain areas. Evidence of 'pruning', after MDMA exposure, provides additional support that MDMA is a 5-HT neurotoxin causing long lasting reorganisation of the CNS pathways (Schnieder 1973; Sachs et al. 1975; Wiklund et al. 1978; Bjorklund et al. 1979; Levitt et al. 1980; Jonsson et al. 1982; Frankfurt et al. 1984; Gustafson et al. 1987; Fritschy et al. 1992; Ricaurte, 2000; Boot et al, 2000). These studies clearly indicate that MDMA is a long lasting 5-HT neurotoxin causing long lasting damage, where recovery of neurons leads to possible reorganisation.

Non-human animal studies demonstrate that exposure to MDMA causes specific long lasting damage to 5-HT axons. This can last for periods ranging from months to years following cessation of the drug MDMA (Fisher et al. 1995; Scheffel et al. 1998; Ricaurte, 2000; Bogen et al. 2003; Bowyer et al. 2003; Escobedo et al. 2005; Galineau et al. 2005). Numerous studies have demonstrated that MDMA causes dose-related reductions in CSF 5-HT and 5-HIAA levels, reductions in the density of SERTs, and reductions in the activity of TPH (Green et al. 1995; Ricaurte et al. 2000; Boot et al. 2000, Curran, 2000; Parrot et al. 2000, Morgan, 2000).

The long lasting damage to brain 5-HT neurons are highly selective to MDMA and are not reproducible for other psychostimulant drugs including: cocaine, heroin, LSD and other 5-HT reuptake inhibitors in non-human primates (Dworkin et al. 1988; Balster, 1998; Ricaurte et al. 2000; Fletcher et al. 2001; Goldstein et al. 2005).

In summary, various non-human animal studies have demonstrated that MDMA is a selective 5-HT neurotoxin, in selected brain regions with either lasting damage or reorganisation. The neuroanatomical region, where altered regeneration of neuronal growth has been reported includes: the amydala, hypothalamus, and the cortex (Table 1.3). Furthermore, this 5-HT neurotoxicity is observed in all non-human species animals including rats and monkeys. There have been various methodologies employed including antibody staining and radio-ligand binding. All the different techniques result in the same conclusion being MDMA is a selective 5-HT neurotoxin (Schnieder 1973; Sachs et al. 1975; Wiklund et al. 1978; Bjorklund et al. 1979; Levitt et al. 1980; Jonsson et al. 1982; Frankfurt et al. 1984; Gustafson et al. 1987; Fritschy et al. 1992; Ricaurte, 2000; Boot et al. 2000).

As the doses administered to non-human primates during these experiments are comparable to the doses consumed by humans during a binge weekend it is plausible to propose that similar damage and re-structuring is occurring in human polydrug users; which requires immediate investigation (de la Torre et al. 2004). The amygdala and hypothalamus play a pivotal role in emotion, memory and reward in humans. If like non-human animals studies, MDMA causes neuronal degeneration and re-organisation in humans, it is probable that disruption will occur to psychological and cognitive functioning.

Studies are now needed investigating the psychological consequences of MDMA use in humans. Possible evidence to add to the mounting case that MDMA is a probable selective

long lasting neurotoxin in humans includes the fact that it is a well-known scientific fact that humans are more susceptible to neurotoxic substances than either rats or primates. An example of this is research investigating the effects of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). Results from these studies indicate that MPTP is mildly toxic in rats however extremely toxic in humans (Ricaurte et al. 2000). In rats, a dose of 5 mg/kg of MDMA causes neurodegeneration of 5-HT neurons, which is comparable to the dose consumed by humans (3 mg/kg or more). As this dose of MDMA causes neurotoxic damage in rats, we can hypothesis that the damage to humans could be even more severe (Ricaurte et al. 2000).

Table 1.3   Selective MDMA induced damage in rats

The table provides a summary of the selective neurotoxicity of MDMA in rats as reported by the literature (Schnieder 1973; Levitt et al. 1980; Jonsson et al. 1982; Gustafson et al. 1987; Fritschy et al. 1992; Sachs et al. 1975; Wiklund et al. 1978; Bjorklund et al. 1979; Frankfurt et al. 1984; Ricaurte, 2000; Boot et al. 2000). The table provides details of selective MDMA induced 5-HT damage and whether this selective damage been shown to be long lasting.

Brain Region	5-HT level Reduced	Long lasting neurotoxicity
Amydala	Yes	Yes
Hypothalamus	Yes	Yes
Cortex	Yes	Yes
Dorsal raphe nuclei	Yes	Yes
Hippocampus	Yes	Not Investigated
Striatum	Yes	Not Investigated

1.8   The possible long lasting neurotoxic effects of MDMA in humans

As MDMA is a neurotoxin in non-human animals, it is possible exposure to MDMA results in long lasting damage to humans. Anatomical studies indicate that MDMA is a neurotoxin to specific regions of the brain including the dorsal raphe nuclei, amydala and the hypothalamus (Green et al. 2004). These brain regions are involved in many areas of psychology including: sleep, memory, cognition, mood, motivation, emotion and appetite (Green et al. 2004). If

MDMA were neurotoxic to these brain regions in humans, it would be plausible to conclude that human MDMA users will experience long lasting behavioural and psychological changes including: sleep, memory, cognition, and mood. The following section will review research investigating the consequences of MDMA in humans.

Brain imaging studies using Positron Emission Tomography (PET) and Single Photon Emission Computed Tomography (SPECT) are a method for visualising 5-HT neurons in individuals (Cowan, 2007). These studies have revealed less SERT binding in the brains of frequent MDMA users in comparison to non-frequent MDMA users (Reneman et al. 2001; de Win et al. 2008; McCann et al. 2005; Cowan, 2007, Nifosi et al. 2009). However, these PET and SPECT findings are not consistent (Cowan, 2007). Results have varied with some studies reporting mild regional brain differences between 5-15%, whilst other studies have reported more substantial differences ranging from 15-70% (Reneman et al. 2001; McCann et al. 2005; de Win et al. 2008; Nifosi et al. 2009). PET and SPECT studies have failed to demonstrate a difference in SERT binding for MDMA polydrug users that have abstained from MDMA for more than 20 weeks (Selvaraj et al. 2009). The authors concluded that this reduction in 5-HT is an acute effect rather than a long-lasting permanent effect as indicated by non-human animal studies.

One of the most compelling MDMA human studies involves the use of PET. A technique that uses a radioligand that selectively labels SERT (McCann et al. 1998). MDMA polydrug users displayed lowered regional and global SERT binding in comparison to a non-MDMA control. PET scan abnormalities found a positive correlation between degree of reduced 5-HT binding and the participants' self-reported MDMA use.

In addition to the imaging studies, other studies include self-reported behavioural studies. Schifano et al (1998) investigated 150 MDMA users whom had 'used MDMA at least once'. The results showed that 31% of MDMA users' self-reported depression, 28% self-reported experiencing psychotic episodes and 27% self-reported cognitive impairment. Participants were recruited whilst attending a drug treatment service, this suggests that all participants were polydrug users; including a majority being heroin addicts. The study found a positive correlation between the self-reported amount of MDMA tablets consumed and psychiatric symptoms (Schifano et al. 1998). The conclusions from this study are limited as there was no control group and participants were in treatment at the time of testing, which may have acted as a confounding variable, however without robustness in the methodology this cannot be confirmed.

Psychiatric cases studies have provided further evidence of possible MDMA induced psychological damage (Cohen et al. 1997). Results have found that MDMA users experience panic attacks, depression and general psychotic symptoms following abstinence from MDMA (McGregor et al. 2003; Milani et al. 2004; Thompson et al. 2004). Within the last 15 years, reports have began to look at the long lasting effects of MDMA consumption and have found that MDMA use can result in psychiatric changes including: long-term depression (McCann et al. 1992), insomnia (McGuire and Fahy, 1991) and hallucinations (Creighton et al. 1991). These individual cases have found that depression, insomnia and hallucinations continued to persist 1 year after drug abstinence (Green et al. 2004). Chronic psychiatric symptoms following the regular use of MDMA include: depersonalisation (McGuire et al. 1994), obsessive-compulsive symptoms (Cassidy and Ballard, 1994), flashbacks (Creighton et al. 1991), and panic attacks (McCann and Ricaurte, 1991; Pallantini and Mazzi, 1992; McGuire et al. 1994).

There are a number of interpretative difficulties with evidence from case studies. Firstly, the sketchy nature of the interpretation of the evidence from these case reports makes it very difficult to determine the risk to the average recreational MDMA user for psychiatric disorders, as current epidemiological evidence suggests that all of these disorders occur with fairly high frequency within the normal population per se. Consequently these small figures indicate that the occurrence of these psychiatric disturbances could be coincidental, having no immediate link to the exposure to MDMA. On the other hand, the majority of these adverse psychiatric problems are linked to lowered 5-HT levels implicating serotonergic neurotoxicity. However, research has clearly demonstrated that lowered 5-HT is reported in most cases of psychiatric disorders irrespective of MDMA use. The case studies failed to report if there was a family history of psychiatric disorders. If the psychiatric problem existed beforehand, the use of MDMA is merely a form of self-medication. These case studies failed to monitor whether these symptoms continued to remain the same, or whether they recovered with time, or got progressively worse with time.

Further studies involve participants performing a battery of psychological tests. These studies investigating current MDMA polydrug users have reported that many psychological areas are affected by the consumption of MDMA including: memory (Curran et al. 2003; Daumann et al. 2003; Daumann et al. 2004), the ability to reason verbally, to sustain attention (Parrot and Lasky, 1998; Morgan et al. 1999; Curran et al. 2003; Gouzoulis-Mayfrank et al. 2005) and maintain regular sleep patterns (Soloff et al. 2000; Balogh et al. 2004; Gardani et al. 2005). Further studies have indicated that MDMA users have milder personalities including lowered scores on personality tests than a matched non-MDMA control group (Dughiero et al, 2001).

The argument remains whether MDMA use caused the milder personality or whether the milder personality resulted in MDMA use (Parrot, 2000; Soar et al. 2001).

Several studies have investigated the concentration of CSF 5-HIAA in regular MDMA users and found a 25% decrease (Ricaurte et al. 2001). This evidence could provide further support for the prediction that MDMA is a selective serotonergic neurotoxin. There is still considerable debate amongst researchers whether lowered serotonin levels actually indicates selective 5-HT neuronal damage or whether it merely indicates that MDMA users already have a lowered level of the chemical and rely on MDMA as an albeit temporary form of self-medication.

Self report studies suggest that a substantial number of MDMA users may use the drug in a way that could increase the risk of 5-HT neurotoxicity (Morgan, 2000; Parrot et al. 2000; Curran, 2000; Aldridge et al. 2008). In one study of 329 Australian MDMA users, one in six users had injected with MDMA at some point (Topp et al. 1999). Further results from this study indicated that 42% of the MDMA users had used MDMA continuously for a period of 48 hours or more at least once in the past 6 months. It can be postulated the intake of multiple tablets on a single occasion is increasing (Boot et al. 2000; Curran, 2000; Parrot et al. 2000). Research suggests that neurotoxicity is dependent on dosage. The higher the dosage and exposure level the more severe the neurotoxicity (Green et al. 2004). These epidemiological studies indicate that MDMA users are continually increasingly the dosage of MDMA and exposing themselves to MDMA for longer periods, any psychological consequences associated with MDMA use will inevitably increase.

Consumption of MDMA often occurs in the dance scene, where the environment includes: increased temperatures, crowded space, noise and limited access to drinking water. These environmental factors have been previously associated with increasing the risk of hyperthermia, which exacerbates MDMA neurotoxicity in rats (Malberg and Seiden, 1998; Cornish et al. 2003; Fantegrossi et al. 2003; Green et al. 2004; Sanchez et al, 2004). These studies indicate that the external environment in which humans use MDMA may increase the likelihood of 5-HT toxicity and further psychological disturbance. It seems using MDMA in the dance scene will increase possible neurotoxicity.

Research seems to indicate that people who take MDMA just a few times in their life are risking long-term, permanent problems with learning and memory (Gouzoulis-Mayfrank et al. 2000; Mechan et al. 2001; Cole et al. 2002; De Win et al. 2008; Green et al. 2004; Murphy et

al. 2009). At present, there is a gap in the research providing sufficient evidence demonstrating the level of exposure of MDMA that is required in humans to cause disruptions to psychological functioning. The majority of these human behavioural studies have looked at the immediate acute effects of MDMA. There is currently insufficient evidence demonstrating whether the psychological problems are acute, or whether, they persist and if so how long do they continue after abstinence from MDMA. Secondly, whether this MDMA induced damage progressively worsens with the normal aging process. That is, does the trajectory of age related deficits continue at a new lower level following initial MDMA-induced neurotoxic damage?

1.9   Recreational drugs of abuse

The major problem with the majority of previous research investigating the current psychological effects of MDMA is that these studies failed to control for other recreational drugs. Arguably, the psychological deficits could be caused by the consumption of and/or the combination of other recreational drugs including: cannabis, amphetamine, alcohol and cocaine.

MDMA users co-use MDMA with other recreational drugs and have a history of general recreational drug use. These additional recreational drugs includes: nicotine, cannabis, cocaine, alcohol, heroin and amphetamines. MDMA polydrug users are often exposed to a cocktail of recreational drugs, it is important to be able to attribute any negative psychological consequences to the exposure of MDMA only and to make sure the psychological deficits are related to MDMA and not any other recreational drug (Curran 2000; Parrott, 2001; Morton, 2005).

The research on recreational drugs is far too extensive to review in this thesis. However, in summary, it has indicated that certain recreational drugs of abuse are associated with a decrease in psychological and cognitive performance (Balster et al. 1988; Dworkin et al. 1988; Di Ciano et al. 1995; Horan et al. 2000; Fletcher et al. 2001; Goldstein et al. 2005). These deficits are tested using a battery of psychological tests, including cognitive and behavioural tests. Many recreational drugs are implicated in lowered cognitive and psychological functioning including: alcohol, nicotine, cannabis, cocaine, amphetamine and meta-amphetamine (Di Fort et al. 2007; Yucel and Lubman, 2007; de Wit, 2009; Stalnaker et al. 2009).

Recreational drug use, as a whole, is increasing worldwide (European monitoring centre for Drugs and Drug Addiction, 2008). MDMA users are generally polydrug users. The most commonly abused recreational drugs (alcohol, nicotine, cannabis, cocaine and amphetamine) are associated with long lasting behavioural and cognitive consequences. It is important that any deficits in psychological functioning reported by MDMA research is due to MDMA itself and not the consequence of other recreational drugs. It is for this reason it is extremely important to control for all other recreational drugs using control groups and statistical methods.

1.10   Summary of research from 2007 - 2011

It is necessary to provide a summary of human and non-human animal MDMA research from 2007 onwards. Even though the hypotheses of this thesis were formulated during the period 2001, it is still remains a relevant and novel area of research in 2011. Robust human psychological studies are still required investigating the long lasting consequences of MDMA.

1.11   Summary of non-human animal and human MDMA studies (2007-2011)

Before 2007, there was evidence that MDMA had been found to be neurotoxic in a number of species, from rodents to non-human primates. However, the data surrounding the sensitivity of different brain regions to MDMA toxicity was questionable. Data examining recovery following MDMA exposure in non-human animal studies was even scarcer. Since 2007, there have been a smaller number of studies investigating the neurotoxicity of MDMA. In summary, the human studies investigating the effects of MDMA on psychological functioning since 2007 have been rather limited. No study during this period had investigated the possible long lasting consequences of MDMA in abstinent polydrug users. Secondly, there are limited studies employing robust control groups controlling for the use of additional recreational drugs.

Kirilly (2010) investigated the SERT mRNA expression in the brainstem and raphe nucleus, 5-HTT immunoreactive fibre density in several brain regions and 16 functional measures of sleep in response to a single dose of MDMA (15mg/kg) in rats. Behavioural experiments were performed 21 days after MDMA exposure. The results found changes in SERT mRNA expression in raphe nuclei. There were increases 7 days after exposure followed by transient decreases 21 days later. Significant reductions (20-40%) in 5-HTT immunoreactive fibre density in most regions of the brain were observed between 7-21 days after exposure to MDMA. Damage occurred in all cortical regions. Finally, functional changes observed in

rapid eye movement sleep latency and increased delta non-REM sleep; however, this was normalised and returned to baseline after 180 days. The authors concluded that a single dose of MDMA resulted in long lasting impairment of the serotonergic system in the rat, which can led to long-lasting cognitive, learning, memory and mood deficits. Kirilly concluded this would be particularly worse if there was a genetic or certain environmental factor(s) present and future studies should control for this (Kirilly, 2010).

Hernandez-Rabaza et al. (2010) investigated the effects of MDMA alone or in combination with alcohol/cocaine on memory performance in adolescent rats. The results found that only rats exposed to combinations of alcohol/MDMA/cocaine exhibited significant memory deficits. The authors concluded that exposure to MDMA and alcohol during adolescence caused neurotoxic alterations and persistent memory deficits, highlighting the risks to modern day MDMA/alcohol drug users (Hernandez-Rabaza et al. 2010).

Scholey et al (2011) investigated the use of the internet as a means of collecting drug related self-reported data. They asked 49 participants to self-report their drug history. The results found a correlation between MDMA hair analysis, self-reported MDMA use and depression levels. They concluded that psychoactive drugs influence long-term mood and cognition (Scholey et al. 2011).

There has been research using human neuroimaging techniques to SERT binding in MDMA users (Kish et al. 2010). The results found that SERT binding occurred significantly less throughout all cerebral cortices (range -19 to -46%) and the hippocampus (mean -21%). These reductions correlated to self-reported drug use including number of years and dosage. In terms of behaviour, the MDMA group reported mild mood disturbances, modest deficits on attention, executive functioning and memory tasks (Kish et al. 2010). This study controlled for exposure to other recreational drugs using statistical analysis. However, the study would have been more robust if they had included separate control groups. Secondly, the study did not investigate the long lasting consequences as participants abstained from MDMA only for a mean period of 45 days prior to participation in the study.

With regard to memory studies, Blagrove et al (2010) investigated the role of MDMA on declarative/procedural memory in MDMA users. The experiment involved a retest, two experimental sessions 24 hours apart, so that the memory consolidation function of sleep was assessed. The study included three groups: drug-naïve control (n=24), recent MDMA users (n=25) that had consumed MDMA at least 3 days prior to the first testing session, and abstinent users (n=17) where users had not used MDMA for 8 days prior to testing. The study

concluded that greater lifetime consumption of MDMA, cannabis and cocaine reflected declarative memory deficits. However, MDMA did not affect memory consolidation. The study failed to monitor the long lasting consequences of MDMA on memory (Blagrove et al. 2010). This study suggests that as MDMA users are polydrug users, it is essential to control for the effects of other recreational drugs.

Mathews and Bruno (2010) investigated the association between depression and MDMA exposure. One hundred regular MDMA polydrug users were interviewed concerning MDMA use, depression and psychological distress. The results concluded that 23% of the sample suffered from an episode of recent depression. The authors acknowledged this percentage of depression was higher than the general population. The level of depression was associated with drug using factors: dosage of MDMA, cannabis and polydrug use, and binge use of illicit drugs (Mathews and Bruno, 2010). The study failed to control for other recreational drugs and did not include a control group. The study did not investigate the long lasting effects of MDMA.

Scott et al (2010) investigated the role of genetics (polymorphism of the SERT gene) and environmental factors (stressful lifetime events, trauma, anxiety and polydrug use) on risk factors for depression in association with previous MDMA use (n=184). The study concluded that only lifetime trauma and stressful events were linked to increased depression. The authors stated that future studies need to report environmental factors and whether MDMA exacerbates pre-existing conditions (Scott et al. 2010).

It has been proposed that the variability in the range of results found concerning MDMA neurotoxic damage on memory and executive functioning could be subjective to the difficulty of the task (Brown et al. 2010). In their study, they compared MDMA users with non-MDMA controls on differing complexity tasks (low, moderate and high). The results concluded that the more complex tasks were associated with more pronounced deficits than the low complexity tasks. They concluded that future MDMA studies needed to employ tasks that involve the use of multiple brain regions or greater contribution from the frontal lobe (Brown et al. 2010).

Randall et al (2009) performed a laboratory-based sleep study on 7 MDMA users and 13 non-MDMA controls. The MDMA users were administered 2mg/kg of MDMA and studied on 3 sessions for 3 nights (baseline, treatment and recovery). The study concluded that MDMA causes acute sleep disruption including REM dysfunction (Randell et al. 2009). This study only compared MDMA users and non-MDMA users, so they failed to control for the history

38

of previous recreational drugs. The study examined only the acute effects of MDMA and not the long lasting consequences.

McCann et al (2009) investigated the effects of MDMA on sleep and cognition in a study that employed 19 abstinent MDMA users (abstained from MDMA for 3 weeks prior to the study) and 21 controls. The participants under went a 40 hour sleep deprivation experiment and were asked to complete a cognitive test battery during this period. The results found that during the sleep deprivation task, only MDMA users were more impulsive and less accurate on the memory task. The authors concluded that future executive functioning and memory tasks need to take into account sleep disturbance (McCann et al. 2009). This study failed to investigate the long lasting consequences of MDMA on sleep, executive functioning and memory.

A web-based study investigated the link between MDMA and sleep (Carhart-Harris et al. 2009). The study included a total sample of 1035 drug users, of which 31 were MDMA only and 58 abstained MDMA only. Current and former MDMA users were compared against controls on: 1) sleep quality, 2) sleep latency, 3) night time awakenings and 4) total sleep time. Both current and former MDMA users complained of sleep disturbances in comparison to non-MDMA controls. Even though abstinence from MDMA was monitored in this study, the period was only 28 days. The MDMA only group had a previous drug history including exposure to cocaine, amphetamine, ketamine, and opiates on less than 10 occasions. They had previously used cannabis use but not within a month of participation of the study (Carhart-Harris et al. 2009). The study failed to statistically control for other recreational drug use. It did not investigate whether these deficits in sleep had a detrimental effect on other psychological functions including: memory, executive functioning, impulsivity, and depression.

A two-year follow up study monitored the neuropsychological profile and cognitive changes of 37 current MDMA/cannabis polydrug users, 23 current cannabis/non-MDMA users, and 34 non-illicit drug users (de Sola Llopis et al. 2008). They measured attention, executive functioning, memory and learning. After two years, the MDMA/cannabis group showed persistent deficits on verbal fluency, working memory and processing speed. This study is the first study to investigate the possible long lasting effects of MDMA. However, the study only monitored MDMA users for a period of two-years. The control of other illicit drug use was rather limited. This study provides evidence of long-term cognitive impairment due to MDMA/cannabis (de Sola Llopis et al. 2008).

In brief, the non-human animal and human studies post 2007 have provided further evidence for the possible acute and long lasting effects of MDMA. These studies have suggested that other psychological functions are needed to be monitored in cognitive tasks: memory, sleep, impulsivity and depression. The human studies have poorly controlled for the effects of other recreational drugs including: alcohol, cocaine, amphetamines and ketamine, with most of the studies not even relying on advanced statistical methods. No study to date has investigated the long lasting consequences of MDMA in abstaining ex-MDMA polydrug users.

1.12   The rationale for this study

Gaining greater understanding and knowledge of the effects of MDMA on psychological and behavioural functioning will be beneficial both scientifically and clinically. Research investigating the long lasting psychological effects of MDMA will help to modify and formulate appropriate therapeutic intervention strategies to rehabilitate or compensate for lost abilities due to the negative consequences of using MDMA, since at present there seems to be no general acceptable guidelines for treatment concerning hypothesised MDMA-induced psychological and behavioural deficits.

Finding reliable and valid evidence that MDMA can cause neurotoxicity to human users and the particular consequences of using MDMA will help to educate current and future MDMA users with the intention of controlling and possibly preventing future use. MDMA has many positive redeeming features including its positive effects of introspection and emotions. If the negative and long lasting effects of MDMA are highlighted and could possibly be eradicated MDMA could again be used in the clinical setting.

A major issue with MDMA research surrounding brain and psychological neurotoxicity are the fluctuations within the published work. Over the past 30 years, research has failed to find consistent results. The majority of studies over the past 20 years have rightfully admitted limiting factor of the methodological flaws associated with their research including limited control groups, and biased sampling of participants like small samples.

In the past 10 years, research has been more robust, however, there are still many methodological issues making it difficult to draw conclusions concerning the long-lasting effects of MDMA on psychological functioning. Research needs to be replicated with more stringent methodologies employed, so robust conclusions can be drawn.

Cognitive and psychological impairments could play a pivotal role in the development of addictive behaviours in addition to being an inhibitory factor for rehabilitation success for substance abusers. Thus, it could be proposed that if substance users exhibit problems with attention and cognitive functioning due to their addictive problems, it would consequently be harder for them to adapt to rehabilitation programs. In particular, those programs require generating new behaviours or techniques aimed at achieving a desired goal; being able to provide adequate motivation in order to be successful in their rehabilitation program; to plan behaviours that fail to accomplish an immediate reward; and finally finding the ability to inhibit inappropriate behaviours or desires.

There are various reasons behind researching the consequences of MDMA use including the fact that results will provide greater understanding of 5-HT and its role in normal psychological functions. This research will provide evidence whether 5-HT damage is reversible or persistent, and will provide an indication of the dosage of MDMA needed in humans for cognitive and other psychological disruptions to occur. The majority of MDMA users feel that it is a harmless drug, with little long lasting effects (Curran, 2000; Parrot, 2001; and Morton, 2005). If the precise long-term effects of MDMA are discovered, users could be educated and it may prevent them from further consumption of the psychedelic drug, whilst also preventing others from experimenting with the drug.

1.13   The research objectives and proposed study

Although there is sufficient evidence indicating that MDMA is neurotoxic resulting in long lasting compensatory alterations on specific brain regions in non-human animals, there is currently a lack of research providing sufficient evidence demonstrating whether similar long lasting effects occur in humans. The issue of the dosage of MDMA required in humans to cause this neurotoxicity is questionable due to species sensitivity of toxic compounds. The frequency, dose and the route of administration of MDMA will play a pivotal role in its possible neurotoxicity. The aim of the current research is to indirectly investigate the long lasting effects of MDMA, by investigating the behavioural and psychological consequences of MDMA use in humans.

By using validated and reliable psychological tests, it is possible to infer the functional sequelae of the putative MDMA-induced serotonin damage. This will highlight the amount of MDMA consumption required for psychological disruptions to occur and secondly to demonstrate whether the symptoms persist indefinitely, if they recover with time or if they get

progressively worse with time. As these tests have previously been linked to normal serotonin activity it is possible to speculate that if MDMA users differed from non-MDMA control users it maybe a result of serotonergic neurotoxcity.

MDMA has been a recreational drug of abuse since the early 1980s. It is plausible to suggest, that now nearly 20-30 years later, there will be a number of MDMA users that had previously been exposed to MDMA and subsequently abstained from MDMA for more than five years, thus allowing us to research the long lasting effects of MDMA and possibly the relationship between MDMA use and its effects on psychological functioning with respect to the normal aging process. To date, no previous study, using human participants, has investigated the psychological and behavioural consequences of MDMA, after five years of abstinence from the drug; making this a novel study.

This study aimed to investigate the relationship between serotonin related psychological functions and exposure to MDMA (Figure 1.4). It compared the relationship between the severity of each psychological problem and the amount of MDMA consumed in a lifetime. The dose-response relationship between severity of each type of psychological problem and the number of years of abstinence from the MDMA was investigated (Figure 1.5).

Figure 1.4: Schematic dose-response curve

This figure shows a typical dose-response curve. The diagram provides the hypothesised relationship between the severities of the psychological problems compared with the number of years of abstinence. These psychological problems include memory deficits, depression, impulsivity, executive functions and sleep. The number of drug free years range from 0 years (current users) to more than 5 years (past-users). The figure demonstrates some possible outcomes; a – no change in the severity of the psychological problem as time progresses; b – a decrease in the severity of the psychological problem as time progresses; c – as time progresses there is an increase in the severity of the psychological problems. Finally not shown on the figure, is there may be no association between severity of the psychological problem and number of drug free years.

Number of drug (MDMA) free years

* Includes depression, executive functioning, sleep, impulsivity and memory
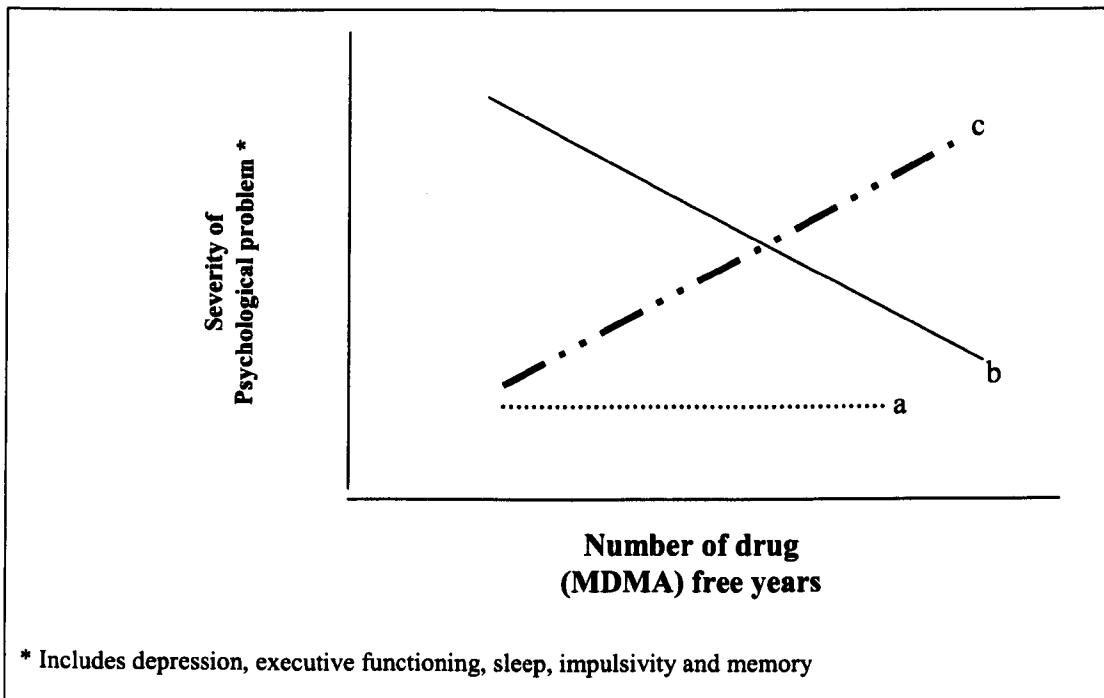
Figure 1.5: Schematic illustration displaying the predicted relationship between MDMA and lifetime consumption

The figure illustrates the hypothesised severity of the psychological problems in relation to the amount of MDMA consumed in a lifetime. The psychological problems include: memory deficits, depression, impulsivity, executive functions, and attention. The figure shows some hypothesised relationships between the severity of the psychological disorder and the amount of MDMA consumed; a – there is no change in the severity of the psychological problem and the amount of MDMA consumed; b – there is a positive increase in the severity of the psychological problem as the amount of MDMA consumed increases; c – there is an initial increase in the severity of the psychological problem as the amount of MDMA consumed increases however this initial increase in the severity of the psychological problems will eventually remain consistent irrespective of continued exposure to MDMA .

Amount of ecstasy
consumed in lifetime

* Includes depression, executive functioning, sleep, impulsivity and memory
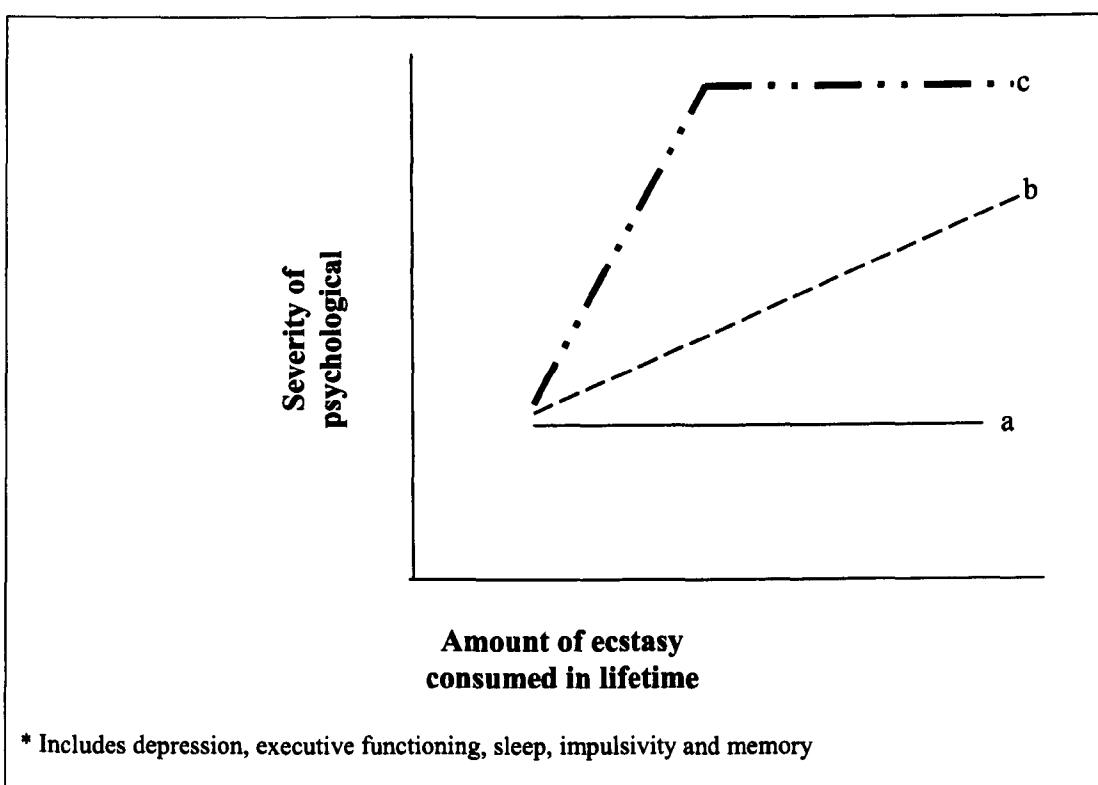
The originality of this study lies in the fact that no previous study within the field of biological psychology has investigated, in one study, the 'pseudo-dose-response' curve demonstrating the relationship between the amount of MDMA consumed and the severity of psychological problem. This study will investigate whether these psychological deficits are acute or long lasting. This study will employ more stringent control groups than previously used in other studies; comparing past and present MDMA users. Finally, the study will investigate whether executive functioning is dependent on the normal functioning of memory, sleep, depression, and impulsivity within drug users.

44

1.14   The proposed study

The techniques employed in this study include measuring for disturbances in executive functioning (Wisconsin Card Sorting Test, and Tower of London), memory (Weschler Memory Scale - Revised), impulsivity (Barratt Impulsiveness Scale), sleep (Pittsburgh Sleep Inventory) and depression (Becks Depression Inventory – version II). This study decomposed each of the functions (executive functioning, memory, impulsivity, and depression) into separate subdomains. The study investigated whether lower order functions (sleep, depression, impulsivity and memory) affect higher functions being executive functioning.

The study compared the pattern of MDMA use between current polydrug MDMA users and past polydrug MDMA users that have abstained for more than 5 years monitoring characteristics like age of initial onset, frequency of use and dosage.

Based on previous results from both non-human animal and human research, the following can be hypothesised. It is predicted that current MDMA users will use MDMA in a more harmful way than past MDMA users (Chapter 2). Experiments testing memory, executive functioning, impulsivity, sleep and mood will find that current polydrug MDMA users will show a decrease in performance in relation to a non-MDMA control group (Chapter 3,4,5,6 & 7). It is hypothesised that the results from the current study will find no difference in psychological performance between the current polydrug MDMA users that had consumed the drug within the last 6 months and the past polydrug MDMA users that had consumed the drug more than 5 years ago in comparison to matched age/occupation control groups (Chapter 3,4,5,6 & 7). There will be a positive dose dependent relationship between level of exposure of MDMA and severity of psychological problems (executive functioning, memory, sleep, depression and impulsivity) (Chapter 3,4,5,6 & 7). There will be a positive relationship between the performances on executive functioning tasks and depression/memory/impulsivity/sleep functioning (Chapter 7).

Chapter 2 – Drug History Questionnaire and Pilot Study

2.1 Aims and objectives

There are two sections to this chapter. The first includes piloting the Drug History Questionnaire (DHQ). The second section provides a profile of the demographics of past and present MDMA polydrug users during the period 2002-2007.

2.2 Pilot Drug History Questionnaire

Over the last two decades, research into drug addiction has increased substantially. An example of this increase would be that in 1996 there were 13 drug-related peer reviewed journals in comparison to 27 in 2007 (European Monitoring Centre for Drugs and Drug Addiction, 2008). To date there is not a single publicised assessment tool specifically targeted at MDMA polydrug users asking basic demographic details and full drug history for a non-clinical population. In order to collect data, the development of a new questionnaire (the DHQ) was required, which included sections on demographic details and also recreational drug use.

In brief, this DHQ needed to include: (1) Essential demographic information: gender, age, residential area, ethnicity, education, and martial status, (2) Health information: present and previous medical problems, depression, psychiatric disorders, (3) Family information: family history of recreational drugs/alcoholism, and (4) Finally, history of recreational drug use including information on any recreational drugs used, the amount consumed, the length of time used, and any periods of abstinence from the recreational drugs.

The second section of this chapter addresses two main questions: (1) Whether MDMA's popularity has increased or declined despite reports over the last decade of its possible psychological deficits and potential structural changes to the brain, during the period 2002-2007, (2) To investigate the demographics of a sample of drug users past and present to provide a profile of MDMA polydrug users within South East England, during the period 2002-2007.

2.2.1 Justification for question inclusion in the DHQ

Clearly, the DHQ needed to document use of all recreational drugs. On the whole, all recreational drugs of abuse to some degree influence areas of psychological health including: mood, memory, attention, impulsivity, decision-making, planning, and psychotic behaviour (Soar et al. 2001; Daumann et al. 2004; Dafters et al. 2004; Daniulaityte et al. 2010; Chou et al. 2011). Previous research examining the psychological consequences of MDMA have failed to robustly control for these recreational drugs (Soar et al. 2001; Daumann et al. 2001; Brecht et al. 2002; Back-Madroga et al. 2003; Morris. 2003; Parrot. 2003; Daumann et al. 2004; Dafters et al. 2004; Moron. 2005; Murphy et al. 2009). This study aimed to stringently control for all recreational drugs that may cause psychological problems: alcohol, nicotine, amphetamine, cannabis, cocaine, heroin and ketamine. This aimed to increase confidence levels in asserting that it is indeed MDMA causing the psychological deficits.

The DHQ required a section on recreational drugs co-used at the same time as MDMA. Epidemiological studies suggest that present and past recreational drug users tend to co-use MDMA with many other substances (Curran, 2000; Parrott, 2001; Morton, 2005; Ramo et al. 2010). This array of drugs needed to be reported in this research. The majority of recreational drug users misuse many different types of recreational drugs: alcohol, nicotine, cannabis, MDMA, amphetamine, opiates and cocaine (Curran, 2000; Parrot, 2001, Morton, 2005; Ramo et al. 2010). A possible rationale for this pattern of use is that all of these drugs have diverse acute and long lasting effects. Certain effects are more desirable at certain times, or in particular situations (Pope et al. 2001). MDMA is a popular drug of abuse and frequently consumed during the weekend at raves (Curran et al. 1997; Parrot. 2009). MDMA use results in an uncomfortable aftermath followed by feelings of depression and lethargy (Parrot et al. 2004). During the week, most MDMA users will use other recreational drugs (such as alcohol and marijuana) to counter balance any negative effects: fatigue, insomnia and depression (Winstock et al. 2001).

Secondly, a cocktail of drugs may have a very different effect than the drug alone with cross-tolerance occurring (Scholey et al. 2004; Galineau et al. 2005). DA levels attenuate the neurotoxic effects of MDMA in non-human animal research (Galineau et al. 2005; Granado et al. 2011). Many recreational drugs co-used with MDMA have been shown to increase DA levels substantially (cocaine and amphetamine) (Peraile et al. 2010). Caution is needed when interpreting findings derived from polydrug MDMA users. Conclusions concerning MDMA neurotoxicity need to be formed on a robust methodology. With previous research it is

difficult to determine if the acute effects are due to MDMA alone or in combination with other recreational drugs (Bankson and Yamamoto, 2004). The DHQ documented whether MDMA is co-used with other recreational drugs. This improved the methodology and increased confidence in derived conclusions.

Detailed questions outlining the frequency of drug use were incorporated into the questionnaire. Any period of abstinence from any type of recreational drug paying particular attention to MDMA was documented. Published reports indicate periods of abstinence from MDMA can result in the reversal of psychological dysfunction (Reneman, 2002; Haddad et al. 2002). More evidence is required concerning long lasting effects, particularly targeting human MDMA users, as the bulk of the current data comes from non-human animal studies (Zakzanis and Young, 2001a, 2001b). This study was interested in the long lasting consequences following MDMA abstinence.

Serotonin pathways innervate most anatomical regions of the brain affecting psychological functions including emotional disorders (Christianson, 1997; Crockett et al. 2010). Serotonin levels can be manipulated within the human body by diet (Rissanen, 1994). Synthesis of serotonin within the CNS is dependent on dietary tryptophan, which is up taken by the blood and crosses the blood brain barrier (Rissanen, 1994; Yao et al. 2011). Protein rich foods contain little tryptophan in relation to other large amino acids. In comparison carbohydrates stimulate insulin secretion, increasing the uptake of large neutral amino acids into the muscles thus allowing tryptophan to cross the blood-brain-barrier effortlessly (Rissanen, 1994; Beyth and Baratta, 1996). Tryptophan depletion triggers rapid lowering of mood (Christianson, 1993; Rissanen, 1994; Toker et al. 2010). Certain foods containing carbohydrates will facilitate an upsurge in 5-HT levels whilst proteins can diminish 5-HT levels subsequently causing a shift in mood (Christianson, 1997; Curzon, 1985; Wurtman, 1990; Jimerson et al. 1990; Toker et al. 2010). It is reasonable to propose that if MDMA is neurotoxic to 5-HT neurons, MDMA users may try to maintain sufficient levels of 5-HT via diet in particular by increasing levels of carbohydrates. Alternatively, MDMA users may already have lower than average levels of brain 5-HT, therefore they consume MDMA and diets high in carbohydrates as a form of self-medication, ultimately trying to increase brain 5-HT. The questionnaire, therefore, paid particular attention to the drug user's diet. Additional details recorded included whether the diet differed only when they exposed to MDMA or whether MDMA users' diets generally differ from other non-MDMA recreational drug users.

Pharmacology has revealed that the effect of a drug is dependent on the route of administration (Green et al. 2004; Kinner and Degenhardt, 2008). Intravenous injection

results in the drug immediately entering the blood stream. This route of administration will ultimately result in a quicker response in comparison to taking a pill orally, which requires gastrointestinal absorption (Curran, 2000; Parrot, 2001; Green et al. 2005). Most recreational drugs can be administered in a variety of ways. MDMA can be ingested orally, nasally, rectally and via intravenous injection (Parrot, 2001). This needs to be considered when investigating MDMA use and its overall effect on psychological performance. If MDMA is neurotoxic it is plausible that intravenous injection would result in enhanced neurotoxicity than oral administration. The questionnaire, therefore, controlled for all routes of administration of MDMA.

In terms of drinking alcohol, current opinion suggests that binge drinking can be more harmful than regular drinking. Binge drinking is where the intention is to become intoxicated as quickly as possible; consuming large amounts of alcohol. It is common in males and young adolescents (Offending Crime and Justice Survey, 2003). As binge drinking is associated with increased health and psychological consequences compared with regular drinking, it is postulated that binge MDMA users may develop more severe and longer lasting consequences compared with regular users.

The environment in which a drug is administered has an effect on the response of the drug. Studies have demonstrated that crowded environments intensify the effects of MDMA and amphetamine (Cornish et al. 2003; Feduccia et al. 2010). Loud environments increase the response and consequences of MDMA in non-human animals (Cornish et al, 2003). Most drug users will administer drugs in a nightclub environment that will include crowded places with loud music (Fantegrossi et al, 2003; Braida et al, 2005; Ramo et al, 2010). Drug users exposed to MDMA in such environments may in fact be increasing the likelihood of psychological effects. The environment that MDMA users are taking MDMA was documented in the questionnaire.

Published research widely accepts the notion that psychiatric disorders including drug addiction have been closely linked with genetics. Drug addiction can be observed between first degree relatives and siblings in behavioural studies (Lin et al. 2004; Chen et al. 2011). Inclusion of family use of recreational drugs was, therefore, included in the questionnaire.

Non-human animal research has demonstrated that MDMA induced damage to selective 5-HT neurons in female rat brains is reversible in comparison to males (Liechti et al. 2001; Verheyden et al. 2006), however this still remains questionable (van den Buuse et al. 2011). Research indicated that the amount of repair on damaged 5-HT neurons is dependent on

biological sex (Liechti et al, 2001 and Verheyden et al, 2006). This research implicates that hormones such as oestrogen and progesterone may provide a neuroprotective role (Liechti et al, 2001; Reneman et al, 2001b; Bubenikova et al, 2005). Thus, the biological sex was documented.

MDMA exposure could lead to depression due to reduced 5-HT levels (Curran, 2000; Parrott, 2001; Ricaurte et al. 2001; Mathews and Bruno, 2010; Scott et al. 2010). It is conceivable that effective treatments for past and present MDMA users would include those that increase 5-HT levels. Current treatments available for depression include Selective Serotonin Reuptake Inhibitors (SSRIs) and non-5HT selective drugs, including Serotonin Noradrenaline Reuptake Inhibitor (SNRIs) and Tricyclic Antidepressants (TCAs) (Dupuy et al. 2011). Individuals' diagnosed with past depression resulting from MDMA exposure may have been prescribed 5-HT-related antidepressants to alleviate symptoms. If serotonergic anti-depressants elevate symptoms, this will provide indirect evidence that MDMA may cause damage to selective 5-HT neurons, providing further support that MDMA is a neurotoxin. The DHQ documented if participants have suffered from past depression and the type of treatment prescribed. Finally, if depression was diagnosed and treatment offered, it was documented whether the treatment had the desired outcome or not

The DHQ recorded information concerning the awareness of psychological disturbances specifically caused by the use of MDMA and not a consequence of other recreational drugs. A number of MDMA users state that MDMA fails to cause any long lasting psychological disturbance (Curran, 2000; Parrot, 2001; Gamma et al. 2005). Nevertheless, research has debated this statement for more than a decade. This discrepancy may result from the possibility that MDMA users and other recreational drug users are unaware of any psychological damage. Alternatively if users are aware of a decline in psychological functioning they fail to associate it with recreational drug use. Another interpretation is that the psychological deficit(s) existed beforehand and the drug user started to use the drug as a form of self-medication. If MDMA initiates deficits in mood, memory and executive functioning, with MDMA users being unaware of this deficit, it may lead to irrational behaviour and an overall decrease in quality of life (Beck and Weishaar, 1990).

Certain individuals seem to have no related psychological deficits following MDMA use (Curran, 2000; Parrot, 2001) whilst others suffer from both behavioural and cognitive problems following exposure to MDMA (Curran, 2000; Parrot, 2001; Morris, 2003; Mathews and Bruno, 2010; Scott et al. 2010). A number of studies have demonstrated that MDMA users suffer from cognitive or behavioural problems after minimal exposure to MDMA

(Morland et al. 2000; Esteban et al. 2001; Mechan et al. 2001; Masi et al. 2002; Balogh et al. 2004; De Win et al. 2008; Green et al. 2004). How can these confounding studies be explained? Is the neurotoxicity dependent on factors such as age of initial exposure to MDMA and brain maturation, initial dose taken typical exposure environment of MDMA, cocktail of drugs used whilst on MDMA, and family history of MDMA? MDMA toxicity may depend on other factors including route of administration of MDMA or content of MDMA pills. This study aimed to answer these questions and attempted to find a more consistent conclusion using the DHQ.

There is insufficient evidence correlating MDMA exposure and increased chance of neurotoxicity. Consequently in a minority of cases within the literature individuals have occasionally taken MDMA, which has resulted in severe consequences (Morland et al. 2000; Esteban et al. 2001; Mechan et al. 2001; Masi et al. 2002; Balogh et al. 2004; De Win et al. 2004; Green et al. 2004). The actual amount consumed needs to be documented in order to establish the relationship between dose and psychological functioning.

In order to evaluate the acute and long lasting effects of MDMA, a demographic and detailed drug history questionnaire (DHQ) documenting all factors that may contribute to a decline in psychological functions was required. This first section described piloting of a demographic drug questionnaire targeting different categories such as demographics, frequency of all recreational drugs, effects of recreational drugs, and drugs co-used with MDMA.

2.2.2 Methodology

2.2.2.1 Pilot Study for demographic and DHQ

2.2.2.2 Design

This study included four pilot studies: (1) A test-retest pilot study involved participants filling out the drug history questionnaire twice with a time interval of a week, (2) Two validation pilot studies comparing responses from the newly formulated DHQ with responses from an unpublished clinical drug history questionnaire, used by the Institute of Psychiatry (IoP). The IoP drug history questionnaire is non-specific to a particular substance, (3) The second validation pilot study compared the responses from the present DHQ with a structured interview, (4) The final part is the main pilot study, where the DHQ was completed by 100 participants (Table 2.1).

Table 2.1   Pilot studies validating and testing the drug history questionnaire

The four different pilot studies performed including the test-retest for the DHQ, comparison of the DHQ with responses from the IoP questionnaire, DHQ self-reported compared with an interview based on the DHQ, and finally the main study where 100 participants were asked to complete the DHQ.

Pilot test	Sample	Measuring
Test-retest	n=20	Reliability
Comparison with IoP	n=20	Validity
Comparison with interview	n=20	Validity
Main pilot study	n=100	Participants had no difficulties

2.2.2.3   Participants

One hundred and sixty participants were involved; based on a power calculation, where n=28 (power=80, D=0.05, df=1 – Cohen, 1992; Faulet al. 2007; Faul et al. 2009). The mean age was 21 years (ranging 18-37 years) 54 % males. Sixty participants were included in the validation/reliability of the questionnaire. 20 participants were interviewed using the unpublished IoP interview, and 20 participants employed in a structured interview based on the DHQ questionnaire. A further 20 participants were used to test the DHQ questionnaires consistency and reliability using a test-retest. Finally, the final DHQ was completed by a further 100 participants, where no further queries were raised by the participants.

For the validity (IoP interview and general interview) and reliability test-retest, participants were recruited from a range of advertisements: (1) Local newspapers, (2) Webpage (www.msn.mywebpage.drugexperiment.co.uk), and (3) London Metropolitan University (formally known as London Guildhall University). For the pilot study, participants were selected from London Metropolitan University (formally known as London Guildhall University) during 2001.

2.2.2.4   Materials

In total, the DHQ consisted of 22 pages. Two pages (page 1 and 11) included instructions with the remaining 20 pages requiring answers to questions. Page 1 (the front cover) was an instructions page explaining that participants were required to put a response to the question asked in the appropriate answer box. It further explained that all participants were required to complete pages 2-10 (questions 1 through to 26). However, participants only needed to complete pages 12-22 if they had consumed MDMA in their lifetime (questions 27 through to 47). Further instructions provided on page 11, reiterate that participants are only required to fill out questions 27 through to 47 if they have used MDMA (Appendix 2.1).

Pages 2-10 and 12-21 asked questions concerning general demographics and drug-history questions. The type of questions asked included a combination of closed, multiple choice and finally open spaced questions (Appendix 2.3). The questionnaire was one-sided, double-spaced throughout, font size 14 and type was Arial.

The DHQ consisted of three sections. 'Section A' demographics on general lifestyle and health related questions including age, ethnicity, employment, mental health, social class, family use of recreational drugs, and general effects of drugs (pages 2-6). Section B consisted of specific use of recreational drugs including asking the types of drugs used currently (within the last 6 months) and previously (not within the last 6 months), and monthly and weekly diet (pages 7-10). Finally, Section C consisted of asking questions particularly concerned with MDMA consumption including total lifetime consumption, pattern of use, and finally questions concerning the acute effects of MDMA: physically and mentally (pages 12-22; Appendix 2.2).

2.2.2.5   Procedure

Forty-seven questions were formulated based upon previous studies (refer to introduction for more details) with six of these questions having sub-questions (Appendix 2.1).

The initial phase of the pilot study was to test for its reliability (Table 2.1). This involved asking 20 participants to complete the questionnaire. These participants were required to fill the questionnaire out twice, including an interval of one week (retest). The responses were analysed (Appendix 2.4).

To test for the validity of the DHQ, 20 participants were interviewed using the standardised IoP drug history form. Participants subsequently self-completed the DHQ. The responses from the DHQ and the IoP interview were compared and analysed (Appendix 2.4).

Finally, a further 20 participants were given a structured interview based on the DHQ. Difficulties were addressed and relevant changes made (Appendix 2.2).

The final phase of the pilot study involved distributing 100 questionnaires to participants from London Metropolitan University (formally London Guildhall University). Participants were supplied with a self-addressed envelope in order for them to return the completed questionnaire. The numbers of responses checked and no further changes implemented to the questionnaire (Appendix 2.2). The DHQ was used to collect data in chapters three through to seven.

2.2.3　　Results

2.2.3.1　　Test-retest reliability pilot study

All the responses for the test-retest pilot study found there were no differences in responses between the initial questionnaire completed and the second questionnaire completed one week later (Chi square=0.9, df=46, p>0.05 – refer to table 2.5 and appendix 2.5).

2.2.3.2　　Interview validity pilot study

The interview suggested that some of the questions needed to be re-structured (table 2.2 appendix 2.1 and appendix 2.2), no further responses for the multiple-choice questions needed to be added.

Table 2.2   Changes to questions

The following table summarises any changes to the DHQ following the validity pilot interview. The table provides details of the questions changed, and the page location on the DHQ.

Question and page location	Change Made
Q23 – Current drug use (page 7)	Addition of times per week, times per month and number of years
Q24 – Previous drug use (page 8)	Addition of times per week, times per month and number of years

2.2.3.3   IoP validity pilot study

Comparison of responses between the drug history questionnaire and the IoP based interview found non significant differences in responses, with no further information being provided from the IoP interview (Chi square=0.2, df=46, p>0.05; appendix 2.5).

2.2.3.4   Replies to the main pilot drug history questionnaire study

For the main pilot study, of the initial 100 questionnaires (Appendix 2.1) sent to participants 88% (n=88) were returned with 84% (n=84) completed.

Responses from one hundred questionnaires were assessed in order to compile a scoring system that would allow the string responses to be transformed into meaningful numerical ordinal and interval data. Of the total forty-seven main questions, only six questions had a numerical response. Seven had a yes or no response. Three had a string response. Twenty-one questions had a multiple-choice response provided. Finally, for statistical analysis purposes ten of the questions required a percentage to be calculated (Appendix 2.4).

2.2.4   Discussion

2.2.4.1   Pilot demographic and drug history questionnaire

The DHQ is able to gain information concerning participants previous and current drug use. To the authors' knowledge, this is the first questionnaire targeting MDMA users. Analysis

from the pilot study suggests the questionnaire is both a reliable and valid assessment tool, which is able to identify drug users, in addition to collecting relevant and meaningful data.

Analysis from the interview ascertained the DHQ asked sufficient information. The interview failed to emphasise additional information, not already recorded from the questionnaire. The interview did reveal a small number of questions that needed to be re-structured. In addition, there were some general comments which required clearer instructions and some re-structuring of the questions. These changes were subsequently completed (refer to appendix 2.1 and appendix 2.2).

The response rate was 84% of the initial questionnaires posted and returned completed suggesting that the questionnaire was adequate in terms of the number of questions asked and the overall length of the questionnaire (Gillham, 2002). Due to the number of completed questionnaires it implies that the questionnaire was fairly easy to complete; as it is suggested a response rate of greater then 65% is considered good (Gillham, 2002).

By producing a validated and reliable questionnaire, which is not only able to accurately quantify a person's drug history but also provide a behavioural account of the subjective effects of recreational drugs, means that results from future research investigating consequences of recreational drug use can be more reliable and increases confidence in subsequent interpretation.

2.2.4.2   Limitations and future suggestions

As with all self-reported questionnaires there are numerous limitations to this drug history questionnaire (for a fuller account on the disadvantages of self-reports refer to chapter 8).

The pilot study suggested the questionnaire was reliable. As with all pilot studies, it had its limitations. The pilot included eleven recreational drug users and only seven MDMA users. Further validity and reliability tests are required in the future, with the inclusion of a more diverse ethnic background and contrasting cultures. However, the findings from the current pilot study suggested the DHQ was adequate and reliable to be used as a demographic and drug history research tool.

Gaining information about participants' diets can be complex using a retrospective questionnaire (Curzon et al, 1990). Participants will often alter their diet. Often people will be unable to recall diets and may require prompting. The prompting may cause false memory

affecting the response. In the DHQ, prompts were given to assist the participants. This may have led to false reporting and inaccuracy of diet. An alternative method would be to ask participants to record a journal/diary (Jimmerson et al, 1990). However, a weakness includes the limitation of time for participants. In addition, it relies heavily on the participant's motivation. Another probable method would include biochemical measures of dietary tryptophan. Research by Schweiger et al. 1990 found that blood amino acid levels of tryptophan in anorexics following both protein-rich and carbohydrate-rich meals were lower in comparison to matched controls (Jimerson et al, 1990). The DHQ is a quick method to provide an estimated account of an individuals overall diet, as is required in this study. If future studies require accurate results concerning diet, it is recommended measuring blood amino acid levels, and subsequently correlating with psychological behavioural deficits.

Ideally, 5-HT levels need to be measured accurately. Laboratory techniques consist of measuring amino acid concentrations from the blood and CSF provide indirect information on the 5-HT precursor L-tryptophan. Ultimately, this has an influence on the amount of 5-HT synthesised (Jimerson et al, 1990). A further indicator of 5-HT metabolism and functioning is the amount of serotonin metabolite 5-hydroxyindole acetic acid (5-HIAA) in the lumbar CSF. The majority of studies on 5-HT functioning have focused on measuring 5-HIAA in plasma, urine and CSF (Boot et al, 2000). Future studies would benefit from correlating the results of the DHQ with blood or CSF analysis to provide more accurate conclusion concerning 5-HT and MDMA. However, the current study is more concerned with MDMA lifetime use and psychological problems, rather than 5-HT levels per se.

Drug users' perception of their own drug history can be distorted and inaccurate (Yacoubian et al, 2003). Most users will often excessively abuse many different types of recreational drugs often simultaneously. This can be difficult to monitor and record accurately using the DHQ. This can result in the drug users being unable to recall what they have consumed. In the majority of cases, the substances consumed will not be known to them as they are commonly mixed with cheaper substances and made in back-street labs (Cole et al, 2002). As drug users may suffer from possible memory related deficits a more accurate and reliable method needs to be adopted to estimate lifetime consumption of each recreational drug other than a DHQ (Daumann et al, 2003). Memory recall may be biased, as various recreational drugs can cause deficits to episodic memory (Parrott et al, 1998). Relying on participants' memories to remember accurate lifetime consumption of drugs can be very difficult and inaccurate. This places a question mark over the results of research that rely on these methodologies and the DHQ. Ideally, drug analysis need to be obtained during the period of psychological testing for example collection of blood, urine or hair analysis; however, such methodologies are

impractical due to health and safety laws, in addition to failing to monitor long-term drug use. Participants may not wish to divulge their drug history using DHQ due to social undesirability or legal reasons (Morgan, 2000). An alternative methodology would involve a longitudinal study. Nevertheless, longitudinal studies are not cost effective and are time consuming, whereas the use of a DHQ is cheap and quick allowing the collection of vast amount of data. Secondly, studies indicate that there are consistencies between self-reported MDMA use and hair sample analysis (Parrott et al. 2011), suggesting that this self-reported questionnaire is a sufficient method to collect drug history information.

2.3   Drug misuse trends across South East England

2.3.1   Introduction and Justification

During the 1990s there was an extraordinary escalation in the number of drug users, young and old (Aldridge et al, 1998; Aldridge et al, 2008; van Nuijs et al. 2010). UK estimates during the period 1999-2001 suggested 4% of 16-59 year olds had taken MDMA. Usage was highest amongst 16-29 year olds (Ramsey et al, 2001). However, in 2010 there seems to be a reduction in the use of MDMA in comparison to previous years (European Monitoring Centre for Drugs and Drug Addiction, 2008). This is considered to be due to increased seizures and the lack of precursor chemicals needed to manufacture MDMA. There are legal substitutes to MDMA, which seem to be popular. Finally, cocaine use has dramatically increased amongst 16-29 year olds from 1% in 1994 to 5% in 2000 (Sharp and Miech, 2001) and seems to be continuing to rise (van Nuijs et al. 2010).

Politically, over the past decade, government legislation has targeted minimising drug use across the UK as well as educating people concerning the effects of drugs. It has been some 3 years since the last published report concerning drug use trends within the UK (Aldridge et al, 2008). One of the largest longitudinal studies published is the Aldridge Report investigating adolescent drug use (Aldridge et al, 1998). However, this report failed to monitor the participant into early adulthood and through later life. Given that MDMA use amongst adults is on the increase, this aging population of drug users need separate investigation. The Aldridge Report provided information concerning the reasons why adolescents initiate recreational drugs however it failed to provide a typical age, ethnicity, educational background of adult drug users. MDMA is a drug commonly associated with Caucasian clubbers in their mid-twenties, however recent studies suggest MDMA is becoming increasingly poplar amongst all ethnicities and ages (Morris, 2003; Montoya, 2002; Morton, 2005). If MDMA is associated with possible health risks and selective brain neurotoxicity,

investigating adults whom are either (1) currently taking MDMA, or (2) those with a history of MDMA use, will provide information regarding potential MDMA induced psychological damage (Curran, 2000; Parrot, 2000).

This section of the study addresses two main questions: (1) To verify whether educational government legislation have proved favourable in reducing overall substance use or as predictions suggest the number of drug users is still escalating within the South East England during the period 2002-2007, (2) To investigate the demographics of a sample of drug users past and present. Findings from this study will provide information on whether current polydrug MDMA users administer drugs in a more or less harmful way than MDMA users 5 years ago. This will further provide information on frequency of MDMA and other substance use, age of initial exposure and co-use of MDMA with other substances, comparing past and present users.

2.3.2   Methods

2.3.2.1 Participants

The total sample size consisted of 1399 participants split into three main groups: 1) Sample of 438 current and past MDMA poly drug users, 2) 716 non-MDMA poly drug users, and 3) 245 non-drug users (Power calculation; minimum of 72 per group, power=0.80, δ=2.80; Cohen, 1992; Faul et al. 2007; Faul et al. 2009). The participants were divided into a further five groups depending on their self-reported illicit drug history as detailed below.

The groups included:

     i)   non-illicit drug users,

     ii)   current regular alcohol/nicotine users,

     iii)   current alcohol, nicotine, cannabis users,

     iv)   current non-MDMA polydrug users that have never consumed MDMA prior to taking part in the study,

     v)   current polydrug MDMA users that had used MDMA in the last 6 months prior to taking part in the study,

     vi)   past MDMA users who had abstained from MDMA at least 1 year prior to taking part in the study (Table 2.1).

In summary, the study compared four non-MDMA control groups with two MDMA poly drug groups: current and past MDMA users (Table 2.1).

Table 2.1: Summary of overall drug groups

The figure provides a detailed account of all drug groups involved in the study, where N=1399. There were six main groups included in the study: non-drug group, alcohol/nicotine group, alcohol/nicotine/cannabis group, non-MDMA polydrug, current MDMA polydrug, and past MDMA polydrug group.

Non drug control group – participants whom have never taken any illicit drugs. The aim of this group is to have a control group that can be compared to other illicit drug users on performance on psychological measures. If performances differ between the control group and the licit/illicit drug users it could be proposed that the difference in performance is due to licit/illicit recreational drugs.

Control group matched for alcohol/nicotine use – participants that used nicotine/alcohol. Participants would not have taken MDMA in their lifetime, nor taken any other illicit drugs. The reason for controlling for alcohol and nicotine is current research demonstrates alcohol and nicotine can affect performance in numerous psychological tests (i.e., short-term and working memory deficits, increased anxiety). By controlling for alcohol and nicotine use it implies that the results are due to the use of MDMA and not nicotine or alcohol.

Control group matched for cannabis use –participants that use alcohol, nicotine and cannabis. Participants would not have taken MDMA in their lifetime, nor taken any other illicit drugs. The reason for controlling for cannabis is that current research demonstrates cannabis affects serotonin levels and thus performance in numerous psychological tests are reportedly affected (i.e., short-term and working memory deficits, increased anxiety). By controlling for cannabis use it implies that the results are due to the use of MDMA and not cannabis.

Control group matched for other illicit drug use including cocaine, amphetamine and heroin - this group will include participants that use cocaine, amphetamine, heroin as well as other illicit drugs. Participants in this group included those that drink alcohol and smoke tobacco. Participants would not have taken MDMA in their lifetime; however they would have taken all other illicit drugs. The reason for controlling for cocaine, heroin, and amphetamine amongst other illicit drugs is that research indicates that repeated use of cocaine/heroin/amphetamine affects similar neurotransmitters as MDMA, by controlling for such drugs it implies that the results are due to the use of MDMA and no other illicit drugs.

Current MDMA users - to confirm current/previous research indicating that current MDMA users have problems with memory and learning as well as testing for other cognitive processes not previously investigated. Such individuals would have taken MDMA more than 20 times in their lifetime. This group highlighted any short-term psychological effects of MDMA use.

Past MDMA users (more than 1 year) – to confirm whether the psychological problems associated with MDMA use in humans is a short-term problem or a long-term problem. A pseudo-dose-response curve was produced showing the severity of each psychological problem in relation to the number of years of abstinence from the drug, MDMA.

The sample was recruited from advertising in the following: 1) London Universities, 2) Supermarkets and local shops, 3) Free magazines/papers including MsLondon, and Loot, 4) Newspapers including the Evening Standard, Metro, Big Issue, 5) Other magazines like Time Out, 6) GP surgeries, 7) drug information and advisory centres, 8) chemists selling herbal ecstasy, 9) night clubs (refer to appendix 2.1).

2.3.2.2   Designs and experimental procedures

Each participant was required to complete the DHQ.

2.3.2.3   Measures/statistics

Data was analysed using Statistical Package for the Social Sciences (SPSS) version 16. Basic demographic details were analysed using t-tests, and chi-squared between the three groups:

non-drug, non-MDMA polydrug and MDMA group. The differences in lifetime use of recreational drug(s) were analysed using t-tests and chi-squared between non-MDMA and MDMA groups. The MDMA demographics concerning the past and present MDMA users were compared using t-test.

2.3.2.4   Ethical considerations

Ethical approval was given by London Metropolitan University Ethics Committee (formally London Guildhall University). Participants were not required to provide personal details such as name or address. In order for participants to remain anonymous, participants were provided with a reference number before they participated in the study (six-digit bar code) and were known only by this number. Participants were able to contact the researcher via telephone and email (separate telephone line and email account was provided for recruiting participants and a webpage – www.drugexperiment123.com).

Participants had a full briefing about the research before they participated and debriefing (Appendix 2.1). They were able to leave the study at any stage. Participants signed a statement providing consent (Appendix 2.2).

These ethical issues applied throughout the remainder of the study (chapter 3 through to 7).

2.3.3   Results

The study included a total sample size of 1399 participants (Table 2.3). Of the total 1399 sample, 17% has never experienced illicit drugs (non-drug and alcohol/nicotine group) in comparison to 83%, which had experienced illicit drugs (Table 2.3). Overall, there was an equal percentage of males/females, similarity in the three age groups and similar percentage in the different areas of residence within the overall sample. Further analysis revealed significant differences in ethnicity, where the majority of the sample 40% were non-UK followed by 33% which were white UK (Chi square 4.38, df=3, p<0.05). Only a minority of participants 8% were Black UK and 19% Asian UK. In terms of employment, the majority of the total sample, 67%, were employed (n=1372). There were an equal number of students 16.5% and unemployed 16.5%. The majority of the sample 60% was single. Other marital status included 13% separated/divorced followed by 27% married (Table 2.3).

Table 2.3 Selected characteristics of the total sample included in the study (n=1399).

The table provides overall demographic details of the total sample including gender, age, are of residence, ethnicity, education, marital status, episode of depression and drug use (one sample chi square).

Selected Characteristics	Total sample %	Total Sample N	p
Gender			
Male	53	741	ns
Female	47	658	
Age in years			
18-25	42	588	ns
26-34	36	503	
35 older	22	308	
Area			
Inner metropolitan	39	545	ns
Outer metropolitan	27	378	
Non-metropolitan	34	476	
Race/ethnicity			
White (UK)	33	461	
Black (UK)	8	112	p<0/05
Asian (UK)	19	266	
Other (Non-UK)	40	560	
Education			
Employed	67	937	
Student	16.5	231	p<0.05
Unemployed	16.5	231	
Current martial status			
Married	27	378	
Separated/divorced/widowed	13	182	p<0.05
Single	60	839	
Past depression			
Yes	26	364	
No	74	1035	p<0.05
Drug use			
No drug use	17	245	-
MDMA drug history	32	438	
Other drug use minus MDMA	51	716	

Comparison between the MDMA poly drug users (past/present) and non-MDMA poly drug users found significant differences in age, area of residence and education but there were non-significant differences in gender, ethnicity, and marital status (Table 2.4). There was a significant difference in age between the MDMA users and non-MDMA groups where 81% (n=355) of MDMA users were older (over 26 years old) in comparison to 69% of the non-MDMA users (n=644) (Chi square=13.85, df=2, p<0.05; 2.2). There was a difference in area of residency with more MDMA users 40% (n=175) living in non-metropolitan areas in comparison to 37% (n=346) of the non-MDMA users (Chi square=11.37, df=2, p<0.05). There was a significant difference in employment with less MDMA users in current employment 58% (n=254) in comparison to non-MDMA users 63% (n=588) (Chi square=12.56, df=2, p<0.05; Table 2.4)).

Finally, comparing the current MDMA polydrug users and past MDMA polydrug users (abstained for mean 5 years; range 5-11 years) found a non-significant difference in gender (Chi squared=0.4, df=2, p>0.05). However, there were significant differences between ages where a majority of 95% (n=206) of past MDMA users were over 26 years old in comparison to 68% (n=150) of the current MDMA users (Chi square=52.85, df=2, p<0.05). A higher proportion of the current MDMA users 42% (n=93) lived in city areas in comparison to 24% (n=52) of past MDMA users. The majority 58% (n=126) of past MDMA users were white UK in comparison to 27% (n=60) of the current MDMA users. A larger proportion of past MDMA users were in employment 78% (n=169) in comparison to 37% (n=82) of current MDMA users. The majority 76% (n=168) of current MDMA users were more likely to be single in comparison to 14% (n=30) of past MDMA users (Table 2.5).

Table 2.4 Selected characteristics comparing the MDMA users (past and present, n=438) with the non-MDMA users (n=961).

The table compares demographic details including gender, age, are of residence, ethnicity, education, marital status, and episode of depression between the MDMA users and the non-MDMA control group.

Selected Characteristics	MDMA (past/present) %(n)	Non-MDMA drug users %(n)	p
Gender			
Male	49 (215)	51 (476)	ns
Female	51 (223)	49 (458)	
Age in years			
18-25	19 (83)	31 (290)	<0.05
26-34	51 (223)	44 (411)	
35 older	30 (132)	25 (233)	
Area			
Inner metropolitan	33 (145)	36 (336)	<0.05
Outer metropolitan	27 (118)	27 (252)	
Non-metropolitan	40 (175)	37 (346)	
Race/ethnicity			
White (UK)	45 (197)	38 (354)	ns
Black (UK)	10 (44)	9 (84)	
Asian (UK)	10 (44)	15 (140)	
Other (Non-UK)	35 (153)	36 (336)	
Education			
Employed	58 (254)	63 (588)	<0.05
Student	24 (105)	21 (196)	
Unemployed	18 (79)	17 (159)	
Current martial status			
Married	36 (158)	32 (298)	ns
Separated/divorced	19 (83)	16 (150)	
Single	45 (197)	52 (486)	
Past depression			
Yes	37 (162)	27 (252)	<0.05
No	63 (276)	73 (682)	

Table 2.5 Selected characteristics comparing the past MDMA polydrug users with the present polydrug users (N=438).

The table compares demographic details including gender, age, are of residence, ethnicity, education, marital status, and episode of depression between the past MDMA users(n=217) and the current MDMA users (n=221). .

Selected Characteristics	Current MDMA % (n)	Past MDMA % (n)	p
Gender			
Male	46 (102)	52 (113)	ns
Female	54 (119)	48 (104)	
Age in years			
18-25	32 (71)	5 (11)	<0.05
26-34	43 (95)	58 (126)	
35 older	25 (55)	37 (80)	
Area			
Inner metropolitan	42 (93)	24 (52)	<0.05
Outer metropolitan	28 (62)	26 (56)	
Non-metropolitan	30 (66)	50 (109)	
Race/ethnicity			
White (UK)	27 (60)	58 (126)	<0.05
Black (UK)	17 (38)	3 (7)	
Asian (UK)	23 (50)	8 (17)	
Other (Non-UK)	33 (73)	31 (67)	
Education			
Employed	37 (82)	78 (169)	<0.05
Student	42 (93)	7 (15)	
Unemployed	21 (46)	15 (33)	
Current martial status			
Married	24 (53)	47 (102)	<0.05
Separated/divorced	0 (0)	39 (85)	
Single	76 (168)	14 (30)	
Past depression			
Yes	39 (86)	35 (76)	ns
No	61 (135)	65 (141)	

2.3.3.1 MDMA usage

With regard to the pattern of usage of MDMA between the current and past MDMA polydrug users the results found past MDMA users reported using MDMA at an older age than current MDMA users (t=11.107, df=436, p<0.05). Current MDMA users reported using a larger dose than past MDMA users during their initial experience with MDMA (t=14.23, df=436, p<0.05). Current MDMA users reported consuming more MDMA pills on a single occasion than past MDMA users (t=11.69, df=436, p<0.05). Current MDMA users reported using nearly double the amount of pills in their lifetime in comparison to past MDMA users (t=2.215, df=436, p<0.05; Table 2.6).

Table 2.6: MDMA demographics

Basic demographics for the current and past-MDMA groups detailing information concerning MDMA use including age first used MDMA; amount of MDMA first used; amount of MDMA normally consumed and lifetime amount of MDMA consumed; (N=438).

	Age first tried MDMA Mean (±SD)	No first used Mean (±SD)	No Used permanently Mean (±SD)	Lifetime use MDMA Mean (±SD)	
Current MDMA Group	18 (±3.46) *	2.74 (±0.81) *	2.3 (±1.15) *	956 (±764) *	(n=221)
Past MDMA Group	25 (±6.2) *	1.2 (±0.58) *	1.5 (±1.2) *	532 (±708) *	(n=217)

* *denotes significant differences between current MDMA and past MDMA group, where p<0.05*

Overall, the type of recreational drugs consumed by the three (non-MDMA poly drug, current MDMA and ex-MDMA poly drug group) drug groups were similar apart from the following tranquillisers; cocaine; LSD; and alkyl nitrites. Current MDMA poly drug users had used more tranquilisers than past MDMA users and non-MDMA poly drug users. With regard to cocaine, the majority of current (56%) and past MDMA users (43%) had tried cocaine in comparison to 35% of non-MDMA drug users. As for LSD, equal numbers of current and past MDMA users had tried it (34%) in comparison to 18% of non-MDMA polydrug users. Finally the majority of current MDMA and past MDMA users had tried alkyl nitrites being

36% and 39% respectively in comparison to 13% of non-MDMA users (Chi squared=69.1, df=60, p>0.05; Table 2.7).

Table 2.7: Table of recreational drug use (percentage)

Presents the percentages of drug users self-reported exposure to common recreation drugs of abuse for the three drug groups (non-MDMA polydrug, current MDMA polydrug and past MDMA polydrug), (Chi squared =69.1, df=60, p>0.05; N=1154. Where LSD=lysergic acid diethylamide.

Recreational Drug	Non-MDMA polydrug group (n=240)	Current MDMA polydrug group (n=221)	Past MDMA polydrug group (n=217)
Amphetamine	59.5%	53%	47%
Nicotine	62.5%	72%	77.5%
Tranquilliser	12%	20%	16.5%
Alcohol	97%	92%	96%
Steroids	13.5%	16.5%	16%
Cannabis	97.5%	93%	95%
Cocaine	35%	56%	43%
LSD	18%	34%	34%
Psilocybin/ Psilocin	26%	31%	34%
Alkyl nitrites	13%	36%	39%

2.3.4   Discussion

During the period 2002-2007, results from this study indicate the typical MDMA user in the South-East England is 27 ± 7.6 years old, either male or female, employed, and of any ethnicity. They usually consume between two or three tablets on a single occasion and co-use MDMA with alcohol, nicotine, amphetamine and cannabis. The usual route of administration is pill/tablet form. Finally, MDMA is consumed with friends. Most MDMA users self-report the following disturbances: mild depression, tiredness, anxiety and sleep disturbance, attributing these effects to MDMA. Most current MDMA users began using MDMA at a mean age of 18 (±3.36) years old, which is younger that past MDMA users. These findings further supported previous non-UK research (Schifano, 2000a). A self-rating questionnaire was administered to 360 young people in north-eastern Italy (69 were football fans and 291 were club-goers). For the club-goers the age of first use ranged from 13 and 31 years old

(mean 18.6±3.1 years). Approximately one third of the users took the drug several times a week. The club-goers were genuine polydrug users, 75.3% took other recreational drugs once per week including cannabinols (75.3%), alcohol (53%), LSD and other psychedelics (50.4%), cocaine (30%), opiates (11.1%). These findings (Schifano, 2000a) are similar to the current findings suggesting current MDMA users are polysubstance users.

In another self-report study, sample size of 737 and mean age 22.5 years, users were exposed to MDMA between the ages 15-18 years old (Schifano, 2000b). These findings are similar to the present results. For 82.2% of the people their first dose was 0.5-1 tablet, however for 25% of the sample, the first dosage of MDMA increased to more than four tablets on a single occasion (Schifano, 2000b). Their study suggested the amount of MDMA consumed on a single occasion is increasing, which supports the current findings. This study suggests that the dosage of MDMA is increasing with current users taking increased dosage on a single occasion in comparison to past MDMA poly drug users. There appears to be an inverse relationship between educational achievement, family income and the tendency to take higher doses of MDMA. Schifano reported the lower the income in the household the greater the intake of MDMA and thus associated MDMA use with social class. However, the current study contradicts this and as we found the majority of MDMA users were employed. In the Schifano study a pattern of polydrug use was found, with 65.9% of them having used cocaine at least once in their lifetime and 87.1% reported having taken high doses of alcohol in the past (Schifano, 2000b). Results from this study show similar statistics in terms of all the MDMA users co-using MDMA with other substances.

Overall this study is supported by previous studies (Schifano, 2000a, 2000b), suggesting that current MDMA users are exposing themselves to greater amounts of MDMA than past users and therefore larger doses. If this increase continues, it is highly likely that MDMA users will suffer from more severe MDMA induced psychological and behavioural consequences as well as possible neurotoxicity. Non-human animal studies have demonstrated that larger amounts of MDMA result in increased selective damage to brain serotonergic neurons (Ricaurte et al. 1988; Mueller et al. 2009a, 2009b; Ricaurte et al. 2000; Perrine et al. 2010; Biezonski and Meyer, 2010; Li IH et al. 2010; Mueller et al. 2011). If these non-human animal studies can predict possible consequences in humans it is therefore likely increased doses of MDMA will result in enhanced psychological damage. It is viable current MDMA will exhibit substantially greater psychological consequences than past MDMA users.

The current study found that drugs users tend to be either male or female. In comparison, previous studies indicate that MDMA drug users are predominantly male (Miller et al. 2007).

This study provides evidence and supports future predictions that females are just as likely to consume illicit drugs in comparison to males supporting current epidemiological predictions (Aldridge et al. 2008). Predicted trends suggest the majority of illicit drug users tend to be younger than 29 years old, live in the city, come from diverse ethical background, are employed, and single. These findings support current predicted trends of drug use across the UK (Aldridge et al. 2008).

The present results found a non-significant difference in the majority of individual characteristics between past/present MDMA substance users and the non-MDMA drug groups. They were similar in demographic detail including gender, ethnicity, marital status, and employment. The results from this study imply that in this sample of drug users, the demographic details fail to provide a reason why certain individuals' use MDMA and others do not. This study involves a diverse area of central London and surrounding areas, which includes a mixture of social background, ethnicities and ages.

This study found that current MDMA users are younger, live in the city, and are more diverse in terms of ethnicity than past MDMA users. Past MDMA users, like the majority of the older drug using population, were more likely to be older in age, live out of the city, Caucasian UK in ethnicity, employed and married/separated in contrast to current MDMA users. This supports the notion that past MDMA users as expected are older, possibly more established in their lives in terms of careers and family life, alternatively they may have 'grown out' of the clubbing and rave scene.

Previous research suggests that past MDMA users were middle class Caucasians (Aldridge et al. 1998; Miller et al. 2007). Recent epidemiological reports predict that MDMA is appealing to all ethnic types, social classes and ages in comparison to 10 years ago were MDMA was associated with white middle class Caucasians (Aldridge et al. 2008). Results from the present study seem to support the prediction that MDMA appeals to all ethnic backgrounds, ages, and social classes. The present results support the notion that the use of MDMA is continually increasing within the UK during the period 2002-2007 despite reports concerning its possible dangers and MDMA related physiological deaths.

The present study found that MDMA users are more likely to co-use multiple substances in comparison to non-MDMA substance users supporting previous research (O'leary et al. 2001; Morton, 2005). The dangers associated with mixing substances in this way is still largely unknown (Gudelsky et al. 2003; Green et al. 2004; Hamida et al. 2009; Daza-Losada et al. 2009). Further investigation into the reasoning behind this multiple use of substances is

required. Possible suggestions include the fact that MDMA results in tolerance, which is still highly debateable (Parrot et al, 2009). Users may combine other substances with MDMA in order to achieve a more desired effect. Secondly, MDMA consumption occurs at weekends, followed by a low, resulting in depression and severe behavioural problems (Curran et al. 1997). It is probable that MDMA users consume other substances during the weekend to counter balance these negative consequences including cannabis, amphetamines and alcohol (Parrot et al. 2005). If MDMA use results in deficits in psychobiological functioning then the combination of different substances may enhance acute and long lasting negative consequences (Di Canio et al. 1995). In particular, non-human animal studies demonstrate combining MDMA with a DA agonist amplifies brain neurotoxicity (Di Canio et al. 1995; Reneman et al. 2002; Hamida et al. 2009; Daza-Losada et al. 2009). The results from this study demonstrate MDMA users co-use a multitude of drugs.

Initial onset of use of MDMA is younger in current MDMA polysubstance users than past MDMA substance users. Results from brain maturation studies in rats have found that the younger the brain of the rat the more severe the MDMA induced neurotoxicity (Piper et al. 2004; Galineau et al. 2005). As current MDMA users are of a younger age and the brain has not fully developed, they could potentially be causing enhanced brain deficits than past MDMA users. The human brain fully matures at the age of 25 years old (Cowen et al. 2003). At this stage, areas like the frontal lobe will fully develop (Sowell et al. 2001a, 2001b; Cowen et al. 2003). These anatomical areas are vital for behavioural control, planning and decision making (Garcia-Osta et al. 2004). If alterations of these brain regions occur during the maturation period, due to exposure to MDMA, these individuals may exhibit problems with impulsivity, planning and decision making in later life. A possible reason for the inconsistencies within the research concerning MDMA induced neurotoxicity amongst MDMA users could be that previous research has failed to control for the age of initial onset. MDMA may only be neurotoxic during the critical periods of development, for example adolescence. Users exposed to MDMA after the brain maturation are less likely to suffer from negative consequences in comparison to those that were exposed to MDMA in early development, which is the vital brain maturation period. This theory needs further investigation in both non-human animal and human studies.

Non-human animal studies have demonstrated that the environment during exposure to MDMA has an effect on possible selective functional changes within the brain (Cornish et al. 2003). This sample of current and past MDMA users in the present study consumed MDMA in similar environments. These 'club' environments suggest that MDMA users, past and present, are using MDMA in hot conditions with loud music, which may intensify the

neurotoxicity. Environmental factors need to investigated, in terms of human MDMA users. A small proportion of the current MDMA users consumed it in quiet environments. Future studies comparing 'quiet environments' with those that consume it in 'hot and crowded conditions' are needed. One might expect both the behavioural and neurotoxic impact of MDMA to be less in the 'quiet' users.

Factors such as diet, family history of drug use and history of mental illness were not highlighted as significant factors affecting the MDMA substance users in this study. For this reason, these factors were not pursued in terms of their effects on psychological functioning: depression, impulsivity, sleep, memory and executive functioning.

2.4   Overall summary

In summary, this section of the thesis described development of a DHQ. It includes pilot studies, and an initial reliability study. The DHQ targeted at MDMA polydrug users asking questions concerning MDMA and other illicit drug use. It is the first questionnaire attempting to gain information concerning co-use of MDMA with other recreational drugs, family history of drug use, diet, and psychiatric history.

The present study reports new findings concerning the pattern of use of amongst MDMA polydrug users and non-MDMA polydrug users. The study reveals previously unaddressed issues concerning differences in pattern of substance use between current MDMA polydrug users and past MDMA polydrug users. Results clearly demonstrate MDMA polydrug users co-use multiple substances either to improve the subjective effects or to counter balance negative effects of MDMA. This pattern of use is highly dangerous and this drug interaction needs to be addressed.

This study demonstrates that MDMA is escalating during the period of investigation (2002-2007). Most MDMA users still do not perceive MDMA as a seriously dangerous drug with adverse behavioural and neurotoxic consequences, particularly within the South-East England. The pattern of use of current MDMA users may exacerbate any MDMA induced psychological deficits and neurological changes. Further still, this study suggests that MDMA users abuse more substances than non-MDMA users in general. This merits the need for increased monitoring of MDMA substance users medically and investigating treatment options. Irrespective of the possible consequences of MDMA induced neurotoxicity, increased substance use per se in this MDMA group will most likely result in complications and increased severity.

The remainder of the study tested a total of 1399 participants on a battery of psychology tests: 997 participants on depression (chapter 3), impulsivity (chapter 4), sleep (chapter 5), memory (chapter 6) and 402 participants on executive functioning (chapter 7).

Chapter 3 – Depression

3.1 Introduction

This section will provide a brief introduction and definition of depression. It will review the evidence supporting the role of 5-HT in depression. Finally, it will evaluate non-human animal studies and human studies concerning MDMA exposure and depression.

3.1.1 The epidemiology of depression

To begin it is essential to provide an epidemiological account of depression and the common causes of depression.

Depression is a common psychiatric disorder occurring at any point throughout an individual's life. Research associates vulnerability towards depression to individual differences including gender; it is twice as likely in females, and age; the mean age ranging between 35-45 years of age (Evans et al. 1981; McGuffin et al. 1991; Hale,1997; Eley et al. 1999). Lifetime prevalence estimates for depression are controversial, with some figures as low as 2%, and others stating figures as high as 15% for the general population (Hale, 1997; Klaus et al. 2006). One major difficulty for predicting lifetime prevalence of depression includes it is often underestimated, as many depressed individual's will refuse help even though it is having a detrimental effect on their lives and consequently leads to increased suicidal rates (Klaus et al. 2006).

Approximately 8% of the population suffer from a combination of depression and anxiety (Hale, 1997). Co-morbidity of depression and other psychiatric disorders is common. Risk factors for the development of depression include divorce or separation, parental death before the age of 11, and family histories of depression and alcoholism (Hale, 1997; Klaus et al. 2006).

Clinical symptoms of depression are divided into physical symptoms (somatisation) and psychological symptoms (cognitive). Somatisation symptoms consist of any of the following: anhedonia, loss of reactivity (loss of emotional reactivity to normally pleasurable surroundings and events), early waking (>2 hours early), psychomotor retardation or agitation, marked loss of appetite, weight loss being more than 5% of body mass in one month, and loss of libido (Hale, 1997). The cognitive symptoms of depression include: loss of interest, guilt, feelings of worthlessness, hopelessness, lack of self-confidence and suicidal ideation (Hale, 1997).

In summary, depression is common and often a disabling disorder affecting all ages and genders. Depression can be attributed to major life events and drug use.

3.1.2   The role of serotonin in depression

This section will summarise the evidence suggesting there is an association CNS levels of 5-HT and depression.

Research suggests the aetiology of depression includes the monoamine theory (Smith et al. 1997). The link between 5-HT and depression was first reported in 1962. Since then the monoamine theory of depression has gone from strength to strength due to the mounting evidence (Reidlinger and Riedlinger, 1994). Low levels of 5-HT are associated with symptoms of depression. Research has suggested the 5-HT1A receptor is associated with depression (Smith et al. 1997). Symptoms that are associated with the 5-HT1A receptor include worthlessness, apathy, fear, fatigue and insomnia (Hale, 1997).

The most compelling evidence for the role of 5-HT in depression comes from studies measuring CSF and brain tissue concentrations of 5-HTT (the 5-HT metabolite) of patients whom are depressed (Smith et al. 1997). Smith et al. (1997) following a rapid depletion of 5-HT, caused by a lack of available tryptophan, found females relapsed into depression (Smith et al. 1997). The authors concluded that depression and relapse is caused by a lack of available CNS 5-HT. Evidence suggesting an association between clinical depression and reduced CNS 5-HT levels comes from the treatment for depression. Pharmacological treatment of depression includes selective serotonin reuptake inhibitors (SSRIs). SSRIs work by blocking the reuptake of 5-HT from the synapse. This will result in a greater amount of 5-HT being available for longer in the synapse hence increasing the chance of 5-HT attaching postsynaptically (Hale,1997; Klaus et al. 2006).

Research has suggested that depression is connected to additional neurotransmitters including DA, noradrenaline and GABA (Hale, 1997; Klaus et al. 2006). Compelling evidence for the role of DA in depression comes from Parkinson's disease and Schizophrenia. In both of these disorders, the primary physiological dysfunction is DA levels. In Parkinson's disease, it is a decrease in DA and in Schizophrenia it is too much DA. Epidemiology studies suggest that depression can be as low as 2% and as high as 70% for those with Parkinson's disease (Frey et al. 1996; Huges et al. 2004).

3.1.3 The role of MDMA in depression

As depression has been linked to 5-HT deficiency and MDMA is an initial 5-HT agonist, this section will summarise the evidence suggesting that MDMA can cause depression.

Experimental evidence has demonstrated that lowered levels of CNS 5-HT can lead to depression. Medical treatment for clinical depression includes SSRIs, which ultimately result in raising brain 5-HT levels. Non-human animal research has demonstrated that MDMA can be neurotoxic to 5-HT terminals. Since MDMA is neurotoxic to selective 5-HT neurons in non-human animals, is it plausible to suggest that similar neurotoxicity is occurring in specific 5-HT neurons in humans following exposure to MDMA. Therefore, it is possible to propose that if MDMA causes lowered 5-HT levels this would consequently result in deficits in psychological functioning including symptoms of depression. More compelling evidence involves experimental studies indicating the role of 5-HT1A receptor in depression. Research has associated MDMA with this 5-HT1A receptor. Non-human animal studies have demonstrated that the hippocampus is damaged following exposure to MDMA, with the full recovery of 5-HT neurons debateable (Klaus et al. 2006; Hale, 1997). Similarly, the hippocampus has been linked to depression. This provides further evidence to hypothesise that MDMA exposure will result in increase symptoms of depression in polydrug MDMA users (Klaus et al. 2006; Hale, 1997).

3.1.4 Non-human animal evidence for the role of MDMA in depression

This section will summarise the evidence suggesting that MDMA causes reduction in CNS 5-HT levels thus inducing depression like symptoms in non-human animal studies.

McGregor et al. (2003) investigated the long-term consequences of MDMA on anxiety and depression in rats. The rats were administered injections of MDMA consecutively for a period of 4 hrs over 2 days (McGregor et al. 2003). Following a period of 8 -18 weeks after drug abstinence, the rats were tested for social interaction, object recognition and the forced swim test demonstrating depression. The results from the study indicated that rats administered MDMA demonstrated increased anxiety as displayed by the social interaction task in addition to showing signs of depression as indicated by a lack of attempts to escape from the forced swim test and increased immobility overall. Post mortem, analysis of the brains of those treated with MDMA indicated a loss of 5-HT in several brain regions including the hippocampus, striatum, amygdala and cortex (Roiser and Sahakian, 2004). Research has proposed that the areas of the brain connected to mood and depression include the amydala,

hippocampus and frontal cortex. This study provides evidence that MDMA reduces 5-HT levels in specific areas of the brain and consequently has a direct effect on behavioural and psychological functioning in particular symptoms of depression. Research studies have found similar results using different methodologies (Thompson et al. 2004). A major criticism of the results from non-human animal studies is whether these results can be extrapolated to human MDMA polydrug users and if they actually represent depression in humans. This argument will be expanded upon in chapter 8.

3.1.5 Human evidence for the role of MDMA in depression

There has been limited evidence demonstrating depression caused by exposure to MDMA in non-human animal studies, predominantly due to the subjective nature of depression. There is, however mounting evidence suggesting that depression is elevated in current and past MDMA users.

The co-morbidity of depression and psychosis is often observed in the medical field (Gouxoulis et al. 1992; McGuire et al. 1994; Series et al. 1994). There have been several reported case studies of individuals' that have suffered from psychosis and depression following ingestion of MDMA. In fact, in three specific cases the individuals' stated they had only used MDMA on a few occasions (one had only ingested it once and two had consumed two doses on two separate occasions). Of these three cases, the psychosis commenced 12 hours following the exposure to MDMA. The three individuals' reported good health prior to the onset of psychosis/depression. The medical background of the individuals failed to provide justification for the persistence of the psychosis/depression and following a six months follow up period, the psychotic/depressive episodes persisted (Alciati et al. 1999). Consequently, all three cases were being prescribed anti psychotics medications (Alciati et al. 1999). These case studies failed to indicate whether the medical treatment improved symptoms and whether the symptoms were long lasting and permanent. However, other MDMA case studies include drug users that are chronic MDMA and polydrug users (Creighton et al. 1991; Schifano, 1991; McGuire et al. 1994). Criticisms of such case reports include the fact that they are only based on a small percentage of MDMA users. In comparison, many other individuals have consumed MDMA and have failed to report any psychological problems associated with the use of MDMA. The accurate recording of medical psychiatric histories, were not possible, instead confirmation was heavily relied upon from peers and family, which is far from reliable. Finally, it is very difficult to link such psychotic episodes with MDMA alone (Creighton et al. 1991; Schifano, 1991; McGuire et al. 1994,).

Other factors that may have caused the psychosis/depression need to be monitored: social factors, history of drug use and other medical factors.

Research has investigated the *acute psychological effects of MDMA*. These studies involved testing current polydrug MDMA users, on a battery of psychological tests, immediately after the ingestion of MDMA and a few days later (Curran and Travill, 1997). One study compared a MDMA polydrug group (n=12) with an alcohol only group (n=12) following a night spent in a club. Mid week (after 5 days) after the use of MDMA, the MDMA polydrug users only reported increased depression, with a few of the MDMA polydrug users self-reporting clinical symptoms of depression. The results from Curran and Travill (1997) found that the use of MDMA caused acute depression. However, a major criticism of the study was that the researchers failed to measure the participants' level of mood before they had consumed MDMA. Another major problem with the methodology of the study was the lack of controlling for the effects of other recreational drugs.

A similar study, investigating the acute psychological effects of MDMA compared regular MDMA users, novice MDMA users and non-MDMA control groups. The results reported two days after the ingestion of MDMA both the novice and regular MDMA groups were significantly more depressed, abnormally antisocial, and unpleasant in comparison to the non-MDMA controls (Parrott and Lasky, 1998). The results from this study indicated that exposure to MDMA can result in increased symptoms of depression. The main explanation provided for the result was that MDMA initially causes a surge in the release of 5-HT, which is subsequently followed by a decrease in CNS 5-HT levels. This change in CNS neurotransmitter levels may provide an explanation for the subsequent psychological and behavioural symptoms experienced following the exposure to MDMA. In summary an initial increase in positive mood was observed as MDMA was consumed, followed by a negative mood several days later as the 5-HT levels are reduced.

In most of these human studies investigating the acute psychological consequences of MDMA, a major flaw is the lack of controlling for other recreational drugs of abuse: nicotine, alcohol, cannabis and amphetamine. However, these results from these studies have recently been replicated by Verheyden et al (2002) following the inclusion of more control groups.

A self-reported psychological study employed a slightly larger sample size (n=29). The MDMA polydrug users reportedly consumed an estimated total lifetime mean of 527 MDMA tablets. The studies results found that MDMA polydrug users demonstrated significantly higher self-reported depression scores in comparison to matched non-MDMA control group.

The authors concluded the elevated depression scores were not a consequence of exposure to any other recreational drugs of abuse: alcohol, cannabis, and amphetamine (McInnes at el. 2001). The results from their study support the prediction that MDMA exposure is associated with increased depression symptoms in MDMA drug users.

A study investigating the behavioural effects of MDMA employed a wide battery of cognitive tests on all participants including monitoring depression as measured using the Beck Depression Inventory ([BDI] Beck et al. 1961) and the Profile of Mood States [PoMS]. The results from the study concluded that MDMA users reported higher levels of self-reported depression in comparison to non-MDMA control drug users (McCardle et al. 2004). The study only compared the MDMA polydrug group with only one control group being a non-MDMA polydrug group; making it difficult to attribute the behavioural results found to MDMA alone and not due to the consequences of other recreational drugs. However, their study does provide further psychological evidence that exposure to MDMA in humans can result in elevated acute depression scores.

A further study investigated the relationship between MDMA use and depression. This study further divided the depression scores into the cognitive-affective and somatic subscales of the BDI (Roiser and Sahakian, 2004). The results revealed that overall the current and ex-MDMA (abstained from MDMA for a mean period of 2.5 years) polydrug users reported higher depression scores in comparison to the drug naïve control group. This study was unable to find a significant difference between MDMA polydrug users and non-MDMA polydrug users even though the mean self-reported depression scores were higher for the current and ex-MDMA polydrug groups. With respect to the subscales of the BDI, there was a progressive positive increase in the cognitive scores between the drug naïve, poly-drug non-MDMA control, current MDMA polydrug and ex-MDMA polydrug groups respectively. This pattern was not observed for the somatic scores which resulted in the self-reported scores being similar across all four groups (current MDMA polydrug, ex-MDMA polydrug, non-MDMA polydrug control and drug naïve control group) (Roiser and Sahakian, 2004). Criticisms of this study include the fact that it only employed one polydrug group and failed to look at the other recreational drugs separately, for example alcohol, nicotine, cannabis, amphetamine and cocaine. The ex-MDMA polydrug users reportedly had consumed more than double the amount of MDMA in a lifetime than the current MDMA polydrug group. The frequency (times per month) of use of MDMA was significantly higher for the ex-MDMA polydrug group than the current MDMA polydrug group, thus the dosage of MDMA consumed in a lifetime for ex-MDMA and current-MDMA groups were not matched fully. The ex-MDMA polydrug group had abstained for a mean period of 2.8 years; suggesting depression caused by

using MDMA is not long lasting as other research and non-human animal studies have concluded. Finally, the sample used by Rosier and Sahakian to represent the population of MDMA users was small in numbers and therefore would not be a true representation of the diverse population of MDMA users. Their study needs to be replicated with larger samples and robust control groups.

Interestingly, there is considerable debate concerning the association between MDMA use and acute depression, with studies varying on the levels of depression and many studies failing to find a relationship between increased depression and MDMA exposure. In another clinical study, nine outpatient MDMA users from a clinical neuroscience research unit were monitored (Krystal et al. 1992). The study reported that the participants' had lowered levels of 5-HT. Their results reported that none of the participants' reported current anxiety or affective symptoms. The conclusions of the authors suggested that lowered levels of 5-HT might be a contributory factor in depression however it was not the exclusive cause (Krystal et al. 1992). They suggested that MDMA users might be attracted to MDMA, as a means of self-medication as they have lowered levels of 5-HT and are more prone to bouts of depression. This theory needs further exploration.

In a study in 2004, De Win and colleagues investigated 23 heavy MDMA polydrug users, 15 moderate MDMA polydrug users, 16 ex-MDMA polydrug users, and 15 non-MDMA polydrug users comparing depression scores using the BDI, in addition to the Composite International Diagnostic Interview (De Win et al. 2004). The results suggested that the depression scores did not significantly differ between any of the groups. There was a non-significant increase in self-reported depression scores for the MDMA groups. The BDI scores were correlated with the level of MDMA exposure. The authors concluded that a prospective study was required to establish the actual relationship between MDMA and mood.

Studies have reported a negative association between suicidal tendency and low levels of CSF 5-HIAA (Ricci and Wellman, 1990). Furthermore, there have been several reported incidents where exposure to MDMA has directly been implicated in suicide attempts (Cox, 1993 & Dowling, 1990). Further evidence is required to provide insight into the relationship between MDMA exposure, depression, suicide and anxiety.

In summary, up to the period 2006 there have been major flaws in the previous research investigating depression in MDMA polydrug users. These criticisms include the relatively small sample sizes employed in all studies, which fail to fully represent the population of current MDMA polydrug users and non-MDMA polydrug users. Where long lasting

consequences have been investigated, the maximum period of abstinence studied was a mean of 24 months. Most of the studies are based on young clubbers and are thus biased towards a particular proportion of MDMA drug users. Epidemiological studies suggest that MDMA is continually being consumed by professional people. The drug is attracting all ages, with many MDMA polydrug users being older than 30 years and this needs to be fully represented in future studies. Previous studies have been unable to fully account for all other recreational drugs: cannabis, alcohol, amphetamine, cocaine, LSD and ketamine; due to the limited control groups. The majority of MDMA users are polydrug users. Additional illicit drugs (including alcohol, nicotine, cocaine, cannabis, and amphetamine) have been associated with elevated mood disturbance and such recreational drugs need to be controlled for in future studies. Finally, another substantial criticism concerning previous work in MDMA and depression is the level of depression reported by the majority of MDMA polydrug users. Most MDMA polydrug users report a higher level of depression in comparison to non-MDMA polydrug users, this level of reported depression is minimal and classified as non-clinically depressed. Table 3.1 provides a brief summary of some of the human experimental and behavioural studies investigating the psychological effects on mood of MDMA.

Table 3.1   Summary of previous research investigating MDMA and depression

Provides a summary of a limited number of studies investigating the link between MDMA and depression during the period 1998 – 2010. The table provides details of authorship, test employed, the control groups included, whether long lasting effects were investigated and finally if they found a significant result.

Author	Test	Controls	Long lasting effects	Result
Bedi et al. 2008	Self reported measure	45 MDMA polydrug 48 THC polydrug 40 polydrug	No	Non-sig
Falck et al. 2008	BDI-11	402 MDMA polydrug	Yes	Non-sig
Durdle et al. 2008	Clinical Interview	226 MDMA polydrug	No	Non-sig
Medina et al. 2007	BDI-11	48 MDMA polydrug 17 THC polydrug	No	Non-sig
Gulliet et al. 2006	BDI-11	Frequent MDMA polydrug Non-MDMA	No	Non-sig
Lamers et al. 2006	Hamiliton Depression Rating Scale	11 MDMA/THC users 15 THC users 15 non-MDMA users	No	Increased depression MDMA vs controls
De Win et al. 2006	Self-report measure	59 MDMA 61 controls	Yes	Non-sig

82

Author	Test	Controls	Long lasting effects	Result
Falck et al. 2006	BDI-11	402 MDMA polydrug	No	MDMA user increased depression
Surnall et al. 2005	Meta-analysis	MDMA polydrug THC controls	No	Non-clinical depression in MDMA users
Soar et al. 2004	Case study	1 MDMA polydrug	Yes	Depression persisted 7 yrs after MDMA abstinence
Milani et al. 2004	SCL-90	228 MDMA polydrug 100 polydrug 96 THC 184 Alcohol/nicotine 149 non-drug	No	Non sig
McCardle et al. 2004	BDI-11	17 MDMA polydrug 15 controls	No	MDMA higher depression scores than controls
De Win et al. 2004	BDI-110 CIDI	38 MDMA polydrug 16 Ex-MDMA 15 polydrug	Yes	Non sig
Daumann et al. 2004	SCL-90	60 MDMA polydrug 30 controls	Yes	Non sig
Mathews and Bruno, 2010	Interview	100 regular MDMA users	No	23% reported depression
Schilt et al. 2010	Self-reported	17 heavy MDMA users 16 Mild MDMA users 20 non-MDMA users	No	Heavy users reported increased depression

Author	Test	Controls	Long lasting effects	Result
Rosier et al. 2004	BDI-11	30 current MDMA 30 polydrug 30 non-drug 20 ex-MDMA	Yes	Non sig
Verheyden et al. 2003	Interview	466 MDMA polydrug	Yes	Factor analysis identified long lasting depression
Parrott et al. 2002	Web questionnaire	282 MDMA polydrug 481 controls	No	MDMA casued depression scores elevated
MacInnes et al. 2002	BDI-11	29 ex-MDMA	Yes	MDMA elevated scores in comparison to controls
Vaiva et al. 2001	Case report	1 ex-MDMA	Yes	Psychosis following MDMA
Gamma et al. 2001	Hamilton	16 MDMA polydrug 17 Control	No	MDMA sign higher scores than controls
Schifano et al. 1998	Interview	150 MDMA polydrug	No	MDMA users presented with psychological problem

3.1.6 Summary of non-human animal and human MDMA studies (2007-2011)

Jaehne et al. (2011) investigated the role of MDMA on rats with a rat model of depression, the Flinders Sensitive Line (FLS). MDMA was administered to Sprawley-Dawley rats with depression and rats without depression. The results found that rats predisposed to depression, exhibited increased 5-HT loss. Post-mortem evaluation revealed further 5-HT neuronal damage in the FLS rats. The authors suggested human MDMA users pre-disposed to depression are more vulnerable and might be more susceptible to developing MDMA induced damage.

Schilt et al. (2010) investigated the role of MDMA in a group of middle-aged MDMA polydrug users. The study included a sample of heavy MDMA polydrug users (n=17), mild MDMA polydrug users (n=16) and a group of non-MDMA users (n=20). The results found that both the heavy and mild MDMA users differed on self-reported depression in comparison to the non-MDMA group. The authors concluded that future drug-related studies were needed to investigate not only young drug users, but also those middle-age drug users, in order to investigate the association between MDMA, 5-HT, cognition and the normal aging process (Schilt et al. 2011). Their study failed to control for other recreational drugs adequately including alcohol, cocaine and heroin. Secondly, the study did not investigate the long lasting consequences of MDMA. Finally, the study did not investigate the link between depression and other psychological functions including memory, executive functioning and sleep.

A longitudinal study monitored 402 MDMA polydrug users for a period of 2 years. During this 2-year period, participants were required to complete the Beck Depression Inventory every six months (Falck et al. 2008). The results found that depression scores decreased over the 2-year period however this was non-significant. Other factors attributed to the depression included gender, ethnicity, education and other drug use. The authors concluded that MDMA does not result in long-term depressive symptomatology. Falck et al. (2008) failed to have a non-MDMA control group to compare. One could argue that a 2-year follow-up would not be enough time to monitor long-term problems.

Even though the hypothesis of this thesis was formulated during 2001, it still remains a relevant and novel area of research in 2011. To date, no study has investigated the long lasting consequences of MDMA on depression including monitoring the effects of aging. Secondly, no single study has included the necessary control groups, monitoring the effects of other recreational drugs on depression including cannabis, cocaine, alcohol and amphetamine.

3.1.7   The measures of depression

The Beck Depression Inventory – Second Edition (BDI-II) is a 21-item self-report instrument measuring the severity of depression in adults and adolescents aged 13 years and older (Beck et al. 1961). The BDI-11 were developed for the assessment of diagnosing depressive symptoms corresponding to the diagnostic criteria for depression as stated in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-1V). Norm tables indicate that non-depressed individuals score a mean = 7.65 (±5.9), mildly depressed mean = 19.14 (±5.7), moderately depressed mean = 27.44 (±10) and severely depressed mean = 32.96 (±12). The BDI-11 is able to detect cognitive, affective, somatic and vegetative symptoms of depression. The BDI is a self-report measure of depression that has gone through extensive reliability and validity testing (Becks et al. 1988).

3.1.8   The research objectives

Research has demonstrated that clinical depression can have a detrimental effect on everyday living. Most persons suffering from long-term depression will eventually find that it encroaches on both their work and family life, predominately causing disruption to one or more. Around one in twenty patients seen by a general physician would be diagnosed with depression in the UK (Ebmeier et al. 2006). Consequently depression can be costly to the NHS as well as society as a whole. Treatment availability for depression includes psychotherapy or medications in the form of anti-depressants. The available and most commonly prescribed antidepressants presently include tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAOIs) (Hale, 1997). If MDMA is causing a person to have a predisposition towards depression or exposure to MDMA resulting in an episode of depression, it is feasible to predict that in 20-30 years time, with the combined aging process, the UK National Health Service (NHS) might experience an influx of MDMA related clinically depressed people. To prevent this increase in depression, more research is needed to clarify the relationship between depression and MDMA. Evidence is needed to locate the aetiology of this MDMA induced depression, which could further help education and government warnings against taking the drug and viewing it as 'safe'. Evidence needs to establish whether this depression is short lived or long lasting.

Based on previous psychological and non-human animal research in related areas, the following can be hypothesised: Firstly, current MDMA polydrug users will self-report elevated depression scores in comparison to other non-MDMA recreational polydrug drug users. Secondly, abstained MDMA

polydrug users will have similar overall self-reported depression scores to current polydrug MDMA users. Thirdly, abstained MDMA polydrug users will have similar self-reported cognitive and somatic symptoms to current polydrug MDMA users. Finally, the study will establish if there is a positive linear relationship between dosage of MDMA and the level of self-reported depression as measured by the BDI-II.

3.2   Methods

3.2.1   Participants

997 of the original 1399 participants were involved in this part of the study, based on a power calculation, where N=432 (Power calculation; minimum of 72 per group, power=0.80, δ=2.80 – Cohen, 1992; Faul et al. 2007; Faul et al. 2009). Overall the mean age of the sample was 25.1 years old (±7.4); with 523 (52%) being males. The participants were recruited from various sources: 1) WebPage (34%), 2) Local newspaper advertisements (6%), 3) snowballing technique (37%), 4) drug advisory centres (22%), and 5) unspecified (1%). All the participants reported good health and had no previous psychiatric history. All participants reported abstaining from using MDMA for at least three weeks prior to participation of the study (mean period 4 weeks).

The majority of participants (88%) were employed or in full time education at the time of participation of the study (34% education; 54% employment). The participants were split into 4 control groups and 2 separate MDMA groups: 182 non-recreational drug control group; 172 alcohol/nicotine control group; 163 cannabis/alcohol/nicotine control group; 169 polydrug control group whom had never used MDMA (had used other illicit substances at least once in lifetime e.g. heroin, ketamine, amphetamine etc); 154 current MDMA polydrug group (used MDMA in the last 6 months); 157 ex-MDMA polydrug group (abstained from MDMA for more than a year). The two MDMA groups were further split into 67 current less frequent MDMA users, 87 current frequent MDMA users, 49 less frequent ex-MDMA users and 108 frequent ex-MDMA users.

3.2.2   Measures

All participants were administered with the DHQ (refer to chapter 2 for full details, appendix 2.2). The structured interview asked 47 questions including basic demographics (age; educational background and ethnicity). Additional information included an extensive drug history, medical history and family drug history. Participants were asked specific questions concerning detailed recreational drug(s) use (MDMA, amphetamine, cannabis, ketamine, alkyl nitrites etc). Drug exposure was calculated by calculating the number of times per week * number of months per year * total number of years.

In addition, participants were given the short-form of the BDI-II (Beck Depression Inventory – Second Edition) to complete. The BDI-II consists of 21 four-choice statements. The overall total score is obtained by adding the highest score circled from each of the 21 items (each item was scored from 0-3). Maximum score was 63. The BDI-II is one of several depression scales developed to detect depression in routine clinical setting or research. The BDI-II was selected because of its simplicity of administration, scoring and interpretation.

The levels of self-reported depression were measured using two separate methods. Firstly, participants were asked to complete the BDI-11. Secondly, participants were asked about their own perceptions concerning the effects of MDMA. They were asked if they would, "describe themselves as depressed" and if so, whether they, "felt the depression was linked to the use of recreation drugs they had previously consumed" and finally, "if the depression was associated with any specific recreational drug(s)".

3.2.3   Ethical Issues

All participants provided written consent to partake in the study. Participants were able to withdraw at any point throughout the study and were informed of this. All data was anonymous and bar-coded. The study was approved by the local Ethics Committee in 2001, London Metropolitan University formally known as London Guildhall University. All participants were provided with a briefing and debriefing concerning the study (Appendix 3.1).

3.2.4   Statistical Analysis

Data was analysed using Statistical Package for the Social Sciences (SPSS) version 16.

A one-way ANCOVA was run; the outcome variable was the mean depression scores measured by the BDI-11; the predictor variable was the drug group (non-recreational drug control group; alcohol/nicotine control group; cannabis/alcohol/nicotine control group; non-MDMA polydrug control; current MDMA polydrug group; ex-MDMA polydrug group) and the covariate was lifetime use of cannabis, amphetamine, cocaine, and ketamine.

The two MDMA groups were further split into 67 current less frequent MDMA users, 87 current frequent MDMA users, 49 less frequent ex-MDMA users and 108 frequent ex-MDMA users depending on whether they had used MDMA less than 20 times (less frequent) and those that had used it more than 21 times (more frequent). The results were further analysed using post hoc Bonferroni test, where

appropriate.

The ANOVAs and ANCOVAs were checked for normality using the Kolmogorov-Smirnov and Shapiro-Wilk test. As the tests were significant, the data was transformed to logs and the normality test re-checked. The log transformed data was non-significant, suggesting the data was normally distributed. The kurtosis and skewness were checked for values between -2 and 2. The log transformed data was plotted using the output of a quantile-quantile (Q-Q) plot. As the data did not stray from the predicted line, the data was linear and normally distributed. The covariate in the analysis was checked for its independence from the experimental manipulation; an ANOVA with the covariate as the outcome and the drug group as the predictor was run for all of the covariates (cannabis, amphetamines, cocaine and ketamine).

For the ANCOVA, the Levene's test of the homogeneity of variance assumption was checked for non-significance relating to the homogeneity of residuals. The residual plot was checked for assumption of equality of variance. The spread vs. level plot was used to check there was no relationship between the mean and standard deviation. The homogeneity of regression slopes was checked by customising the ANCOVA model in SPSS to look at the independent variable * covariate interaction. The interaction term was tested in addition to the main effects. The log transformed interaction term (independent variable * covariate interaction) was non-significant; the assumption of homogeneity of regression slopes was not broken.

Log transformed self-reported BDI-11 depression scores were correlated with log transformed self-reported lifetime MDMA exposure using the Pearson correlation coefficient.

Multiple regression analysis was performed on the log transformed BDI-11 depression scores with the log transformed lifetime exposure to recreational drugs (MDMA, alcohol, cannabis, nicotine, amphetamine, cocaine, LSD, steroids and ketamine) as the predictor variables. Using SPSS, the variance inflation factor (VIF) and tolerance statistics were checked. The VIF values were below 10 and the tolerance statistics were all above 0.2. The residual statistics was checked for extreme cases. The standardised residuals were all between -2 and 2. The Cook's distance was checked and all values were below 1. 5. The DFBeta statistics was checked to make sure no value was greater than 1. Examination of the residual plots demonstrated the data did not stray from the predicted line; the data was linear and normally distributed. The Levene's test was checked; it was non-significant thus homogeneity of variance was assumed. Homoscedasticity and hetroscedasticity were checked visually by plotting the standardised residuals (the errors) by the regression standardised predicted value. The residuals were randomly scattered around the horizontal line (0) (Tabachnick and Fidell, 2001).

Median lifetime exposure to all recreational drugs was compared using the Kruskal Wallis test. If the Kruskal Wallis test was significant, the data was further analysed using the Mann Whitney test.

Two one-way ANOVAs were run; the outcome variables were the subscales of the BDI being the cognitive and somatic scores and the predictor variable being the drug group. The cognitive subscale of the BDI-II was calculated by adding the scores for each person on the following items: sadness, past failures, loss of pleasure, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal thoughts, crying, agitation, loss of interest, indecisiveness, worthlessness, and irritability. The somatic subscale was calculated by adding the scores from the following items: loss of energy, changes in sleeping pattern, changes in appetite, concentration difficulty, and tiredness.

3.3   Results

3.3.1   BDI-II Scores

The ANOVAs checking the covariates independence from the experimental manipulation were non-significant; demonstrating independence between the predictor and covariate for the ANCOVA. For the ANCOVA, the data was checked for homogeneity of residuals, equality of variance, normality and the homogeneity of the regression slopes were all checked for the ANCOVA.

For the multiple regression analysis, the data was checked for multicollineraity, curvilineraity, hetroscedasticity and homogeneity of variance, and finally normality.

The covariate, cannabis, was non-significantly related to the depression scores, $F(1, 991) = 0.019$, $p > 0.05$. The covariate, amphetamine, was non-significantly related to the depression scores, $F(1, 991) = 0.127$, $p > 0.05$. The covariate, cocaine, was non-significantly related to the depression scores, $F(1, 991) = 0.058$, $p > 0.05$. The covariate, ketamine, was non-significantly related to the depression scores, $F(1, 991) = 0.014$, $p > 0.05$. There was an overall significant effect of depression scores on drug group controlling for the effect of cannabis, amphetamine, cocaine and ketamine, $F(5, 991) = 137$, $p < 0.01$.

The four MDMA groups reported overall elevated mean depression scores in comparison to the four non-MDMA control groups. There was a difference in self-reported depression scores as measured by the BDI-II was between the four control groups (non-drug, alcohol/nicotine control, alcohol/nicotine/cannabis control, and non-MDMA polydrug control) and the four MDMA groups (less frequent current MDMA polydrug users, frequent MDMA polydrug users, less frequent ex-MDMA polydrug users and frequent ex-MDMA polydrug users) controlling for lifetime exposure to cannabis, ampethamine, cocaine and ketamine (Figure 3.1).

Further analysis demonstrated that there was a non-significant difference in self-reported depression scores between the current MDMA polydrug users and ex-MDMA polydrug users (Bonferroni Post Hoc, mean diff=0.85 p>0.05; Figure 3.1), with past and present MDMA users reporting similar levels of depression.

The mean scores between the less frequent current MDMA polydrug users and the frequent current MDMA users were similar in self-reported depression scores between less frequent current MDMA polydrug users and frequent MDMA polydrug users (Bonferroni Post Hoc, mean diff=0.54, p>0.05; Figure 3.1).

Further statistical analysis failed to find a significant difference in self-reported depression scores between less frequent ex-MDMA polydrug users and frequent ex-MDMA polydrug users (Bonferroni Post Hoc, mean diff=0.75 p>0.05; Figure 3.1), with the mean depression scores reported being similar.

Figure 3.1: The overall BDI scores for each drug group (mean ± S.E.M), N=997, where * p<0.05.

The figures display the mean overall BDI score for each drug group. Where the groups include: non-recreational drug control group (non-drug)=182; alcohol/nicotine control group (alcohol/nicotine)=172; alcohol/nicotine/cannabis control group (alcohol/nicotine/cannabis)=163; non-MDMA polydrug control group (polydrug non-MDMA)=169; current frequent MDMA polydrug group (current frequent MDMA)=87; current less frequent MDMA polydrug group (current less frequent MDMA)=67, ex-frequent MDMA polydrug group (ex-frequent MDMA)=108, ex-less frequent MDMA polydrug group (ex-less frequent MDMA)=49.

*denotes a significant difference between non-drug & alcohol/nicotine & nicotine/alcohol/cannabis & non-MDMA polydrug groups in comparison to the current less frequent MDMA & current frequent MDMA & ex-less frequent MDMA & ex-frequent MDMA groups, where p<0.01

There was a significant positive correlation between the self-reported depression score as measured by the BDI-II and the total amount of self-reported reported lifetime MDMA consumed (r=0.61, p<0.01), indicating increased exposure to MDMA results in elevated depression scores.

3.3.2 Somatic dimension of the BDI-II

For the somatic dimension of the BDI-II, the overall mean score progressively increased for each drug group.

The results found that the lowest mean somatic depression score was for the non-drug group. The alcohol/nicotine group reported a lower mean somatic score in comparison to the alcohol/nicotine/cannabis group. The non-MDMA polydrug displayed a lower mean somatic score than the two MDMA groups (current-MDMA polydrug, and ex-MDMA polydrug group); which displayed similar somatic scores, $F(5, 991) = 56.7$, $p<0.01$; further analysed using Bonferroni Post hoc test.

The results demonstrated that elevated exposure to recreational drug results in higher scores for loss of energy, changes in sleeping pattern, changes in appetite, concentration difficulty, and tiredness (Figure 3.2).

There was a non-significant difference in mean somatic scores between current and ex-MDMA polydrug users, with the past-MDMA users reporting increased mean somatic scores in comparison to the current-MDMA users (Bonferroni Post Hoc test, $p>0.05$, Figure 3.2).

Figure 3.2: The somatic subscale scores of the BDI-II for each drug group (mean±s.e.m), N=997.

The figure shows the mean scores for the somatic subscale of the BDI-II for the different groups. Where the groups include: non-recreational drug control group (non-drug)=182; alcohol/nicotine control group (alcohol/nicotine)=172; alcohol/nicotine/cannabis control group (alcohol/nicotine/cannabis)=163; non-MDMA polydrug control group (polydrug non-MDMA)=169; current-MDMA polydrug group (current-MDMA)=154; ex-MDMA polydrug group (ex-MDMA)=157.
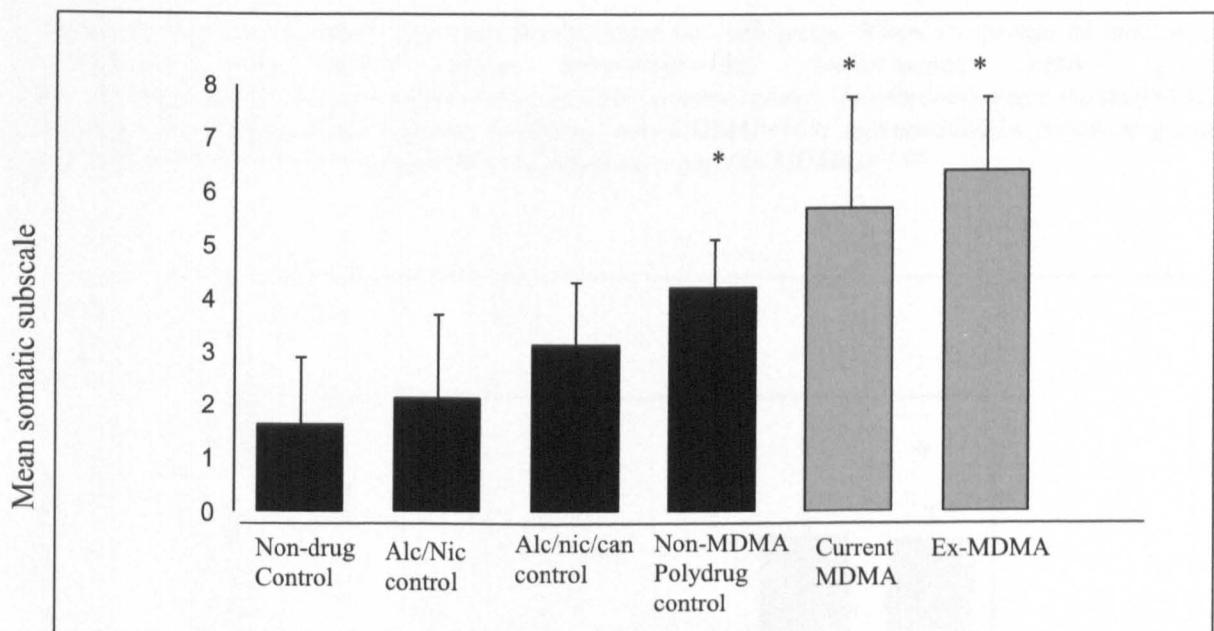
* denotes a significant difference between non-drug & alcohol/nicotine & alcohol/nicotine/cannabis groups in comparison to current-MDMA and ex-MDMA polydrug groups, where p<0.01

* denotes a significant difference between non-drug group & alcohol/nicotine groups in comparison to non-MDMA polydrug group, where p<0.01

3.3.3   Cognitive-Affective dimension of the BDI-II

Overall, the self-reported mean scores for the cognitive affective dimension of the BDI was similar between the control groups. Statistical analysis revealed there was a non-significant difference in overall mean cognitive-affective dimension scores between the four control groups: non-drug, alcohol/nicotine control group, alcohol/nicotine/cannabis control group, and non MDMA polydrug control group, analysed using Bonferroni Post hoc test, p>0.05.

On the other hand, there was a significant difference in mean cognitive-affective scores between the four control groups and the two MDMA groups: current-MDMA polydrug group, and ex-MDMA polydrug group, $F(5, 991) = 171$, p<0.01; further analysed using Bonferroni Post hoc test, (Figure 3.3),

where the current and past MDMA users reported increased mean scores. This suggests that exposure to MDMA affects the cognitive-affective dimension of depression only. There was a non-significant difference in mean cognitive-affective scores between current and ex-MDMA polydrug users (Bonferroni Post Hoc test, $p>0.05$), with past and present MDMA users reporting similar mean cognitive-affective scores.

Figure 3.3: Cognitive-affective subscale of the BDI-II for each drug group (mean±SEM), N=997, * where p<0.01.

The figure displays the mean cognitive-affective score for each group. Where the groups include: non-recreational drug control group (non-drug)=182; alcohol/nicotine control group (alcohol/nicotine)=172; alcohol/nicotine/cannabis control group (alcohol/nicotine/cannabis)=163; non-MDMA polydrug control group (polydrug non-MDMA)=169; current-MDMA polydrug group (current-MDMA)=154; ex-frequent MDMA polydrug group (ex-MDMA)=157.
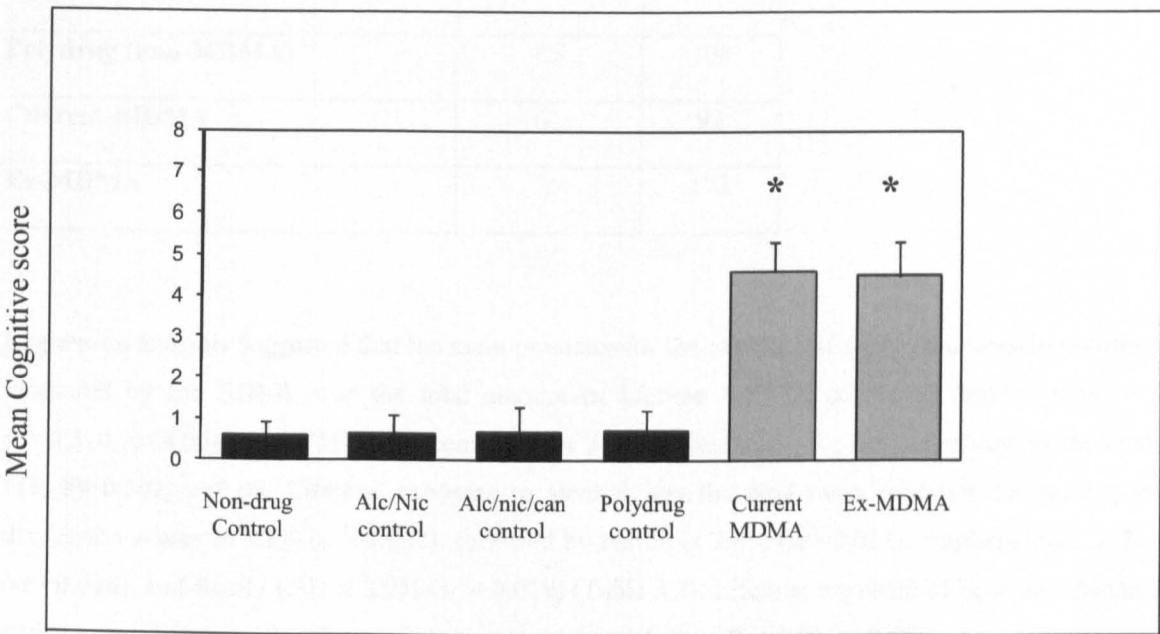
* denotes a significant difference between non-drug & alcohol/nicotine & nicotine/alcohol/cannabis & non-MDMA polydrug groups in comparison to the current less frequent MDMA & current frequent MDMA & ex-less frequent MDMA & ex-frequent MDMA groups

There was a non-significant difference in the self-reported responses to the overall depression question, which asked participants if they were depressed and experienced symptoms of depression. The question only required a 'yes' or 'no' response. The response were similar between all four control groups (non-drug, alcohol/nicotine, alcohol/nicotine/cannabis, and non-MDMA polydrug) and the two MDMA groups (current-MDMA polydrug and ex-MDMA polydrug group) with equal percentage of response between all respondents (Table 3.2; Chi square = 0.973, df=5, $p>0.05$).

Table 3.2: Responses to self-reported depression

The table demonstrates the percentages of participants that acknowledged depression (Chi square = 0.973; df=5, p>0.05). There were no differences in responses between the six groups (non-drug control, alcohol/nicotine control, alcohol/nicotine/cannabis control, non-MDMA polydrug control, current MDMA polydrug and ex-MDMA polydrug group, where N=997.

	Yes	No
Non-drug	68	114
Alcohol/nicotine	67	105
Alcohol/nicotine/cannabis	64	99
Polydrug (non-MDMA)	65	104
Current-MDMA	61	93
Ex-MDMA	55	102

Regression analysis suggested that the main predictor for the overall self-reported depression scores, as measured by the BDI-II, was the total amount of lifetime MDMA consumed (beta = 0.39; t=13, sr^2=0.324, p<0.00), where MDMA accounted for 38% of the reason for the depression in the model, $F_{(3, 8)}$=9.302, p<0.05. Lifetime exposure to alcohol was the next main predictor for self-reported depression scores at 7.2% (sr^2=0.062), followed by heroin at 3.8% (sr^2=0.021), amphetamines at 3.3% (sr^2=0.018), and finally LSD at 3.2% (sr^2= 0.019) (Table 3.3). Lifetime exposure of ketamine, cannabis, and cocaine were non-significant predictors in this model, $F_{(3, 8)}$=9.302, p<0.05.

Table 3.3   Regression coefficients for BDI-II and drugs of abuse

The table provide details of the regression coefficients for each drug of abuse (MDMA, ketamine, tobacco, heroin, alcohol, amphetamines, cannabis, LSD and cocaine) and the overall BDI-II scores. The regression was only performed on the past and present MDMA users (n=311).

Drug	Predicts	Beta	t	p
MDMA	38	0.39	13.28	0.00
Ketamine	0.3	0.05	1.67	0.096 (ns)
Tobacco	3.1	0.17	5.5	0.000
Heroin	3.8	0.31	6.46	0.000
Alcohol	7.2	-6.24	-9.92	0.000
Amphetamine	3.3	1,46	7.24	0.000
Cannabis	0.1	-.03	-0.47	0.64 (ns)
LSD	3.2	0.23	7.55	0.000
Cocaine	1	-0.06	-1.163	0.103 (ns)

3.3.4   Demographics of previous drug use

For a full account of the demographic details for the different groups including age, ethnicity, working status etc refer to chapter 2.

The ex-MDMA polydrug group indicated they had initially consumed MDMA for the first time at an older age (mean age 23) in comparison to the current-MDMA polydrug group (mean age 18). The current polydrug MDMA group reported consuming a larger dose of MDMA (mean tablets of 1.3) during their first experience of using the drug than the ex-MDMA polydrug group (mean tablets of 1.25). The current-MDMA polydrug group self-reported being exposed to a larger dose of MDMA on average during a single occasion (mean tablets on a single occasion was 2.19) in comparison to the ex-MDMA polydrug group (mean tablets on a single occasion 1.5). Finally, the current-MDMA polydrug group self-reported consuming more MDMA tablets in a lifetime (mean lifetime tablets 922) than the ex-MDMA polydrug group (mean lifetime tablets 482) (Table 3.4). Finally, all MDMA participants reported that their usual route of administration of MDMA was via tablet and they normally consumed MDMA with friends.

Table 3.4: Basic demographics for the current and ex-MDMA groups.

The table provides basic demographic details concerning history of MDMA use. Including information concerning MDMA use including age first used MDMA; amount of MDMA first used; amount of MDMA normally consumed and lifetime amount of MDMA consumed; (n=311). *p<0.05.

	Age first tried MDMA	No first Used	No Used Permanently	Total used in lifetime
Current MDMA group	18.0*	1.32	2.19	922*
	(3.72)	(0.79)	(1.05)	(750)
EX-MDMA group	23.4*	1.25	1.54	482*
	(6.14)	(0.58)	(1.22)	(727)

* denotes significant different between current MDMA group and ex-MDMA group (p<0.05)

There was a slight variation in the percentage of users exposed to other recreational drugs of abuse amongst the different drug groups (non-MDMA polydrug, current-MDMA polydrug, ex-MDMA polydrug) (Table 3.5a). Overall the percentage of current MDMA polydrug users that had been exposed to alcohol and cannabis was less in comparison to the other two drug groups being ex-MDMA polydrug and non-MDMA polydrug users (Chi square=64.2, df=60, p>0.05). The percentage of non-MDMA polydrug users exposed to nicotine, tranquilisers, steroids, cocaine, LSD, psilocybin and alkyl nitrites was less than in the two MDMA groups. Finally, the ex-MDMA polydrug users were less likely to use amphetamines in comparison to the non-MDMA polydrug and current MDMA polydrug users. Psilocybin, alkyl nitrites, and LSD were used more by the ex-MDMA polydrug users in comparison to the non-MDMA polydrug and current MDMA polydrug users.

Table 3.5a: Exposure to other recreational drugs

The table provides the percentage of drug users self-reported exposure to recreation drugs of abuse for the three drug groups, which includes non-MDMA polydrug, current MDMA polydrug and ex-MDMA polydrug groups (Chi square =64.2, df=60, p>0.05). Where LSD=lysergic acid diethylamide.

Recreational Drug	Non-MDMA polydrug user	Current MDMA Polydrug user	Ex-MDMA Polydrug User
Amphetamines	49%	52%	45%
Nicotine	63%	77%	75%
Tranquilisers	13%	18%	16%
Alcohol	98%	91%	95%
Steroids	13%	17%	15%
Cannabis	98%	90%	93%
Cocaine	40%	58%	44%
LSD	19%	29%	32%
Psilocybin/psilocin	24%	28%	29%
Alkyl nitrites	12%	33%	37%

In terms of overall self-reported lifetime exposure to recreational drugs there were several differences observed between the different drug groups (current-MDMA polydrug group, ex-MDMA polydrug group, non-MDMA polydrug group) (Table 3.5b). The current MDMA polydrug groups reported less exposure to alcohol (U=21, p<0.05), nicotine (U=7.6, p<0.05), LSD (U=24, p<0.05), alkyl nitrites (U=26, p<0.05) and gases (U=22.4, p<0.05) in comparison to the non-MDMA polydrug and ex-MDMA polydrug groups. The current-MDMA polydrug group did report greater lifetime exposure to cocaine (U=28, p<0.05) and ketamine (U=28.7, p<0.05) than the other two groups; non-MDMA polydrug and ex-MDMA polydrug group. The ex-MDMA polydrug group self-reported elevated exposure to alcohol (U=21, p<0.05), nicotine (U=7.6, p<0.05), amphetamines (U=17, p<0.05), steroids (U=22, p<0.05), cocaine (U=28, p<0.05), LSD (U=24, p<0.05), alkyl nitrites (U=26, p<0.05) and gases (U=22.4, p<0.05). Finally, the non-MDMA polydrug group self-reported less exposure to amphetamines (U=17, p<0.05), steroids (U=22, p<0.05), cocaine (U=28, p<0.05) and ketamine (U=28.7, p<0.05).

Table 3.5b: Lifetime exposure to recreational drugs

*Table illustrates the total self-reported lifetime exposure to recreational drugs of abuse (mean/SD), N=997. Calculated using formula (no of occasions per week * no of months per year* no of years). Where * Mann-Whitney test, p<0.05.*

	Nicotine/alcohol	Nicotine/ alcohol/Cannabis
Alcohol	1188 (1172)	759 (754)
Nicotine	46649 (41057)	31631 (26422)

	Polydrug (non-MDMA)	Current MDMA	Ex-MDMA
Alcohol	1390 (1138)	697 (739)	2171 (980) *
Cannabis	1026 (1031)	2351 (693)	3476 (567) *
Nicotine	53710 (29852)	29454 (25875)	81025 (34313) *
Amphetamine	46 (94)	103 (61)	168 (81)*
Tranquillisers	1.92 (3.9)	14.3 (2.5)	17.04 (3.4)
Steroids	7.69 (15.8)	12.31 (10.26)	28.15 (13.6) *
Cocaine	2.18 (3.89)	13.59 (2.5)	17.25 (3.3) *
Crack	45 (39)	84 (46)	75 (26)
LSD	85 (22)	58 (30)	194 (280) *
Psilocybin/Psilocin	5.71 (2.65)	12.21 (4.3)	14.13 (3.7)
Alkyl Nitrates	45.2 (39)	29.6 (33)	65.11 (35.7) *
Gases	25.99 (23.6)	11.53 (15.4)	42.2 (20.4) *
Heroin	1.96 (3.9)	4.53 (3.3)	6.51 (3.57)
GHB	0.64 (1.68)	11.67 (1.09)	2.81 (1.41)
Ketamine	0.54 (0.24)	13.79 (1.4)	1.25 (1.2) *

* p<0.05 polydrug vs current MDMA and ex MDMA polydrug

3.4   Discussion

The findings from this study found past (abstained for a mean of 5 years; range 5-11 years) and present MDMA polydrug users had similar overall BDI scores and these were elevated in comparison to other non-MDMA users. These findings are in agreement with previous research in the field (McGuire et al. 1994, Creighton et al. 1991, Schifano, 1991, Curran and Travill, 1997, Roiser and Sahakian, 2004, Thompson et al. 2004). The study found that MDMA users past and present reported increased cognitive scores on the BD-II in comparison to other drug users. To date, this is the first study based on human participants to have found a similarity in self-reported depression scores between past and present MDMA users (abstained for a mean period of 5 years; range 5-11 years). The results from the present study, suggest that exposure to MDMA may led to increased self-reported acute and long lasting depression, irrespective of how long the users has abstained from the drug. Similar findings reported in non-human animal studies, where non-human primates have failed to show complete regeneration of damaged 5-HT nerve 7 years following MDMA exposure (Ricaurte et al. 2000). Concerning the somatic dimension of depression, it seems illicit drugs effect this dimension of depression and it is more likely to be associated with the overall use of illicit drugs rather than MDMA itself.

The results from this study indicate that the elevated depression scores were unlikely to be a result of exposure to other recreational drugs including alcohol, cannabis, amphetamine and cocaine. The other recreational drugs were included as covariates in the ANCOVA calculation and were not significant predictors in the regression model for the prediction of self-reported depression in MDMA polydrug users. There is currently a considerable amount of research and suggestions that depression is caused by cannabis use alone and is not the consequence of MDMA use (Croft et al. 2001; Dafters et al. 2004a; Parrott et al. 2003; Daumann et al. 2004; Braida et al. 2005; Sala et al. 2005). This study included a separate cannabis control group in a regression model and correlation analysis. These findings from this study contradict previous research, which has failed to control for previous exposure to other illicit drugs, suggesting that exposure to MDMA does not cause elevated self-reported depression.

The results from this study revealed that there was a non-significant difference in depression levels between those that had used MDMA frequently (more than 20 occasions) and those that had used it less frequently (less than 20 occasions) in their life time. This may suggest that taking MDMA just a few times in one's lifetime may cause irreversible selective 5-HT neuronal damage, which is supported by evidence from non-human animal studies (Schnieder, 1973; Sachs et al. 1975; Wiklund et al. 1978; Bjorklund et al. 1979; Levitt et al. 1980; Jonsson et al. 1982; Frankfurt et al. 1984; Gustafson et al. 1987; Fritschy et al. 1992a, 1992b; Ricaurte, 2000a, 2000b, 2000c; Boot et al. 2000; Mueller et al.

2009a, 2009b; Perrine et al. 2010; Biezonski and Meyer, 2010; Li IH et al. 2010; Mueller et al. 2011). However, it is plausible to predict that certain individuals are more prone to MDMA-induced neurotoxicity and depression. The possible MDMA induced depression needs investigating with non-human animal and human studies, with regard to amount of exposure and dosage of MDMA.

Results from this study concluded that MDMA polydrug users were unable to acknowledge or were aware of any 'feelings of depression'. This study found that the majority of MDMA polydrug users failed to recognise and admit overall depression. However, they were aware of individual symptoms as measured by the BDI-II. MDMA polydrug users failed to associate these individual symptoms of depression as measured by the BDI-II to the exposure to MDMA. This finding in itself may be problematic, as a lack of insight into the dimensions of depression (notably suicidal ideation, hopelessness and pessimism) may lead to future work related and social problems. These individual symptoms may additionally increase the chance of more drastic behavioural problems and could increase the risk of suicide in past and present MDMA polydrug users. Evidence for this notion comes from research by Beck, 1988 that found the BDI-II pessimism item was nearly as predictive of eventual suicide in 211 suicidal ideators as the 20-item Beck Hopelessness Scale (Beck et al. 1988 & Beck and Steer, 1988). A case study reported by Cox in 1993 highlights the risk of suicide due to MDMA use, where the case study linked MDMA use and suicide. A 21-year-old man was admitted to a psychiatric hospital 24 hours after the use of MDMA. He had no previous history of MDMA use and no other recreational drugs apart from alcohol, cannabis, amphetamine, and nicotine on one occasion. Following the MDMA ingestion, reports of his behaviour were increasingly 'bizarre' and he was threatening to commit suicide. After 8 days, he was released from hospital and subsequently committed suicide. The author concluded that the suicide was 'almost certainly' associated to the use of MDMA (Cox, 1993). However, this was an isolated case study; large scale surveys of suicidal ideation are required. This finding has a considerable impact on quality of life for future, present and past MDMA polydrug users. MDMA users need to be aware of possible suicidal ideations and psychiatric problems. Another major consideration would be for possible treatment and therapy session for past MDMA polydrug users, since cognitive biases may be detrimental in preventing rehabilitation and causing probable relapse. MDMA users past and present continue to use other illicit drugs. MDMA users may continue to mask any suicidal tendencies due to continual drug use and self-medication, which is very problematic in itself. This needs further exploration with MDMA users becoming aware of the possible risk factors associated with MDMA use.

From the results presented, it is possible that present, past and future MDMA users will develop severe depression. Most MDMA users are young adults when they begin using this drug. The mean age of the past MDMA users in this study was 32 years old. Previous studies demonstrate that depression peaks during the mid 40s within the non-clinical population (Hale, 1997; Klaus et al. 2006). The majority of

the sample of current MDMA polydrug users included in this study was in their mid 20s, implying that during their mid 40s, these MDMA polydrug users may experience severe symptoms of depression which may manifest as clinical depression. Health care professionals need to be aware of this possible sudden influx of depressed persons in the next 10-20 years. Treatment strategies and rehabilitation would need planning to accommodate this sudden MDMA induced epidemic.

A major criticism of previous research investigating MDMA abuse and its association to elevated depression has been the somewhat marginal increase in depression scores for MDMA users. Previous studies have reported that MDMA polydrug users self-report a mean BDI-11 score ranging 7-9. The critics argue that this level of depression reported in previous studies is regarded as normal and would not be deemed clinically depressed in the medical field. Results from this study revealed that the mean BDI-II scores ranged from 12-15 for current and past MDMA polydrug users. The depression scores are above baseline normality for depression in the clinical setting; although these individuals are not deemed clinically depressed. However, it needs to be raised that the objective of this research is to attempt to suggest and predict what may happen in the future if young adults continually abuse MDMA. In respect to the results from this study, it is highly improbable to suggest that a 30-year-old MDMA polydrug user, whom is employed with a comfortable lifestyle, will experience clinical depression. In addition, it could be elaborated further to predict that as this abstained MDMA polydrug user ages and with the continual life pressures this level of depression will continue to progressively increase and reach clinical levels, which would not have happened if the person had never been exposed to MDMA. These findings provide evidence of this proposal, however future studies need to provide clear evidence to support this theory.

Previous studies investigating MDMA with elevated depression scores and symptoms have been highly criticised with regards to the restricted control groups employed in the studies. These studies have lacked the control of other essential illicit drugs, which have been associated with increased depression, for example cannabis. Secondly, the sample sizes and method of recruitment for previous studies have failed to fully represent the population of MDMA polydrug users. These studies have been biased towards young adults in the dance/rave scene. This study robustly controlled for other illicit substances: cannabis, alcohol, nicotine, amphetamines, cocaine and heroin. The sample size and the recruitment of drug users in this study more closely resembled modern drug users than previous studies.

3.4.1 Limitations and future studies

This study relied heavily on self-reported measures of depression including the use of the validated and reliable BDI-II as well as self-reported closed question. These measures can be inconsistent and is dependent on the participant accurately filling out the questionnaire. Future studies measuring

depression may need to use a combination of self-reported measures, in addition to experimental techniques. One technique measuring depression would include 'learned helplessness'. This experimental method has been a reliable and valid measure for depression and employed in non-human animal and human research (Becks et al. 1988). Diagnosis of depression by a psychiatrist in addition to self-reported measures of depression may also prove to be beneficial in future studies. However, it should be noted that the BDI-II is an established clinical tool, which has been through validation and reliability testing.

The present results cannot conclusively state whether MDMA alone or a combination of MDMA with other recreational drugs (amphetamine, cannabis, and cocaine) caused the increase in depression. In order to provide a more comprehensive answer to this hypothesis, a sample of MDMA only users, which had only been exposed to MDMA would need to be compared with users that have been exposed to a combination of MDMA and other recreational drugs. This gap in the research may provide an explanation for the discrepancies in the findings in previous research, in addition to explaining the differences in results between the non-human animal and human studies. In the non-human animal studies, the history of the animal and the lack of exposure to other recreational drugs are recorded, in addition to the level of exposure of MDMA being accurate. Previous non-human animal studies have mainly focussed on the effects of MDMA alone; future studies should focus on the combination of MDMA and other recreational drugs. In human experiments, it is reliant on memory and self-reported techniques, leading to possible false information with incorrect conclusions being formulated. The inclusion of longitudinal studies in future human MDMA research would be beneficial for tackling this problem. However, if it is indeed the consequence a cocktail of drugs including MDMA, this is even more of a concern as drug users seem to be co-using illicit drugs more in modern day society.

The literature on the aetiology of depression is exhaustive. Research suggests a possible genetic cause for depression. Some MDMA polydrug users may already be genetically prone towards depression; consequently they require the exposure of an additional factor for symptoms to begin to occur. It is plausible that MDMA polydrug users genetically prone to depression are more likely to suffer severe depression and possible clinical depression following exposure to MDMA, as the exposure to MDMA results in reduced levels of brain 5-HT. This MDMA exposure may be the triggering factor for the onset of depression. Those individuals that use MDMA and are not genetically prone to depression are less likely to suffer from depression in later life. This may explain the inconsistencies in the current research findings. A possible way to investigate this theory would be to compare identical twins that have used MDMA or to compare first-degree relatives. If this is the case, then individuals more susceptible to MDMA induced depression need to be screened and offered medical assistance.

Causal effects for depression include life events such as divorce, losing a parent at a young age and sexual abuse. These factors were not controlled for in this study. It is possible that MDMA polydrug drug users seek MDMA to try to escape from memories and/or thoughts concerning stressful life events. MDMA is a psychotropic drug that improves mood, thoughts and empathy. Future studies investigating mood and MDMA use needs to control for life events including the history taking of any divorce, sexual abuse and loss of a loved one.

The literature on depression indicates there is a high co-morbidity rate between depression and other psychiatric disorders: anxiety, personality disorders, and obsessive-compulsive disorder. In fact, illegal drug users per se are associated with some form(s) of psychiatric problems: increased anxiety, personality disorders and Obsessive Compulsive Disorder (OCD) (McCann and Ricaurte, 1991; Pallantini and Mazzi, 1992; McGuire et al. 1994). It is highly plausible that as MDMA reduces 5-HT levels, which may not fully return to baseline levels after abstinence from MDMA exposure. MDMA may trigger psychiatric disorders in past and present MDMA polydrug users. Present and past MDMA users need monitored for anxiety related disorders, personality disorders and possible OCD, as they may be more vulnerable due to a combination of the normal aging process and MDMA in later life.

Depression has a high concordance rate with gender. Research reveals females are twice as likely to display symptoms of depression and diagnosed with clinical depression in comparison to males (Hale, 1997; Klaus et al. 2006). These figures could be subject to bias, as males are probably underestimated. Perhaps the statistics for males are under reported as they are frequently able to mask the depressive symptoms and depression with violence, aggression and drug use. The role of gender in MDMA needs examination. If females are more prone to depression than males in the normal population, the causality of this depression in females needs to be further investigated and secondly it might be plausible that females are more at risk from MDMA induced depression than males. This needs further exploration. Possible theories for this female induced vulnerability include cognitive processing, hormonal properties and coping mechanisms.

For a more in depth discussion of the limitations associated with self-reported studies as well as studies surrounding the use of illicit drug(s), refer to chapter 8.

3.4.2 Summary of the findings

Even though the hypothesis for this study was formulated in 2001, it is still to date the largest single study investigating the association between depression and MDMA use, which includes a sample that is a true 'real-life' representation of the general population, including a diverse range of ages and a large selection of educated individuals. This is the only study to robustly control for the use of other

recreational drugs (amphetamine, cocaine, cannabis, heroin and alcohol). Previous studies are predominantly based on student samples and/or younger adults. This study includes a larger representation of the population of MDMA polydrug users during the period 2002-2006.

This is the first study to date to find that abstinence from MDMA (a mean time of 7 years) results in elevated depression symptoms, specifically the cognitive-affective dimension of depression. In fact past and present MDMA users suffer from similar levels of depression, suggesting that depression may have been initially present before the use of MDMA or that MDMA is neurotoxic to the brain resulted in long lasting damage, which is irreparable as found in non-human animal studies (Ricaurte et al, 1988). As past MDMA users still reported increased depression scores it may support the notion that MDMA polydrug users are drawn to use MDMA as it alleviates symptoms of depression and is a 'serotonergic agonist'.

In summary, this study supports previous data suggesting that polydrug MDMA users have elevated depression scores in comparison to non-MDMA polydrug users. Implicating that MDMA alone or a combination of MDMA and other recreational drugs may contribute to elevated depression scores. There was no significant difference in depression scores between present and past MDMA polydrug users. These results are supported by non-human animal studies suggesting that MDMA may cause neurotoxicity to selective 5-HT neurons resulting in long lasting depression, which persist for more than 5 years. There was a significant positive relationship between the level of exposure to MDMA and the level of self-reported depression confirming previous studies. The results are unable to answer whether depression already existed and MDMA users seek the drug as a means of self-medication. The initial acute effect of MDMA is of an anti-depressant, increasing the levels of serotonin resulting in an increase in positive mood. MDMA users may initially use MDMA as a form of self-medication. This theory warrants further exploration.

Chapter 4 – Impulsivity

4.1   Introduction

This section will provide a brief introduction and definition of impulsivity. It will evaluate the evidence supporting impulsivity and the role of 5-HT. Finally, it will assess non-human animal studies and human studies concerning MDMA exposure and impulsivity.

4.1.1   The definition of impulsivity

Impulsivity concerns the ability of an individual to modulate their cognition and behaviour to appropriately adjust to the requirements of a given environment (Patton et al. 1995; Hollander et al. 2001; Everton et al. 2005; Diamantopoulou et al. 2007). Impulsivity can be divided into a 'behavioural' aspect and 'personality' trait of impulsivity (Evenden, 1999).

Behavioural definitions of impulsiveness include the making of premature responses in situations in which the postponement of action is required. Increased impulsivity is associated with the selection of a small immediate gain in preference to a larger delayed gain. Impulsivity is a tendency to react quickly to a stimulus without prior deliberation and evaluation of the possible consequences (Buss and Plomin, 1975).

Impulsivity, can be considered to be a dimension of personality, it is the failure to resist an impulse, drive or temptation that is harmful to one self or others. It is now widely recognised that 'impulsiveness' is a complex construct and may not yield to a single behavioural definition (Barratt, 1985). Impulsivity can be defined as swift action without forethought or conscious judgement, behaviour without adequate thought, the tendency to act with less forethought than do most individuals of equal ability and knowledge.

It is often regarded as a measurable feature of behaviour, manifesting as impatience (including the inability to wait for rewards), carelessness, risk-taking, sensation seeking and pleasure-seeking, an underestimated sense of harm and extroversion (Barratt and Patton, 1983; Moller et al. 2001). Impulsivity has been studied within the normal non-clinical population in addition to the clinical setting.

Impulsivity is a core symptom of a broad spectrum of psychiatric disorders being included in the DSM-IV with a separate section for disorders of impulse control (pathological gambling, intermittent explosive disorder, pyromania, kleptomania and trichotillomania). Additional psychiatric disorders linked to impulsivity includes: impulsive aggressive personality disorder (borderline antisocial

behaviour; histrionic and narcissistic), neurological disorders associated with disinhibition of behaviour, and substance abuse (American Psychiatric Association, 2000; Moller et al. 2001, Houston et al. 2003, Swann et al. 2004). Further still there are additional psychiatric disorders affecting children notably attention deficit hyperactivity disorder and mania (American Psychiatric Association, 2000). Research using MRI and fMRI techniques have associated addiction, impulsivity, risk taking and gambling with an overly active DA system (Buckholtz et al. 2010). Researchers have suggested that children with high propensity for risk-taking, impulsivity and novelty-seeking, are more likely to develop alcoholism and other additions later in life (Hanson, 2010). The trait of impulsivity is a potential marker of addiction being related to reward, memory and motivation. Some researchers believe that the behaviour itself does not seem to cause the addiction instead the use of drugs seems to normalise the central nervous system (Hanson, 2010).

It is clear that impulsivity is a complicated process. The remainder of the chapter will be focussed on the personality trait of impulsivity.

4.1.2   The association between serotonin, dopamine and impulsivity

Even though most research associates dopamine with behavioural impulsivity, research using both non-human animals and humans indicates that 5-HT has been linked to impulse control and impulsive personality. Previous non-human animal research have demonstrated that rats whose serotonin pathways have been destroyed are more likely than rats with intact 5-HT pathways to select a smaller, immediate reinforcer rather than wait for a larger delayed reinforcer, which is often referred to as a impulsive choice (Patton et al. 1995; Mobini et al. 2000; Hollander et al. 2001; Everton et al. 2005; Diamantopoulou et al. 2007).

Lesion studies in non-human animals have begun to elucidate the neurocircuitry of impulsivity. Cardinal et al. (2001) have reported that lesions of the nucleus accumbens core (a key brain region of reward and reinforcement) induce persistent impulsive choices in rats. These rats will consistently chose small or poor rewards that were immediately available in preference to larger rewards that were delayed (Patton et al. 1995; Hollander et al. 2001; Moller et al. 2001; Everton et al. 2005; Diamantopoulou et al. 2007).

Additional non-human animal studies include knock-out mice lacking the 5-HT receptor 5-HT1B. These rats will display increased impulsive aggression and a liking for particular drugs including cocaine and alcohol. The polymorphisms of tryptophan hydroxylase have been associated with impulsive behaviours (Patton et al. 1995; Hollander et al. 2001; Moller et al. 2001; Everton et al. 2005; Diamantopoulou et al. 2007). Studies suggest that 5-HT plays a role in impulsivity and that reduced 5-

HT results in increased impulsivity. Clearly results from these animal studies have linked serotonin to impulsivity.

Human studies investigating the relationship between 5-HT and impulsivity have discovered that in psychiatric patients displaying pathologically impulsive behaviour as well as persons from a non-clinical population whom display elevated impulsivity as a personality trait, have generally supported the putative relationship between diminished 5-HT function and poor impulsive control (Linnoila et al. 1983; Virkkunen et al. 1987; Patton et al. 1995; Hollander et al. 2001; Everton et al. 2005; Diamantopoulou et al. 2007).

Some research to date has been focussed on modulation of 5-HT transmission and impulsivity (Patton et al. 1995; Moller et al. 2001; Hollander et al. 2001; Everton et al. 2005; Diamantopoulou et al. 2007). SSRIs and other enhancers of serotoninergic transmission have been shown to reduce impulsive behaviours in a wide range of different disorders known to be associated with increased impulsivity including pathological gambling, borderline personality disorders, sexual addictions and disorders in the obsessive-compulsive spectrum (Patton et al. 1995; Moller et al. 2001; Hollander et al. 2001; Everton et al. 2005; Diamantopoulou et al. 2007). These medications would increase 5-HT activity within the CNS ultimately decreasing impulsiveness providing further evidence for the association between 5-HT and impulsivity.

Supplementary biological evidence comes from studies investigating impulsive persons who plan aggressive acts. These studies have demonstrated that such individuals display higher CSF 5-HT metabolite levels than those impulsive persons that do not plan similar aggressive acts (Patton et al. 1995; Moller et al. 2001; Hollander et al. 2001; Everton et al. 2005; Diamantopoulou et al. 2007). This study suggests that 5-HT may be linked to increased aggression rather than impulsivity per se.

Experimental studies have demonstrated that those with a short allele polymorphism of the gene 5-HTTLPR, being a polymorphism of the 5-HT transporter gene, produce a reduced level of brain 5-HT. This reduced level of 5-HT has been correlated to reduced impulsivity scores as measured by the Barratt Impulsiveness Rating Scale (Baca-Garcia et al. 2005). This study was only investigated using a sample of females. Furthermore, the author concluded this reduced 5-HTTLPR was associated with 'attentional' impulsiveness predominantly. Regrettably, not all experiments have found this causal relationship between 5-HTTLPR and 'attentional' impulsivity (Paaver et al. 2007). Additionally, 5-HT genes have been associated with elevated impulsivity including: the TPH2 gene (Lara et al. 2007), the 5-HT 2a receptor gene (Bjork et al. 2002) and the 5-HT1b receptor gene (Zouk et al. 2007).

Impulsive disorders have been shown to be mediated and associated with other neurotransmitter

systems including DA (Patton et al. 1995; Hollander and Evers, 2001; Hollander et al. 2001; Everton et al. 2005; Diamantopoulou et al. 2007). Specific impulse-control disorders, including pathological gambling, have been linked to abnormalities of DA receptors; in addition to disruption to DA pathways and the overactivity of DA (Martins et al. 2004). DA pathways seem to play a critical role in the mediation of reward and reinforcement behaviours (Patton et al. 1995; Hollander & Evers. 2001; Hollander et al. 2001; Everton et al. 2005; Diamantopoulou et al. 2007). Association studies of genes related to DA receptors have supported a genetic influence in impulsive behaviours. This may suggest that other recreational drugs of abuse that involve DA pathways may cause elevated impulsivity scores for example cocaine and amphetamine (Balster et al. 1988; Dworkin et al. 1988; Di Ciano et al. 1995; Horan et al. 2000; Fletcher et al. 2001; Goldstein et al. 2005). Behavioural research indicating current MDMA polydrug users have elevated impulsivity scores fail to control for other recreational drugs including amphetamine and cocaine.

In humans, patients with impulsive disorders, such as stimulant, opioid and alcohol abuse have been found to have overactive nucleus accumbens activity notably increased DA levels (Patton et al. 1995; Hollander et al. 2001; Moller et al. 2001; Everton et al. 2005; Diamantopoulou et al. 2007). It is unclear whether such individuals seek out these DA drugs as a form of self-medication to normalise the CNS activity or whether the use of these drugs results in changes to the neurotransmitter activity within the CNS. These patients will show a disregard for future consequences that is related to but not entirely explained by the construct of impulsivity. Additional areas of the brain have been linked to increased impulsivity, including the amygdala and the frontal lobe (Patton et al. 1995; Moller et al. 2001; Hollander et al. 2001; Everton et al. 2005; Diamantopoulou et al. 2007).

MDMA has been shown to have effects on the serotonergic pathways in the frontal cortex and the amydala (Ricaurte et al. 1988; 2000a, 2000b, 2000c; 2001). Additional research using both non-human animals and humans is required in the frontal lobe and amygdala in order to provide conclusive evidence for their role in impulsivity as well as provide more detail concerning neurotransmitter activity.

In summary current theories suggest that impulsivity is far more complicated than initially thought. It has been proposed from studies that impulsivity can manifest into conflicting definitions. It is generally assumed there are two forms of impulsivity being personality trait of impulsivity and the behavioural aspect of impulsivity. The personality trait has been measured using self-reported personality inventory questionnaires, which has several independent factors and possibly separate biological bases including the serotonergic system. The behavioural aspect of impulsivity is often measured using objective computerised tests (e.g. Go/No-go task). These studies have concluded that the behavioural aspect of impulsivity reflects different aspects of impulsivity and is related to different neurobiological systems

including the dopaminergic system (Evenden, 1999). It is apparent that MDMA studies need to control for the use of other illicit drugs.

4.1.3 Non-human animal studies on impulsivity and MDMA

As it is clear that impulsivity is related to the activity of 5-HT with MDMA being a possible 5-HT neurotoxin, the non-human animal data suggesting that MDMA affects impulsivity may help support this theory.

Meyer (2008) measured impulsivity in adolescent rats whilst being exposed to MDMA. The rats were administered MDMA intermittently, with similar frequency of doses as would be observed in humans during a binge weekend. The findings found that there were reductions in 5-HT levels within the hippocampus, however this reduction in 5-HT was not observed in the neocortex. The behavioural consequence of this loss of 5-HT included elevated behavioural impulsivity in the plus-maze task. These non-human animal studies have provided further support indicating that MDMA induces long lasting damage to 5-HT neurons, which consequently results in behavioural deficits for example enhanced impulsivity (Meyer et al. 2008).

Saadat et al (2006) used rats to test for impulsivity levels employing a visuospatial discrimination procedure. Before commencement of the study, the rats were trained to lever press for a food reward in response to a light-stimulus. During the task the rats were subsequently required to withhold from pressing the lever, this was the way of measuring impulsivity in the study. Rats were exposed to MDMA. The findings found that exposure to MDMA resulted in reduced cortical 5-HT; there were however no significant differences in behavioural impulsivity up to 80 days after the exposure to MDMA. The authors concluded that despite signs of MDMA induced neurotransmitter damage, the study failed to demonstrate that MDMA exposure resulted in elevated behavioural impulsivity (Saadat et al. 2006). It is possible that a certain level of neurotoxicity at the neurotransmitter level is required before behavioural consequences can be observed, as is the case with Parkinson's disease where 80% degeneration of DA neurons is needed before behavioural consequences manifest. MDMA users are polydrug users and they often co-use MDMA with other DA related drugs for example amphetamine and cocaine. Research has clearly demonstrated an association between the hypersensitive dopamine system and the nucleus accumbens with elevated impulsivity (Taylor et al. 2001).

4.1.4 Human studies on impulsivity and MDMA

It has been established that impulsivity is related to the activity of 5-HT and MDMA. As MDMA is a possible 5-HT neurotoxin, and the non-human data suggests that MDMA affects impulsivity, the evidence will now be evaluated suggesting that MDMA affects impulsivity levels in humans.

Non-human animal studies suggest that exposure to MDMA results in decreased 5-HT CNS activity which occasionally causes behavioural deficits. The personality trait dimension of impulsivity requires human studies and introspection. Schiano investigated the association between MDMA exposure in human polydrug users and impulsivity (Schiano et al. 1998). The study comprised of 150 patients who had been referred to an Addiction centre in Italy. The results concluded that only 14% of the MDMA users met the DSM-III-R impulse control disorder criteria. The diagnosis was given by a psychiatrist blinded to the drug history of each patient. The authors concluded that this psychiatric disorder could manifest itself in certain individuals only (Schiano et al. 1998). Criticism of the study is that the sample consisted of general problematic recreational drug users that had been referred to the clinic, due to a cocktail of illicit recreational drugs including benzodiazepines, opiates, cocaine, THC, and alcohol. All of these drug users are complicated when used alone and even more so when combined and co-abused. Further factors which need to be considered include the consequences of the other illicit drugs, as well as the consequences of co-using illicit drugs. Research has clearly demonstrated a positive association between impulsivity/sensation seeking and frequency of drug use. Future studies need to account for frequency of drug use. As it would be predicted that the more illicit drugs used the higher the sensation seeking/impulsivity score irrespective of MDMA usage.

In 2003, Butler and Montgomery presented 254 undergraduate MDMA users. This study did not include a vulnerable complicated clinical sample but a sample from a non-clinical population. The participants were required to complete the impulsiveness venturesomeness and empathy questionnaire (Eysenck et al. 1985) as well as a novel risk-taking task (Butler and Montgomery, 2003). The results concluded both the MDMA group and the non-MDMA polydrug control group displayed higher levels of the personality trait of impulsivity in comparison to the non-recreational drug group. The overall results supported the notion that drug users display elevated personality domain of impulsivity. Finally, the frequent MDMA users scored higher on the risk-taking task than the other groups (less frequent MDMA users, non-drug control group, and cannabis users) indicating that MDMA may cause elevated behavioural impulsivity. The authors concluded that consideration needs to be taken that increased impulsivity maybe the cause of the MDMA use. Such conclusions raised by the author are not successfully supported by the studies' findings. It seems the authors have been too daring in their conclusions as they were unable to clearly associate the increased impulsivity with MDMA alone as the frequent MDMA group were MDMA polydrug users and overall their frequency of drug use was higher

than the other groups. Secondly not all studies have agreed with such conclusions. Another study using the impulsiveness and venturesomeness questionnaire found there was a non-significant difference in scores between MDMA users and non-MDMA polydrug users (Morgan, 1998). Encouragingly the study did reveal an apparent correlation between lifetime use of MDMA and an elevated personality trait of impulsivity. A study by Parrot (2000) confirmed the conclusions that frequent MDMA users had increased behavioural impulsivity scores in comparison to other recreational drug users, however was unsuccessful in producing a difference in venturesomeness scores between the MDMA and non-MDMA polydrug users indicating that there was no difference in the personality trait of impulsivity between the groups (Parrott, 2000a).

Clark and co-workers (2009) measured impulsivity scores on 15 current MDMA users, 14 past MDMA users, 15 cannabis users and 19 non-drug controls. The result found a non-significant difference in mean scores between the MDMA user groups. The cannabis users were less certain in their decision making. The authors concluded that the relationship between behavioural impulsivity, MDMA and 5-HT is far more complicated. Other recreational drugs need to be considered including cannabis, amphetamine and opiates in addition to frequency of drug use.

Studies to date seem to concur conclusively that an increased frequency of illicit and licit drugs results in enhanced behavioural impulsivity irrespective of the drug type. It is long established that recreational drug use results in amplified risk-taking behaviour (Plant and Plant, 1992). Experimental evidence supports the notion that MDMA users are polydrug users (Morgan, 1998; Parrott et al. 2000; Schifano et al. 2000b) and will co-use MDMA with other recreational drugs including cannabis, nicotine, alcohol, cocaine, amphetamines, and LSD (Hammersley et al. 1999). This pattern and frequency of drug abuse would be regarded as enhanced risk taking behaviour. Consequently this binging will result in elevated impulsivity behaviour for this diverse group of MDMA drug users. Clearly future studies need to control for frequency of drug use.

These past studies investigating the association between MDMA use and elevated impulsivity have been unable to draw adequate conclusions. These studies have relied on small sample sizes that fail to represent the diverse population of MDMA users. These studies have failed to control for other dopamine related drugs including amphetamine and cocaine. There has only been one study investigating the long lasting effects of MDMA and the period of abstinence was less than 24 months, indicating that the long lasting effects of MDMA and impulsivity have yet to be fully investigated (Clarke et al. 2009). Table 4.1 summarises some of the studies investigating the association between MDMA and impulsivity.

Table 4.1   Summary of previous research investigating MDMA and impulsivity

Provides a summary of a limited number of studies investigating the link between MDMA and impulsivity during the period 1998 – 2010. The table provides details of authorship, test employed, the control groups included, whether long lasting effects were investigated and finally if they found a significant result

Author	Test	Groups	Long lasting effects	Result
Clark et al. 2009	Information sampling test	46 current MDMA 14 non-MDMA polydrug 15 cannabis 19 non-drug controls	Yes	Non sig
Loxton et al. 2008	Reward drive Rash impulsivity	360 club users 303 non drug controls	No	Club users are more impulsive
Valdes et al. 2006	fMRI BIS	15 MDMA 19 non MDMA controls	No	BIS and imaging scores correlated
De Win et al. 2006	Sensation Seeking	59 MDMA 61 controls	No	MDMA users elevated
Morgan et al. 2006	RDMT CARROT	MDMA polydrug Non-MDMA polydrug Non drug control	No	MDMA users more impulsive
Schilt et al. 2010	BIS	17 heavy MDMA polydrug 16 mild MDMA polydrug 20 non-MDMA controls	No	Heavy MDMA users increase impulsivity to controls

114

Author	Test	Groups	Long lasting effects	Result
Dafters et al. 2004	IVE BIS	18 MDMA polydrug 18 non-MDMA polydrug	No	Cannabis main predictor Increased impulsivity with drug freq
Butler et al. 2003	IVE TPQ	48 MDMA polydrug 37 non-MDMA polydrug 55 cannabis 116 non-drug control	No	Increased impulsivity with drug use
Morgan, 1998	IVE	MDMA polydrug Non-MDMA polydrug Non-drug controls	No	MDMA elevated scores. Associated with increased exposure

115

4.1.5 The Barrat Impulsiveness Scale

The Barrat Impulsiveness Scale (BIS - 11th edition) is a 30 item self-report personality trait impulsivity measure. It is designed to assess personality construct of impulsivity. It is arguably the most widely used clinical and research impulsivity questionnaire being highly regarded within research. The BIS has been validated within the normal and clinical population. In March 2009 the BIS-11th edition had 551 citations (Stanford et al. 2009). The BIS has been correlated with the Taylor Manifest Anxiety Scale and Cattel Anxiety Scale in addition to being positively correlated against Eysenck's Extraversion dimension and Zuckerman's Sensation-Seeking Scale (Patton et al. 1995). The BIS is designed to measure three substrates of impulsivity including attentional impulsiveness, motor impulsiveness and non-planning impulsiveness (Barratt, 1985). Attentional impulsiveness deals with an inability to focus attention and concentration. Motor impulsiveness includes behaviour without thinking about the consequences and weighing up all possible outcomes. Non-planning impulsiveness involves a lack of planning. It is proposed that a score of 74 and above indicates an individual with high impulsivity. The normal range of impulsivity would include scores ranging from 52-71. Score below 51 would indicate that the individual was not honest when completing the questionnaire (Knyazev et al. 2006). The split-half reliability is 0.752 and the test-re-test reliability is 0.825, and the Cronbach coefficient was 0.794 (Li et al. 2006). The BIS was included in this study as it is an excellent clinical tool, easy to complete/score and has undergone extensive validity and reliability testing.

4.1.6 The role of MDMA in impulsivity

Impulsivity has been correlated to lowered levels of serotonin in both non-human animal and human experimental studies, including specific genes of the 5-HT system. Studies indicate that the personality trait of impulsivity deficits have been linked to psychiatric disorders where the main problem causing this abnormal impulsivity level is the lowered 5-HT activity. Exposure to MDMA causes an initial acute brain increase in 5-HT in both humans and animal studies followed by a possible long lasting reduction in 5-HT, as demonstrated in non-human animal studies. As the acute effects of MDMA are similar between animals and humans it is possible the long lasting and neurotoxic effects of MDMA are similar. Therefore it is plausible that past and present polydrug MDMA users will exhibit enhanced personality trait impulsive scores in comparison to non-MDMA polydrug users.

4.1.7   The aims of the study

Research investigating pathological impulsivity is of great clinical and public-health relevance. Notably there is an association with impulsivity to a vast number of psychiatric disorders. Elevated impulsivity is detrimental to morality, social and family stability, job dysfunction, increased accidents, suicidal tendencies, violence, aggression, criminality, excessive use of health-care, government, and financial resources. Irrespective of whether this enhanced impulsive behaviour is a consequence of MDMA-induced toxicity or excessive illicit/licit drugs per se, conclusive results are essential.

Based on previous research in related areas, the following can be hypothesised. Firstly, MDMA polydrug users will display enhanced personality trait of impulsivity in comparison to non-drug controls. Secondly, non-MDMA polydrug users will report lowered levels of personality trait of impulsivity in comparison to MDMA polydrug users, controlling for the use of and frequency of other illicit drugs. Thirdly, past and present MDMA polydrug users will report similar personality trait impulsivity scores. Finally, there will be a positive dose-dependent relationship between level of exposure of MDMA and the level of self-reported personality trait impulsivity scores.

4.2   Methodology

4.2.1   Participants

997 of the original 1399 participants were involved in this part of the study, based on a power calculation, where N=432 (Power calculation; minimum of 72 per group, power=0.80, δ=2.80 – Cohen, 1992; Faul et al. 2007; Faul et al. 2009; minimum of 72 per group, power=0.80, δ=2.80). Refer to chapter 3 for full demographic details of the participants.

4.2.2   Measures

All participants were administered with a DHQ (refer to chapter 2 for full details, appendix 2.2).

Participants were given the Barrat Impulsiveness Scale - 11th edition (BIS) to complete. The BIS consists of 30 statements. Participants were required to read each statement and put an 'X' on the appropriate response. Each statement was scored out of 0-4. Minimum possible score was 0 and the maximum possible score was 120. It was selected because of its simplicity of administration, scoring and interpretation.

4.2.3 Ethical Issues

All participants provided written consent. Participants were able to withdraw at any point throughout the study. All data was anonymous. The study was approved by the local Ethics Committee, London Metropolitan University (formally London Guildhall University). Participants were given a briefing and debriefing (Appendix 2.1).

4.2.4 Statistical Analysis

Data was analysed using SPSS. A one-way ANCOVA was run; the outcome variable was the log transformed impulsivity scores measured by the BIS; the predictor variable was the drug group (non-recreational drug control group; alcohol/nicotine control group; cannabis/alcohol/nicotine control group; non MDMA polydrug control; current MDMA polydrug group; ex-MDMA polydrug group) and the covariate were lifetime use of cannabis, amphetamine, cocaine and ketamine.

The two MDMA groups were further split into 67 current less frequent MDMA users, 87 current frequent MDMA users, 49 less frequent ex-MDMA users and 108 frequent ex-MDMA users depending on whether they had used MDMA less than 20 times (less frequent) and those that had used it more than 20 times (more frequent). The results were further analysed using the Bonferroni test where required.

For the ANOVA and ANCOVA, the Kolmogorov-Smirnov and Shapiro-Wilk tests were used to test for normality. As the tests were significant the data was transformed to logs and the normality test re-checked. The log transformed data was non-significant, suggesting the data was normally distributed. The kurtosis and skewness were checked for values between -2 and 2. The log transformed data was plotted using the output of a quantile-quantile (Q-Q) plot. As the data did not stray from the predicted line, the data was linear and normally distributed. The covariate in the analysis was checked for its independence from the experimental manipulation; an ANOVA with the covariate as the outcome and the drug group as the predictor was run for all of the covariates (cannabis, amphetamines, cocaine and ketamine). For the ANCOVA the Levene's test of the homogeneity of variance assumption was checked for non-significance relating to the homogeneity of residuals. The residual plot was checked for assumption of equality of variance. The spread vs. level plot was used to check there was no relationship between the mean and standard deviation. The homogeneity of regression slopes was checked by customising the ANCOVA model in SPSS to look at the independent variable * covariate interaction. The interaction term was tested in addition to the main effects. The log transformed interaction term (independent variable * covariate interaction) was non-significant; the assumption of homogeneity of regression slopes was not broken.

Log transformed self-reported BIS impulsivity scores were correlated with log transformed self-reported lifetime MDMA exposure using the Pearson correlation coefficient.

Multiple regression analysis was performed on the log transformed BIS impulsivity scores with the log transformed lifetime exposure to recreational drugs (alcohol, cannabis, nicotine, amphetamine, cocaine, LSD and ketamine) as the predictor variables. Using SPSS, the variance inflation factor (VIF) and tolerance statistics were checked. The VIF values were below 10 and the tolerance statistics were all above 0.2. The residual statistics was checked for extreme cases. The standardised residuals were all between -2 and 2. The Cook's distance was checked and all values were below 1. The DFBeta statistics was checked to make sure no value was greater than 1. Examination of the residual plots demonstrated the data did not stray from the predicted line; the data was linear and normally distributed. The Levene's test was checked; it was non-significant thus homogeneity of variance was assumed. Homoscedasticity and hetroscedasticity were checked visually by plotting the standardised residuals (the errors) by the regression standardised predicted value. The residuals were randomly scattered around the horizontal line (0) (Tabachnick and Fidell, 2001).

The BIS was then further divided into psychological, behaviour and motives subscales. Three one-way ANOVAs were run; the outcome variable was attention, planning and motor subscales of the BIS and the predictor variable was the drug group.

4.3   Results

4.3.1   Demographics

For a full account of the demographical and the drug frequency details including MDMA exposure for the different groups refer to chapter 3.

4.3.2   Barrat Impulsivity Inventory

The ANOVAs were non-significant demonstrating independence between the predictor variable and the covariates for the ANCOVA. The homogeneity of residuals, normality, equality of variance and the homogeneity of the regression slopes were all checked for the ANCOVA.

For the multiple regression, the data was checked for multicollineraity, curvilineraity, hetroscedasticity and homogeneity of variance, and finally normality.

There was an overall difference in mean self-reported BIS scores between the four control groups (non-drug, alcohol/nicotine control group, alcohol/nicotine/cannabis control group, and non MDMA polydrug control group) and the four MDMA groups (less frequent current MDMA users, frequent MDMA users, less frequent ex-MDMA users and frequent ex-MDMA users), where the four MDMA groups demonstrated overall increased mean personality trait impulsivity scores in comparison to the four non-MDMA polydrug control groups (Figure 4.1).

The covariate, cannabis, was non-significantly related to the impulsivity scores, $F(1, 991) = 0.061$, $p > 0.05$). The covariate, amphetamine, was non-significantly related to the impulsivity scores, $F(1, 991) = 1.7$, $p > 0.05$). The covariate, cocaine, was non-significantly related to the impulsivity scores, $F(1, 991) = 2.1$, $p > 0.05$). The covariate, ketamine, was non-significantly related to the impulsivity scores, $F(1, 991) = 0.14$, $p > 0.05$). There was an overall significant effect of impulsivity scores on drug group controlling for the effect of cannabis, amphetamine, cocaine and ketamine, $F(5, 991) = 196.4$, $p < 0.01$).

Further analysis demonstrated a non-significant difference in mean self-reported BIS scores between current MDMA polydrug users and ex-MDMA polydrug users (Bonferroni Post Hoc test, mean diff=0.43 $p > 0.05$), with the overall mean personality trait impulsivity scores being alike between the two groups (Figure 4.1).

Between less frequent current MDMA users and frequent current MDMA users there was a non-significant difference in mean self-reported BIS scores (Bonferroni Post Hoc test, mean diff=0.45, $p > 0.05$), with both the frequent and non-frequent MDMA polydrug users scoring similar overall mean personality trait impulsivity scores . There was a non-significant difference in mean self-reported BIS scores between less frequent ex-MDMA users and frequent ex-MDMA users (Bonferroni Post Hoc test, mean diff=0.32 $p > 0.05$), again with no difference in mean personality trait impulsivity scores between the two groups (Figure 4.1).

Figure 4.1: The mean BIS scores

The figure plots the overall BIS scores for each drug group (mean ± S.E.M), N=997. Non-recreational drug control group (non-drug)=182; alcohol/nicotine control group (alcohol/nicotine)=172; alcohol/nicotine/cannabis control group (alcohol/nicotine/cannabis)=163; non-MDMA polydrug control group (polydrug non-MDMA)=169; current frequent MDMA polydrug group (current frequent MDMA)=87; current less frequent MDMA polydrug group (current less frequent MDMA)=67, ex-frequent MDMA polydrug group (ex-frequent MDMA)=108, ex-less frequent MDMA polydrug group (ex-less frequent MDMA)=49.

* denotes significant difference between non-drug & alcohol/nicotine & alcohol/nicotine/cannabis & non-MDMA polydrug compared with the current less frequent MDMA & current frequent MDMA & ex-less frequent MDMA & ex-frequent MDMA users (p<0.05)

There was a significant positive correlation between the level of self-reported personality trait impulsivity scores as measured by the BIS and the amount of self-reported reported lifetime MDMA consumed (r=0.44, p<0.01) indicating that the more MDMA used there is an elevated score for the personality trait of impulsivity.

Regression analysis was performed on the MDMA polydrug group, $F(9, 302)=157.87$, $p<0.01$. The results found that the main predictor of overall self-reported personality trait of impulsivity was life time use of MDMA (beta=0.39; t=15.5, $sr^2=0.427$, $p<0.00$). Alcohol ($sr^2=0.101$) was the next predictor of self-reported depression scores followed by cannabis ($sr^2=0.092$) and LSD ($sr^2= 0.052$) (Table 4.2).

Table 4.2 Regression coefficients for type of drug and the BIS (N=311)

The table provide details of the regression coefficients for each drug of abuse (MDMA, ketamine, tobacco, heroin, alcohol, amphetamines, cannabis, LSD and cocaine) and the overall BSI score. The regression was only performed on the past and present MDMA users (n=311).

Drug	% predicts	Beta	t	p
MDMA	44	0.39	15.5	0.000
Ketamine	2.9	0.163	5.78	0.000
Tobacco	1.6	0.13	4.41	0.000
Heroin	5	0.38	8.41	0.000
Alcohol	12.2	-5.07	-8.37	0.000
Amp	2.3	1.27	6.47	0.000
Cannabis	10.1	-0.13	-1.65	0.099 (ns)
LSD	9.9	0.42	15.7	0.000
Cocaine	0.2	-0.83	-2.59	0.010

4.3.3   Subscale of the BIS

The personality trait of impulsivity was further investigated by analysing the three subscales of the BIS including attentional impulsiveness, motor impulsiveness and non-planning impulsiveness (Figures 4.2, 4.3 and 4.4).

4.3.3.1   Attentional subscale of the BIS

For the attentional impulsiveness subscale of the BIS the mean self-reported impulsivity score was significantly different between the four control groups (non-drug, alcohol/nicotine control group, alcohol/nicotine/cannabis control group, and non MDMA polydrug control group) and the two MDMA groups (current-MDMA users, frequent-MDMA users, ex-MDMA users); $F(5, 991) = 171.7$, $p<0.01$, where the mean scores were increased for the MDMA groups in comparison to the mean scores for the non-MDMA control groups. Further analysis found a non-significant difference between the non drug control group and nicotine/alcohol control group with the mean scores being comparable (Bonferroni Post Hoc test, mean diff = 0.46, $p>0.05$). There was a non-significant difference between non-drug control group and nicotine/alcohol/cannabis control group (Bonferroni Post Hoc test, mean diff = 0.24,

p>0.05) with the mean attentional impulsiveness scores being alike. There was a significant mean difference between the non-MDMA polydrug control group and the current MDMA polydrug group (Bonferroni Post Hoc test, mean diff = 6.7, p<0.01), where the mean attentional impulsiveness score was elevated for the current MDMA polydrug group in comparison to the non-MDMA polydrug group. Between the non-MDMA polydrug control group and the ex-MDMA polydrug group there was a significant mean difference (Bonferroni Post Hoc test, mean diff = 6.6, p<0.01) with the ex-MDMA polydrug group reporting an elevated mean attentional impulsiveness score in comparison to the non-MDMA polydrug group. Finally there was a non-significant mean difference between the current-MDMA polydrug group and the ex-MDMA polydrug group (Bonferroni Post Hoc test, mean diff = 0.2, p>0.05), where the mean attentional impulsiveness scores were similar for both past and present MDMA polydrug groups (Figure 4.2).

Figure 4.2: Mean 'Attentional' Impulsiveness scores

The figure plots the mean attentional impulsiveness subscale of the BIS. Mean self-reported impulsivity score for each drug group (mean±s.e.m), N=997. Non-recreational drug control group (non-drug)=182; alcohol/nicotine control group (alcohol/nicotine)=172; alcohol/nicotine/cannabis control group (alcohol/nicotine/cannabis)=163; non-MDMA polydrug control group (polydrug non-MDMA)=169; current-MDMA polydrug group (current MDMA)=154; ex- MDMA polydrug group=157; where p>0.05.
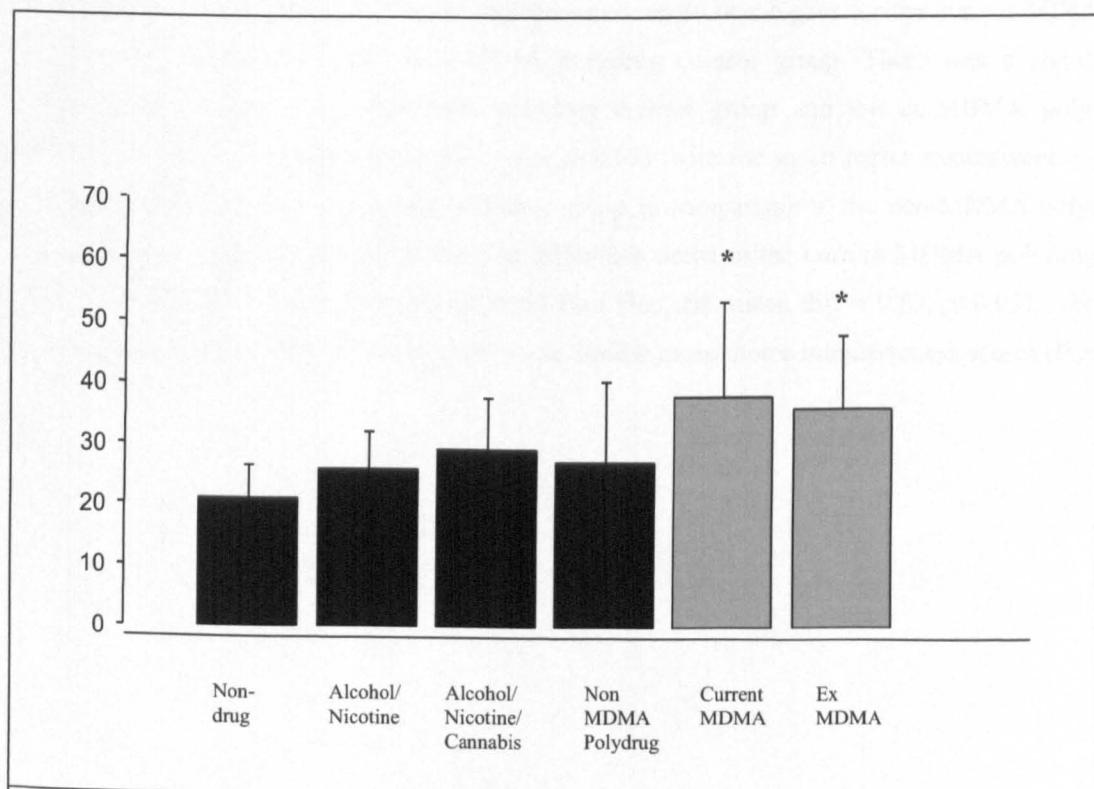
4.3.3.2 Motor subscale of the BIS

For the motor impulsiveness subscale of the BIS the mean self-reported impulsivity scores were significantly lower between the four control groups (non-drug, alcohol/nicotine control group, alcohol/nicotine/cannabis control group, and non MDMA polydrug control group) and the two MDMA groups (current MDMA users, frequent MDMA users, ex-MDMA users); $F(5, 991) = 6.61$, $p<0.01$. Further analysis indicated that there was a significant difference between the non-drug control group and nicotine/alcohol control group (Bonferroni Post Hoc test, mean diff = 7.83, $p<0.05$), with the nicotine/alcohol control group scoring an elevated mean 'motor' impulsiveness score in comparison to the non-drug control group. There was a significant difference between non-drug control group and nicotine/alcohol/cannabis control group (Bonferroni Post Hoc test, mean diff = 3.84, $p<0.05$), with the non-drug control group scoring a lower mean motor impulsiveness score than the nicotine/alcohol/cannabis group. There was a significant mean difference between the non-MDMA polydrug control group and the current MDMA polydrug group (Bonferroni Post Hoc test, mean diff = 8.1, $p<0.01$), where the mean motor impulsiveness score was higher for the current MDMA polydrug group in comparison to the non-MDMA polydrug control group. There was a significant mean difference between the non-MDMA polydrug control group and the ex-MDMA polydrug group (Bonferroni Post Hoc test, mean diff = 7.6, $p<0.01$), with the mean motor impulsiveness score being slightly higher for the ex-MDMA polydrug group in comparison to the non-MDMA polydrug group. Finally there was a non-significant mean difference between the current MDMA polydrug group and the ex-MDMA polydrug group (Bonferroni Post Hoc test, mean diff = 0.53, $p>0.05$), where both the past and present MDMA polydrug users score similar mean motor impulsiveness scores (Figure 4.3).

Figure 4.3: Mean Motor Impulsiveness scores

*The figure plots the mean motor impulsiveness subscale of the BIS. Mean self-reported score for each drug group (mean±SEM), N=997, * represents p<0.01. Non-recreational drug control group (non-drug)=182; alcohol/nicotine control group (alcohol/nicotine)=172; alcohol/nicotine/cannabis control group (alcohol/nicotine/cannabis)=163; non-MDMA polydrug control group (polydrug non-MDMA)=169; current-MDMA polydrug group (current MDMA)=154; ex-frequent MMDA polydrug group (ex-MDMA)=157.*
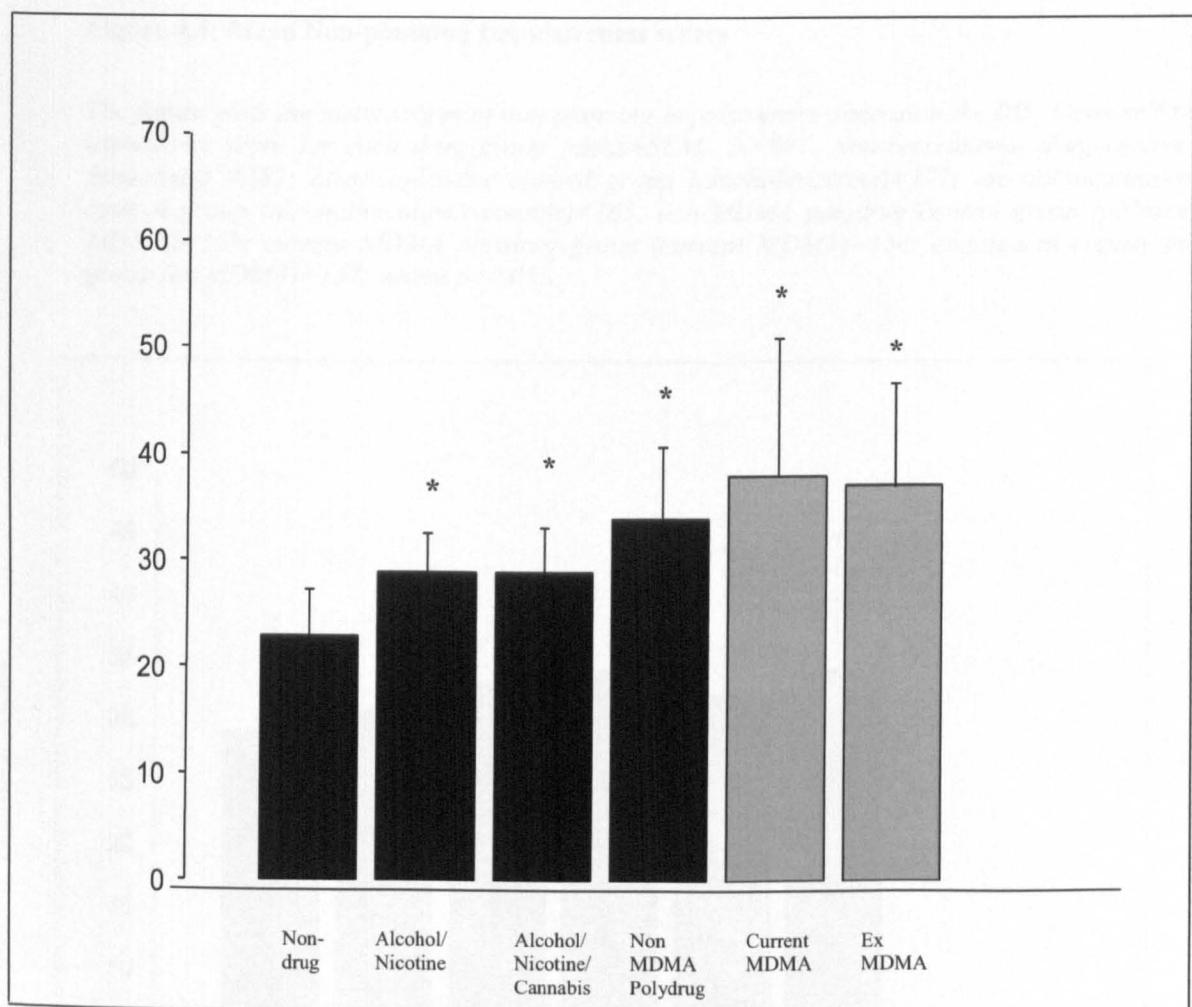
denotes significant difference between non-drug compared with the alcohol/nicotine & alcohol/nicotine/cannabis & non-MDMA polydrug & current less frequent MDMA & current frequent MDMA & ex-less frequent MDMA & ex-frequent MDMA users (p<0.01)

4.3.3.3 Non-planning subscale of the BIS

For the non-planning impulsiveness subscale the mean self-reported impulsivity score was a non-significant difference between the four control groups (non-drug control group, alcohol/nicotine control group, alcohol/nicotine/cannabis control group, and non MDMA polydrug control group) and the two MDMA groups (current MDMA users, and ex-MDMA polydrug users); $F(5, 991) = 90.6$, $p>0.05$, with all six groups scoring similar mean non-planning impulsiveness scores. Further analysis was therefore not required (Figure 4.4).

Figure 4.4: Mean Non-planning Impulsiveness scores

The figure plots the mean scores of non-planning impulsiveness dimension the BIS. Mean self-reported impulsivity score for each drug group (mean±SEM), N=997. Non-recreational drug control group (non-drug) =182; alcohol/nicotine control group (alcohol/nicotine)=172; alcohol/nicotine/cannabis control group (alcohol/nicotine/cannabis)=163; non-MDMA polydrug control group (polydrug non-MDMA)=169; current MDMA polydrug group (current MDMA)=154; ex-frequent ecstasy polydrug group (ex-MDMA)=157; where p>0.05.

123
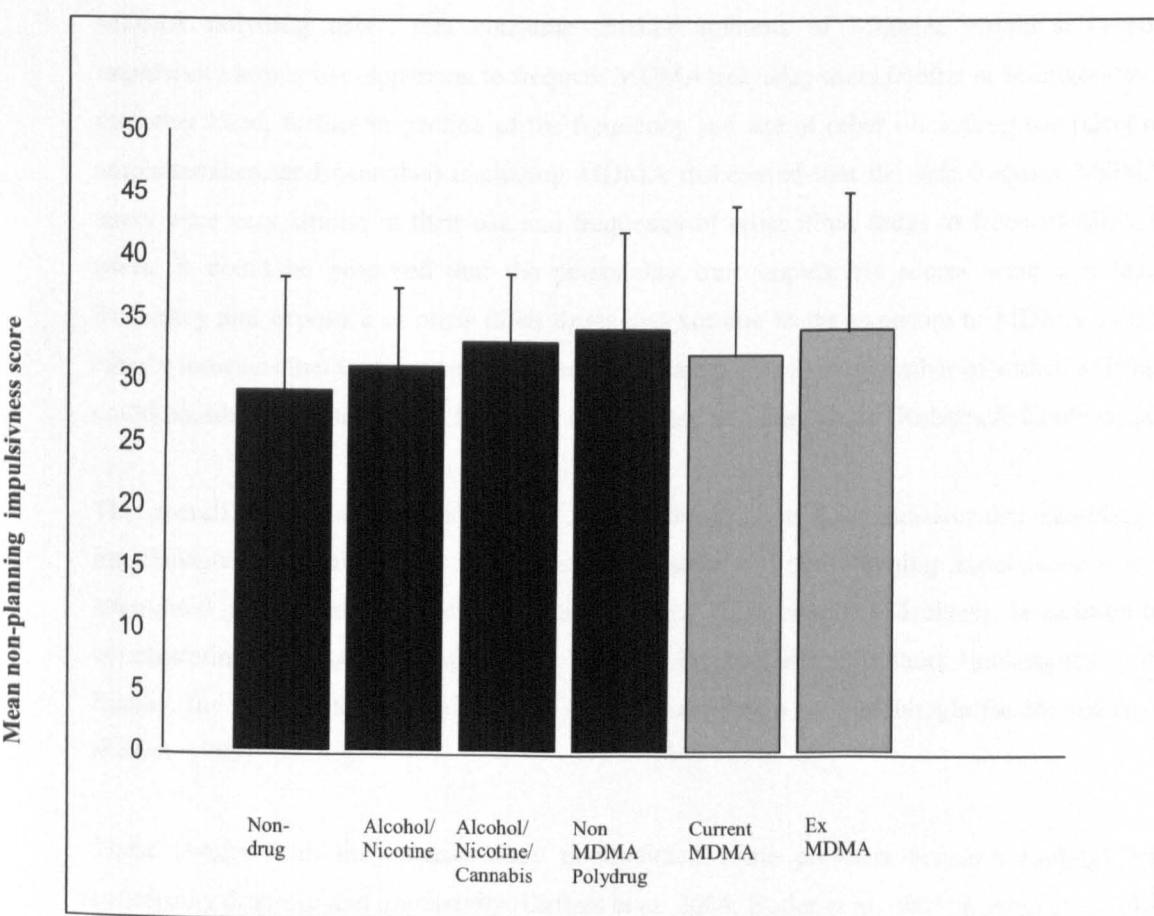
4.4   Discussion

The overall BIS impulsivity scores were higher for the MDMA polydrug users in comparison to non-MDMA polydrug recreational drug users. This confirms previous research in the area suggesting that MDMA polydrug users self-report elevated personality trait impulsivity scores in comparison to other non-MDMA recreational drug users confirming the acute effects of MDMA (Schifano et al. 1998; Morgan, 1998; Hammersley et al. 1999; Schifano, 2000b; Parrott. 2000a, 2000b; Butler & Montgomery. 2003). This finding was further clarified from the correlation and regression analysis demonstrating that the main predictor of the personality trait impulsivity scores was exposure to MDMA.

There was a non-significant difference found in the overall mean BIS impulsivity scores between the present and past MDMA polydrug users (abstained for a mean of 5 years; range 5-11 years).

Interestingly, there were no differences in overall BIS impulsivity scores between the frequent and less frequent polydrug MDMA users. This contradicts previous research which suggests that less frequent MDMA polydrug users, that consume smaller amounts of MDMA, would self-report reduced impulsivity scores in comparison to frequent MDMA polydrug users (Butler & Montgomery, 2003). On the other hand, further inspection of the frequency and use of other illicit drug use (alcohol, nicotine, amphetamines, and cannabis) excluding MDMA discovered that the less frequent MDMA polydrug users were very similar in their use and frequency of other illicit drugs to frequent MDMA polydrug users. It could be proposed that the personality trait impulsivity scores were a reflection of the frequency and exposure of other illicit drugs and not due to the exposure to MDMA alone. Evidence clearly indicates that impulse control impairments are common to a number of addictive behaviours and could possibly constitute a risk factor for dependency and drug abuse (Roberts & Garavan, 2010).

The overall BIS impulsivity score was further divided into three sub-domains including attentional impulsiveness subscale, motor impulsiveness subscale and non-planning impulsiveness subscale. The attentional impulsiveness subscale measures making quick cognitive decisions in addition to a lack of concentration. The motor impulsiveness subscale involves acting without thinking and prior thought. Finally, the non-planning impulsiveness subscale involves a lack of thought for the future or planning (Barrat, 1985).

These results from the current study contradicted some previous research findings and theories concerning drug use and impulsivity (Dafters et al. 2004; Butler et al. 2003; Loxton et al. 2008; Clark et al. 2009). It seems from these results, the association between impulsivity and drug use is far more complex.

For the attentional impulsiveness subscale, the results found a non-significant difference in attentional impulsiveness scores between the alcohol/nicotine/cannabis control group and the non-MDMA poly drug control group. There was however a significant difference between the current-MDMA polydrug drug group and the non-MDMA polydrug control group on the attentional impulsiveness scale. This suggests that alcohol, nicotine, cannabis, amphetamines and cocaine may not increase the attentional aspect of impulsivity; which involves making quick cognitive decisions. These results suggest that MDMA affects the 'attentional' aspect of impulsivity.

The results from this study suggest that people exposed to MDMA tend to make quick cognitive decisions and display a lack of concentration when making decisions (Barrat, 1985). Previous personality trait research investigating impulsivity has proposed that cocaine and amphetamine users display elevated overall impulsivity scores, with increased impulsivity being a risk factor for drug abuse and dependency (Hayaki et al. 2005). Non-human animal studies have previously located impulsivity to increased activity in the nucleus accumbens (Di Canio et al. 1995; Iravani et al. 2000). Previous research suggests that an overactive DA system results in increased impulsivity which is not a reflection of the personality trait of impulsivity (Evenden, 1999). Interestingly the major neurotransmitter in the nucleus accumbens is DA suggesting an overactive DAergic system. Recreational drugs like cocaine and amphetamine will have an effect in this brain region increasing the activity of DA (Balster, 1988; Moller et al 2001). It has been proposed that MDMA initially increases serotonin and this consequently increases DA levels in the nucleus accumbens (De la Torre et al. 2004). If this prediction occurred and MDMA affected DA activity in the nucleus accumbens, we would expect to see similar behavioural impulsivity scores between MDMA polydrug users and polydrug users that use amphetamine and cocaine only. Interestingly, further inspection of the drug groups found the frequency of use of amphetamine and cocaine reveals that the MDMA polydrug users had been exposed to more cocaine and amphetamine in terms of frequency and used more than the non-MDMA polydrug users. This may suggest that this elevated cognitive and attentional impulsivity result is due to the effects of amphetamine and cocaine use rather than MDMA use. On the other hand, amphetamine and cocaine alone were not significant predictors for the 'attentional' impulsiveness subscale scores. The link between DA, MDMA, cocaine, amphetamine, behavioural and personality trait of impulsivity needs further exploration. A possibility would be to have a separate amphetamine polydrug group in addition to a separate cocaine polydrug group and finally a separate MDMA polydrug group in future studies. Secondly, future studies need to measure both the personality trait and the behavioural aspect of impulsivity (Evenden, 1999).

For the motor impulsiveness subscale there was a significant difference between the non-drug control group and the non-MDMA polydrug drug group. There were non-significant differences in motor

impulsiveness scores between the three non-MDMA control groups. These results suggest that it does not matter which illicit drugs were been consumed e.g., cannabis, alcohol, nicotine, cocaine, amphetamine, and heroin. The result may support data suggesting that substance users display increased motor impulsivity resulting in the person acting without thinking. This suggests that the motor aspect of impulsivity maybe affected by the frequency and amount of recreational drugs used, not the type of recreational drug used. Further support for this theory comes from results from this study. The significant difference between the MDMA group and the non-MDMA polydrug group suggests that MDMA users report higher motor impulsive scores than other non-MDMA illicit drug users. These results could be explained by the fact that the frequency and amount of all illicit drugs were higher for MDMA polydrug users than the non-MDMA polydrug users. On the other hand, as MDMA users scores were elevated it may be argued that MDMA induced neurotoxicity results in damage to the 5-HT system causing an increase in motor impulsivity scores and subsequently the person having difficulty considering the consequences of an action before making a decision to proceed.

Finally, for the non-planning subscale there were no significant differences between the non-drug control group and the other illicit drug using groups. This result suggests that the use of illicit drugs do not play a role in predicting scores on the motives non-planning subscale, suggesting that illicit drug use does not affect the ability to plan for the future when making a decision.

Previous research has associated illicit/licit drug use as an indicator of increased impulsivity. In particular some studies have highlighted MDMA polydrug users as displaying elevated impulsivity scores in comparison to non-MDMA polydrug users (Plant & Plant, 1992; Mogan, 1998; Schifano et al. 1998; Parrott et al. 2000a, 2000b; Schifano, 2000a, 2000b). These studies have been widely criticised as theorists argue that MDMA users tend to be polydrug users. They will continually abuse different types of illicit drugs with greater frequency and exposure amount, in comparison to non-MDMA polydrug users (Nutt et al. 2009). These critics point out that previous research investigating MDMA and impulsivity need to take particular care in controlling for all other recreational drugs including frequency of use and exposure amount, as it has been implicated that the more recreational drugs used the more likely they are to demonstrate risk taking behaviours and elevated impulsivity. In the current study, there were significant differences between the three illicit drug groups (non-MDMA polydrug drug control group and the two MDMA groups) concerning the different types, frequency and total amount of exposure of the other recreational drugs previously consumed. This implies that the elevated personality trait impulsivity scores might be a consequence of drug type, frequency of drug use and exposure amount. However, MDMA was shown to be the main predictor of the elevated personality trait impulsiveness scores providing further additional support the elevated impulsivity was a consequence of MDMA.

There is a considerable amount of research implying that the elevated impulsivity scores seen in substance users are caused by cannabis use and not MDMA (Croft et al. 2001; Gouzoulis-Mayfrank et al. 2002; Dafters et al. 2004a; Daumann et al. 2004; Parrott et al. 2004; Lundqvist et al. 2005; Sala et al. 2005). However, previous studies have failed to acknowledge the differences and debate whether cannabis affects the behavioural side of impulsivity or the personality side of impulsivity (Evenden, 1999). In this study there was the inclusion of a separate cannabis control group and the personality trait of impulsivity was measured. The findings from this study clearly suggest that it is MDMA and not cannabis exposure that causes elevated self reported personality trait impulsivity scores.

Further inspection of previous research investigating the effect of MDMA inducing elevated impulsivity scores has revealed that the personality trait of impulsivity for the MDMA users normally ranges at a mean of about 60 (Croft et al. 2001; Gouzoulis-Mayfrank et al. 2002; Dafters et al. 2004; Daumann et al. 2004; Parrott et al. 2004; Lundqvist et al. 2005; Sala et al. 2005). This mean score is considered to fall within the normal range of impulsivity levels amongst the non-clinical population. This level of impulsivity is not deemed problematic, suggesting that previous research has failed to find MDMA users with elevated impulsivity scores that would be considered highly impulsive (Barratt, 1985). Mean scores for the MDMA polydrug group in this study was 80. This level of impulsivity is deemed as highly impulsive and considered problematic. The non-MDMA polydrug control groups mean scores ranged from 65-75 suggesting these drug users were within the normal range of impulsivity (Patton et al. 1995). The findings from this study suggest that MDMA users demonstrate higher personality trait impulsivity scores which are deemed as highly impulsive and need future attention.

4.4.1 Limitations and future studies

One major concern with the methodology employed in this study is it is very difficult to prove that the MDMA exposure alone caused an increase in personality impulsivity levels. It could be argued that MDMA polydrug users displayed increased impulsive personality traits before using MDMA and they use MDMA as a form of self-medication (Chapter 8). This could consequently lead them to seek recreational drugs such as MDMA, which would then normalise their system. The only plausible way to measure this theory, would be to perform longitudinal studies, which can be very costly and time consuming. If individuals are seeking MDMA because they have increased impulsivity beforehand, this is equally disturbing. This is of particular concern as past non-human animal studies have demonstrated MDMA is damaging to specific brain areas and nerve terminals (Ricaurte et al. 1988; 2000a, 2000b; 2001). This theory would suggest that individuals using MDMA as a self-medication are risking possible neurotoxicity damage, which could be long lasting. If MDMA users are using MDMA as a self-medication it raises serious health issues. MDMA is illegal and produced in back street laboratories

and often mixed with a cocktail of substances. If the MDMA polydrug user already exhibits heightened impulsivity levels before using MDMA this raises even more concerns. This heightened system would elevate behaviours including more risk taking and increased sensation seeking. These MDMA polydrug users are co-using MDMA with other substances, in addition to constantly increasing frequency and dosage of recreational drugs.

In this study the BIS has been divided into three subscales. These subscales include risk taking, lack of planning, and making up one's mind quickly (Patton et al. 1995). Patton and workers separated impulsivity into three components which included acting on the spur of the moment, which they referred to as motor activation not focusing on the task at hand, known as attention and finally not planning/thinking carefully thus referred to as lack of planning (Patton et al. 1995). If these three subscales are dimensions of impulsivity, it would be feasible that each one of these subscales would be exclusive of each other and measurable. There is considerable debate concerning the validity and reliability of these subscales which suggests a major limitation of the study (Patton et al. 1995). To date there are no studies have investigated the reliability and validity of the three subscales of the BIS. Secondly, there is considerable debate concerning measuring and defining impulsivity. Some authors argue that impulsivity and compulsivity are at opposite ends of the spectrum. Since the definition of impulsivity is still being debated it is very difficult to measure it as a single measurable number and it has been suggested that rather than measure impulsivity as a whole each component should be measured separately (Balster et al. 1988; Dworkin et al. 1988; Di Ciano et al. 1995; Horan et al. 2000; Moeller et al. 2001; Fletcher et al. 2001; Goldstein et al. 2005). Most researchers argue that impulsivity is very complicated and cannot be defined as one measurable component. Most researchers agree there is a distinction between the personality trait and the behavioural trait of impulsivity; however this needs further clarification (Evenden, 1999). Caution is needed when interpreting these results concerning the subscales of the BIS.

The current study measured the personality trait of impulsivity. Other research studies have combined the use of the personality trait impulsivity questionnaires and computerised tests of behavioural impulsivity (Horesh, 2001). These studies have found a significant relationship between personality trait impulsivity and behavioural impulsivity; however this correlation is very weak. This study suggests that future research need to focus on more accurate measures for both the personality trait and behavioural aspect of impulsivity. Possible suggestions include event-related cortical potentials and laboratory behavioural tasks that measure behavioural inhibition, for example delay discounting and the Go/Nogo tasks.

Enhanced impulsivity has been correlated to a number of psychiatric disorders. These disorders include aggression, ADHD, borderline personality disorder, antisocial personality disorder, intermittent

explosive disorder, kleptomania, pyromania, and pathological gambling (McGregor et al. 2003; Milani et al. 2004; Thompson et al. 2004a). It is generally accepted there is high co-morbidity amongst these disorders. It is plausible that MDMA polydrug users are more prone to these psychiatric disorders, due to changes in the neurotransmitter system. This needs further consideration, in terms, of the interpretation of future experimental results. MDMA polydrug users may present with one main psychiatric disorder, however secondary disorders could be masked and undiagnosed. MDMA polydrug users with elevated impulsivity scores will need careful medical screening and full psychiatric assessments.

Correlation studies indicate that scores on the BIS are positively associated with scores on the Zuckerman Sensation Seeking scale and anxiety tests (Zuckermann, 1984). As MDMA polydrug users demonstrated elevated BIS scores, it is highly plausible that they will demonstrate elevated scores on the Zuckerman Sensation Seeking Scale and anxiety tests. This relationship between anxiety, Sensation Seeking and impulsivity needs to be investigated in future MDMA polydrug studies.

As it is envisaged that MDMA polydrug users have probable MDMA-induced neurotoxicity, resulting in increased impulsivity, possible treatment options need to be considered. As this MDMA-induced toxicity is likely to be a result of reduced CNS 5-HT levels, treatment options would include increasing CNS levels of 5-HT. SSRIs would be one option; however if 5-HT levels are very low, SSRIs will not be beneficial. A further option would include 5-HT agonists. Future studies, including non-human animal research in addition to human studies, need to investigate possible treatment options for MDMA induced impulsivity deficits.

4.4.2   Summary

Even though the hypotheses for this study were formulated in 2001, it is still to date the largest single study investigating the association between impulsivity and MDMA use, which includes a sample that is a true 'real-life' representation of the general population, including a diverse range of ages and a large selection of educated individuals. This is the only study to date that robustly controls the use of other recreational drugs: amphetamine, cocaine, cannabis, heroin and alcohol. Previous studies are predominantly based on student samples and/or younger adults. This study includes a larger representation of the population of MDMA polydrug users during the period 2002-2007.

The present study found that impulsivity levels were enhanced for both past and present MDMA polydrug users in comparison to non-MDMA polydrug users. These results suggest that MDMA polydrug users demonstrate higher levels of the personality trait of impulsivity, which initially causes them to seek MDMA in order to normalise their impulsivity levels. Alternatively MDMA induced

neurotoxicity causes damage to 5-HT neuronal terminals as demonstrated in non-human animal studies resulting in enhanced personality trait of impulsivity. Irrespective of the cause, MDMA polydrug drug users demonstrated increased impulsivity scores in comparison to non-MDMA drug controls. The range of impulsivity scores for the past and present MDMA polydrug users only were not deemed within the normal range and were considered highly problematic. In favour of the MDMA induced neurotoxicity theory, MDMA was the main predictor of the increased impulsivity scores as shown from the regression analysis. There was a positive correlation between lifetime use of MDMA and impulsivity levels. Separating the BIS into the three sub-domains of personality trait of impulsivity indicated that MDMA is specific and affects the cognitive-affective aspect of impulsivity; however caution needs to be taken interpreting these results, and further exploration is required. Finally, future research needs to target the behavioural aspect of impulsivity, in addition to the personality trait of impulsivity.

Chapter 5 - Sleep

5.1   Introduction

This section will provide a brief account of the neuroanatomy, neuropharmacology and neurophysiology of sleep. It will assess the evidence supporting role of serotonin (5-HT) in sleep. Finally, it will evaluate both non-human animal and human studies concerning MDMA exposure and sleep disturbances.

5.1.1   The neurophysiology and neuropharmacology of sleep

All animals sleep. Every animal has a different optimum level of sleep (Buysee et al. 1998; Monk et al. 2000; Colbron et al. 2002; Roman et al. 2005). Research suggests that sleep is required for survival. The actual role of sleep is still largely unknown however there are many theories that attempt to account for the function of sleep.

In humans, the average time spent sleeping is between 7-9 hours with some needing 8 hours per night, others needing around 10 hours and some need as little as 5 hours sleep per night. In 2003 a human study suggested that less than 8 hours sleep per 24 hours results in decreased cognitive processes in humans (Everson, 2003). Each individual is different and the amount of sleep one requires in order to function correctly is thought to be dictated by the circadian clock (Buysee et al. 1998; Monk et al. 2000; Colbron et al. 2002; Roman et al. 2005). The hypothesised master clock, known as the 'circadian clock' is reportedly located in the hypothalamus and is known as the suprachiasmatic nuclei (SCN). The SCN is controlled primarily by light. The mechanism of action is predominately from the retina via the retinohypothalamic tract to the SCN. Furthermore, research has demonstrated there are cues other than light that can set by the 'master clock' including exercise and social stimuli (Buysee et al. 1998; Monk et al. 2000; Colbron et al. 2002; Roman et al. 2005). When it is dark, the hormone melatonin is produced, which indicates to the body to slow down and initiate sleep (Reinoso-Suarez et al. 2011).

Physiologically there are two distinct stages of sleep, which are often referred to in the literature as REM sleep (rapid eye movement sleep) and NREM sleep (non-rapid eye movement sleep) (Buysee et al. 1998; Monk et al. 2000; Colbron et al. 2002; Roman et al. 2005).

NREM can be further divided into four stages (stage 1, stage 2, stage 3 and stage 4). NREM sleep is often referred to as slow wave sleep since electrical activity of the brain during this stage as measured by EEG recorders show the activity of the waves to be slower (0.5 to 2.0 Hz) whereas the amplitude (75

millivolts) is increased. During sleep there is a progression from stage 1 (drowsy sleep), 2 (light sleep), 3 (deep sleep) and finally stage 4 (deep sleep). Stage 4 sleep is the deep sleep that is known as slow wave sleep and consequently has the highest arousal threshold. NREM sleep (stages 1, 2, 3, and 4) is regulated by GABA (see table 5.1) (Buysee et al. 1998; Monk et al. 2000; Colbron et al. 2002; Roman et al. 2005).

During REM sleep the electrooculogram (EOG) measures bursts of rapid eye movement. During REM sleep most of the muscles are paralysed due to a suppression of certain nerve cells: pons and medulla. 5-HT has been associated with REM. Research has shown 5-HT increases REM sleep significantly (Buysee et al. 1998; Monk et al. 2000; Colbron et al. 2002; Roman et al. 2005). In addition, 5-HT increases the amount of time spent in deep sleep (stages 3/4) whilst reducing the amount of time spent in stages 1 and 2. Evidence suggests reduced levels of 5-HT will result in less time spent in deep wave sleep and more time spent in stages 1 and 2 (Buysee et al. 1998; Monk et al. 2000; Colbron et al. 2002; Roman et al. 2005). This will result in sleep being restless and waking feeling physically and psychologically tired. REM is governed by the neurotransmitter acetylcholine (see table 5.1) (Buysee et al. 1998; Monk et al. 2000; Colbron et al. 2002; Roman et al. 2005).

The pineal gland has been linked with sleep (Buysee et al. 1998; Monk et al. 2000; Colbron et al. 2002; Roman et al. 2005) and is associated with 5-HT. Data suggests that 5-HT maybe involved in regulation of the SCN and the synthesis of melatonin (Meyer-Bernstein et al. 1997; Buysee et al. 1998; Monk et al. 2000; Colbron et al. 2002; Roman et al. 2005). This 5-HT is converted to the hormone melatonin. Melatonin is then converted back to 5-HT. This process is cyclic and runs about 25 hours if left to free run. Nonetheless external zeitgebers like 'day and light' will reset the cycle after 24 hours. Low melatonin levels have been connected to sleep disturbances and insomnia (Chase and Gidal, 1997). Reduced 5-HT levels in the pineal gland will result in lower levels of 5-HT being converted into melatonin consequently resulting in less melatonin. This could ultimately result in sleep related problems. During the night melatonin will be produced, causing onset of sleep. Melatonin has been administered clinically to induce sleep (Buysee et al. 1998; Monk et al. 2000; Colbron et al. 2002; Roman et al. 2005). It can be hypothesised a lack of 5-HT would ultimately result in a limited amount of melatonin and therefore a lack of sleep onset.

Localising the sleep anatomy began with Moruzzi and Magoun (1949) who defined the reticular activating system (RAS) as a set of ascending pathways originating in the upper brainstem. It was discovered that wakefulness is an active process maintain by activity of the RAS. The RAS connects the brainstem to the cortex. The RAS is composed of several neuronal circuits: reticular formation, mesencephalic nucleus, intralaminar nucleus, dorsal hypothalamus, and tegmentum (Steriade, 1996). Sleep is associated with inhibition of the RAS and inhibition of sensory information. The

neurotransmitters involved in maintaining wakefulness and the RAS include noradrenaline within the locus coeruleus of the pons. These noradrenergic neurons innervate the cortex. In addition, 5-HT neurons in the dorsal raphe nuclei are active during wakefulness and less active during sleep. DA neurones in the ventral tegmentum of the mid-brain are active during wakefulness (Table 5.1) (Buysee et al. 1998; Monk et al. 2000; Colbron et al. 2002; Roman et al. 2005).

The onset of sleep ('wakefulness' state into stage 1 and 2 sleep) is considered to be initiated by 5-HT neurons in the anterior raphe nucleus. The 5-HT pathway from the raphe nuclei stimulates the preoptic area of the anterior hypothalamus. Research suggests that this stimulation of the preoptic area of the anterior hypothalamus by 5-HT results in inhibition of the wakefulness state in the RAS via GABAergic neurons.

5-HT is the main neurotransmitter involved in the process of going from the wakefulness state to NREM sleep. With several studies suggesting the role of many 5-HT receptor subtypes in the regulation of sleep/wake cycle including 5-HT1A, 5-HT1B, 5-HT2A, 5-HT2C, 5-HT3 and 5-HT7 (Borbely et al. 1988; Monti and Jantos 1992; Kantor et al. 2001; Chapin and Andrade 2001a, 2001b; Filakovszky et al. 2001; Monckton & McCormick, 2003).

Physiological experiments demonstrate the dorsal raphe nucleus 5-HT neurons fire rapidly during the state of wakefulness. During slow wave sleep activity of 5-HT dorsal raphe neurons are reduced (Table 5.1). REM sleep is initiated in the anterodorsal tegmentum of the pons due to cholinergic neurones. REM is associated with the disinhibition of 5-HT of the raphe nuclei, and decrease in DA of the locus coeruleus (Buysee et al. 1998; Monk et al. 2000; Colbron et al. 2002; Roman et al. 2005).

Table 5.1   The neuroanatomy of sleep

The table shows the neuroanatomy of sleep and the neurotransmitter active during each state of sleep/wake (Buysee et al. 1998; Monk et al. 2000; Colbron et al. 2002; Roman et al. 2005)

Brain region	Wakefulness	NREM	REM	Neurotransmitter
Locus coeruleus	Active	Non-active	Non-active	NA
Dorsal Raphe Nuclei	Active	Non-Active	Non-active	5-HT
Ventral tegmentum	Active	Non-active	Non-active	DA
Locus coeruleus	Inactive	Active	Non-active	GABA
Dorsal Raphe Nuclei	Inactive	Active	Non-active	GABA
Ventral tegmentum	Inactive	Active	Non-active	GABA
Anteriordorsal tegmentum	Non-active	Non-active	Active	Cholinergic

Roman et al. (2005) investigated the link between chronic sleep restriction and the serotonergic system involved rats being subjected to a schedule of 4 hours of restricted sleep per day. The results found that following 8 days of restricted sleep the 5-HT1A receptors were desensitised. The 5-HT1A receptors subsequently remained desensitised for many days afterwards, even though recovery sleep was allowed. Normalisation occurred gradually but required at least 7 days (Roman et al. 2005). This study suggests that 5-HT1A receptors are affected during periods of restricted sleep, which might be relevant to MDMA users with reduced 5-HT levels.

Non-human animal research has demonstrated MDMA may cause long lasting possibly permanent depletion of brain serotonin (Parrott, 2000; Curran, 2000; Morgan, 2001). As the acute effects of MDMA between non-human animals and humans are similar it is plausible the neurotoxic effects of MDMA are similar in humans. Studies have indicated that 5-HT is involved in sleep and that lowered levels of 5-HT can result in sleep disturbance (Buysee et al. 1998; Monk et al. 2000; Colbron et al. 2002; Roman et al. 2005). 5-HT has been associated with the SCN which maintains the 'sleep/wake' cycle (Buysee et al. 1998; Monk et al. 2000; Colbron et al. 2002; Roman et al. 2005).

If MDMA induces selective neurotoxicity to 5-HT consequently this will result in sleep dysfunction in terms of disrupting sleep patterns and maintaining the 24 hour rhythm. MDMA induced selective 5-HT may disrupt the raphe nucleus resulting in abnormal onset of sleep. Finally 5-HT is linked with melatonin production. Abnormal levels of melatonin can result in a lack of sleep and insomnia. MDMA may result in lowered 5-HT which consequently leads to reduced melatonin levels and insomnia (Buysee et al. 1998; Monk et al. 2000; Colbron et al. 2002).

In summary, it is clear that 5-HT plays a vital role in sleep including sleep onset, and the regulation of the SCN/melatonin. Non-human animal studies have demonstrated that restricted sleep can desensitise 5-HT receptors. As MDMA is a possible 5-HT neurotoxin it is plausible that MDMA users will have problems with sleep. Secondly, other recreational drugs affecting dopamine and acetylcholine levels (nicotine, cocaine, amphetamine, cannabis and alcohol) need to be controlled as these may affect sleep.

5.1.2   The role of MDMA in sleep

It is clear that the normal activity of sleep is related to the levels of 5-HT. As MDMA is a possible 5-HT neurotoxin, the non-human animal data suggesting that MDMA causes sleep disruption will now be evaluated.

5.1.3   Non-human animal studies investigating MDMA and sleep

Controlled sleep studies have been performed on non-human animals. An experimental study investigated the effect of MDMA on circadian patterns using rats measuring EEG and EMG. The short term results found that MDMA resulted in less stage 1, 2, 3, 4, and REM sleep. Longer lasting effects included phase shifting the circadian pattern and a decrease in the circadian amplitude. The authors concluded that MDMA prevented non-photic stimuli resetting the SCN. They localised the phase shift to altered 5-HT1A receptor. The authors suggested that this altering of the circadian rhythm was due to MDMA ability to cause long lasting alterations in 5-HT caused by abnormal re-growth and the pruning effect (Balogh et al. 2004). This study suggests that MDMA causes disruption to maintaining a normal circadian rhythm by disrupting the SCN which is long lasting in non-human animals.

Biello and Dafters, (2001) further studies tested MDMA and its ability to phase shift the SCN of rat *in vitro* brain slices. Coronal hypothalamic slices of the SCN from rats were prepared. The experiment included control rats and those pre-treated with MDMA. Three minute recordings of the firing rates of cells were performed for a 12 hour period. Findings found MDMA was able to disrupt the phase shift (disrupt the ability of the SCN cells to adapt to daily and annual environmental changes) of the circadian clock of rats. The authors suggested this was due to MDMA's ability to reduce 5-HT (Biello and Dafters, 2001). This could consequently mean that MDMA users may have difficulty adjusting to daily environmental changes.

Colbron et al. (2002) performed a similar study on hamsters. This study involved a light stimulus to test the ability to of MDMA to phase shift. The results found that repeated exposure to MDMA altered the ability of the circadian clock to phase shift to a photic stimuli (Colbron et al. 2002). These findings suggest that the disruption of the circadian function caused by exposure to MDMA can led to a variety of clinical problems including sleep disturbance, mood dysfunction and depression. This would be particularly troublesome for those MDMA users, past and present, involved in shift work.

Alvarenga et al. (2010) investigated the role of sleep loss on MDMA/cocaine exposure on DNA damage to organs in mice. The results found that sleep-deprived mice demonstrated increased DNA damage when exposed to MDMA and cocaine. These results suggest that sleep disturbances could increase the neurotoxic damage of MDMA and cocaine (Alvarenga et al. 2010).

The non-human animal studies clearly demonstrate that MDMA causes sleep disturbances, which could subsequently be troublesome for both past and present MDMA users.

5.1.4   Human studies investigating MDMA and sleep

An evaluation of the evidence suggesting that MDMA exposure causes sleep dysfunction in users will be examined. Human studies investigating MDMA and sleep have been somewhat limited (Table 5.2).

A double blind, placebo-controlled study measuring sleep disturbance was monitored using six healthy participants (Gouzoulis et al. 1992). MDMA and MDE (the metabolite of MDMA) are very similar pharmacologically and most MDMA tablets will contain some MDE (Dancesafe, 1994). MDE (3,4-methylenedioxyamphetamine) or placebo was administered at 11pm each night. Participants' sleep pattern was recorded using an electroencephalogram for two consecutive nights. The results found that MDE decreased total sleep time. Secondly, REM was totally suppressed in MDE exposed participants (Gouzoulis et al. 1992). The authors concluded that the effects of MDE on sleep are similar to that of amphetamines. The study suggests that since MDE caused disturbance in sleep it is postulated that MDMA causes neurotoxicity to brain 5-HT levels and this lowered 5-HT causes sleep disturbances, which maybe relevant to past and present MDMA users.

A study by Cohen (1995) asked 500 participants to report subjective effects of MDMA. The participants were mainly males and Caucasian and their ages ranged from 18-25 years old. Data was collected using a survey. The self-reported exposure to MDMA ranged from one single occasion up to two hundred and fifty occasions. Of the 500 participants 38% reported that several days after the ingestion of MDMA they experienced insomnia (Allen et al. 1993). This implies that MDMA use is associated with acute sleep problems in current users. However, the results fail to speculate whether this sleep disturbance is short lived or long lasting and permanent.

Davison and Parrott, (1997) employed a similar study investigating 20 recreational drug users (55% males). Participants were asked to describe the psychological and physiological effects of MDMA (Parrott, 1997). The sample consisted of 5 participants whom had consumed MDMA on a single occasion, nine participants had consumed MDMA between 2-9 times and six participants had consumed MDMA over 10 times. Participants were interviewed concerning the effects of MDMA. The results found that following ingestion of MDMA the participants experienced insomnia (Parrott, 1997). Since MDMA causes an initial increase in 5-HT followed by a decrease it is feasible to suggest that this insomnia is caused by a decrease in 5-HT caused by the neurotoxicity of MDMA. However, this study failed to adequately control for the exposure to other illicit drugs and secondly it failed to investigate past MDMA users.

Allen et al (1993) investigated the association of sleep and MDMA. The study compared 23 MDMA drug users with 22 matched controls. Sleep disturbance was measured using a polysomnogram recorder.

The results found that MDMA users had 19 minutes less of 'total sleep' in comparison to the control group. The MDMA group had 23 minutes less of 'REM sleep' than the controls. In particular, for the NREM sleep it was documented that only stage 2 sleep was affected for the MDMA users; with no significant differences found in the other stages being 1, 3 and 4. Participants were asked about current marijuana use. It was concluded that the results were not a consequence of marijuana use (Allen et al. 1993). Later the same researchers claimed MDMA polydrug users demonstrated longer overall sleep times. This increase time spent in sleep was mainly due to an increase in stages 3 and 4 (McCann et al. 2000). The findings from these studies predict MDMA causes short-term sleep problems to sleep physiology, which could manifest as sleep disturbances clinically.

In a case study, a 26 year old Caucasian man allegedly took large amounts of MDMA; total estimated lifetime consumption was 750 MDMA tablets. In addition, he consumed other recreational drugs: amphetamines, cocaine, crack, LSD, solvents, nitrates, and cannabis. Following MDMA, he developed depression, suicidal thoughts, visual illusions, panic attacks, social phobia, sexual impotence and sleep disturbance. He stopped taking MDMA. Seven years after abstinence from MDMA the sleep disturbance continued. The authors concluded that further experimental research in this area is required using larger samples of current and past MDMA polydrug users (Soar et al. 2004).

McCann et al. (2009) investigated sleep apnoea in young abstinent MDMA users (drug free for 2 weeks). Sleep apnoea is a 5-HT breathing disorder. The study included 71 MDMA users and 62 control groups. Methodology included polysomnography. The results found that MDMA users had significantly increased obstructive sleep apnoea in comparison to the controls. This sleep apnoea was correlated to lifetime exposure to MDMA (McCann et al. 2009).

Even though the hypothesis for this study was formulated in 2001, there are still to date limited studies investigating MDMA and sleep disturbances. In all of the studies during the period 2001-2010 investigating the association between MDMA and sleep disturbance the authors failed to control for: 1) Other recreational drugs which is particularly important as other drugs have been linked to sleep disruption: cannabis, alcohol, nicotine, cocaine and amphetamine, 2) Secondly, previous experimental research has investigated the short term consequences of MDMA on sleep, failing to investigate the long lasting effects of MDMA on sleep and whether disturbances remain in abstinence MDMA polydrug users, 3) Finally, no single study had investigated the association between MDMA, sleep, depression and impulsivity.

Figure 5.2 Summary of previous research investigating MDMA and sleep

Provides a summary of a limited number of studies investigating the link between MDMA and sleep during the period 1992 – 2009. The table provides details of authorship, test employed, the control groups included, whether long lasting effects were investigated and finally if they found a significant result

Author	Test	Groups	Long lasting effects	Result
Montogmery et al. 2007	ESS KSS	104 MDMA 103 non-drug controls	No	Non-significant
McCann et al. 2007	EEG	25 MDMA 23 controls	Yes 1 year abstinence	Sleep alterations in abstinence users
Soar et al. 2004	Self-report	1 case study	Yes	Sleep disruptions
Parrott et al. 2000	SCl-90	16 MDMA 22 non-drug controls	No	MDMA users reported restless sleep
Williamson et al. 1997	Interview	158 MDMA polydrug	No	Sleep disturbances
Allen et al. 1993	EEG	23 MDMA 22 controls	No	MDMA users less non-REM sleep
Gouzoulis et al. 1992	EEG	6 MDE 6 controls	No	No REM sleep in MDE group
Fisk and Montgomery, 2009	PSQI	117 MDMA polydrug 53 cannabis 57 controls	No	MDMA users more evening types MDMA users elevated sleep disturbances
Carhart-Harris et al. 2009	EEG	12 MDMA 12 control	No	Non significant

Sleep disorders can be classified into three general categories including, too much sleep (excessive sleepiness), too little sleep (sleeplessness) and finally parasomnia (a category of sleep disturbances that involve abnormal movements, emotions, perceptions and dreams during sleep (Lee-Chiong, 2007)). When assessing sleep various factors need to be taken into account, for example duration of sleep, periods of waking, time of sleep and whether the timing of the sleep is appropriate. The Pittsburgh Sleep Quality Inventory is a non-invasive method for determining sleep disturbance. It is made up of seven parts, which eventually provide an overall sleep score. The seven parts includes subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, use of sleep medication and day-time dysfunction. The questionnaire includes evening and daytime sleepiness. There is an internal consistency and reliability coefficient (Cronbach's alpha) of r=0.8 for the seven components (Buysee et al. 1998). The Pittsburgh Sleep Quality Inventory has undergone extensive validation and reliability tests (Buysee et al. 1989). It has been used for research and clinical practice in clinical and normal populations. A global sleep quality score of greater than 5 is recommended for defining sleep dysfunction.

5.1.6   The aims of the study

Research investigating the relationship between sleep and MDMA is important. If MDMA is connected to sleep disturbances, it would mean that MDMA users may increase their chance of developing sleep disturbances in later life. Sleep disturbance and a general lack of sleep can be very dangerous as it has been shown to affect memory, energy levels, mental abilities and overall mood. Sleep problems can cause confusion, frustration and depression. Sleep disturbance can result in severe consequences on every day activities including family, employment, and everyday tasks like driving. Sleep deprivation has been blamed for many accidents at work and home.

Based on previous research in related areas, the following can be hypothesised. Current MDMA polydrug users will demonstrate sleep disturbance as measured by the Pittsburgh Sleep Inventory in comparison to non-MDMA polydrug users. There will be a non-significant difference in sleep scores as measured by the Pittsburgh Sleep Inventory between present and past MDMA polydrug users. There will be a positive correlation between the level of sleep disturbance as measured by the Pittsburgh Sleep Inventory and lifetime exposure of MDMA. There will be a positive correlation between sleep disturbances, as measured by the Pittsburgh

Sleep Inventory, levels of depression measured by the Becks Depression Inventory, and increased impulsivity measured by the Baratt Impulsivity Scale.

5.2   Methodology

5.2.1   Participants

997 of the original 1399 participants were involved in this part of the study, based on a power calculation, where N=432 (Power calculation; minimum of 72 per group, power=0.80, δ=2.80 – Cohen, 1992; Faul et al. 2007; Faul et al. 2009; minimum of 72 per group, power=0.80, δ=2.80). Refer to chapter 3 for full demographic details of the participants.

5.2.2   Measures

All participants were administered with a DHQ (see chapter 2 and appendix 2.2).

Participants were further required to fill out the self-reported Pittsburgh Sleep Quality Inventory (PSQI). The questionnaire is made up of seven areas of sleep and the participant is required to self-rate each area providing a score of 0-3. A score of 0 indicates a 'good' sleeper and a score of 3 indicates a 'poor' sleeper. Finally the scores are added up to provide an overall global score. An overall score of 5 indicates sleep disturbance (Buysse et al, 1989).

5.2.3   Procedure

Participants were asked to read the briefing form (Appendix 2.3). They were asked to complete the consent form which contained contact details of the experimenter and information concerning the study. The participant was informed they were required to complete two questionnaires, the DHQ and the PSQI. Participants were informed that they were free to withdraw from the study at any point during participation. Total time for completion of task was around 30 minutes per participant.

5.2.4 Ethical Issues

All participants provided written consent. Participants were able to withdraw at any point throughout the study. All data was anonymous. The study was approved by the local Ethics Committee in 2001, London Metropolitan University, formally known as London Guildhall University. Participants were given a briefing and debriefing (Appendix 2.3).

5.2.5 Statistical Analysis

Data was analysed using Statistical Package for the Social Sciences (SPSS) version 16. A one-way ANCOVA was run; the outcome variable was the mean log transformed PSQI scores; the predictor variable was the drug group (non-recreational drug control group; alcohol/nicotine control group; cannabis/alcohol/nicotine control group; non MDMA polydrug control; current MDMA polydrug group; ex-MDMA polydrug group) and the covariants were lifetime use of cannabis, amphetamine, cocaine and ketamine.

The results were further analysed using post hoc Bonferroni test where appropriate. The two MDMA groups were further split into 67 current less frequent MDMA users, 87 current frequent MDMA users, 49 less frequent ex-MDMA users and 108 frequent ex-MDMA users depending on whether they had used MDMA less than 20 times (less frequent) and those that had used it more than 20 times (more frequent). The results were further analysed using the Bonferonni test where required.

The ANOVAs and ANCOVAs were checked for normality using the Kolmogorov-Smirnov and Shapiro-Wilk test. As the tests were significant, the data was transformed to logs and the normality test re-checked. The log transformed data was non-significant, suggesting the data was normally distributed. The kurtosis and skewness were checked for values between -2 and 2. The log transformed data was plotted using the output of a quantile-quantile (Q-Q) plot. As the data did not stray from the predicted line, the data was linear and normally distributed. The covariate in the analysis was checked for its independence from the experimental manipulation; an ANOVA with the covariate as the outcome and the drug group as the predictor was run for all of the covariates (cannabis, amphetamines, cocaine and ketamine).

The covariate in the analysis was checked for its independence from the experimental manipulation; an ANOVA with the covariate as the outcome and the drug group as the predictor was run for all of the covariates (cannabis, amphetamines, cocaine and ketamine).

For the ANCOVA the Levene's test of the homogeneity of variance assumption was checked for non-significance relating to the homogeneity of residuals. The residual plot was checked for assumption of equality of variance. The spread vs. level plot was used to check there was no relationship between the mean and standard deviation. The homogeneity of regression slopes was checked by customising the ANCOVA model in SPSS to look at the independent variable * covariate interaction. The interaction term was tested in addition to the main effects. The log transformed interaction term (independent variable * covariate interaction) was non-significant; the assumption of homogeneity of regression slopes was not broken.

Log transformed self-reported PSQI sleep scores were correlated with log transformed self-reported lifetime MDMA exposure using the Pearson correlation coefficient.

Multiple regression analysis was performed on the log transformed PSQI sleep scores with the log transformed lifetime exposure to recreational drugs (alcohol, cannabis, nicotine, amphetamine, cocaine, LSD and ketamine) as the predictor variables. Using SPSS, the variance inflation factor (VIF) and tolerance statistics were checked. The VIF values were below 10 and the tolerance statistics were all above 0.2. The residual statistics was checked for extreme cases. The standardised residuals were all between -2 and 2. The Cook's distance was checked and all values were below 1. 5. The DFBeta statistics was checked to make sure no value was greater than 1. Examination of the residual plots demonstrated the data did not stray from the predicted line; the data was linear and normally distributed. The Levene's test was checked; it was non-significant thus homogeneity of variance was assumed. Homoscedasticity and hetroscedasticity were checked visually by plotting the standardised residuals (the errors) by the regression standardised predicted value. The residuals were randomly scattered around the horizontal line (0) (Tabachnick and Fidell, 2001).

5.3   Results

5.3.1   Demographics

For an account of the demographics details and full drug history of the participants refer to chapter 2.

5.3.2   PSQI

The ANOVAs were non-significant demonstrating independence between the predictor variable and the covariates. The homogeneity of residuals, normality, equality of variance and the homogeneity of the regression slopes were all checked for the ANCOVA.

For the multiple regression, the data was checked for multicollineraity, curvilineraity, hetroscedasticity and homogeneity of variance, and finally normality.

There was a significant overall difference in self-reported mean PQSI scores between the four control groups (non-drug, alcohol/nicotine group, alcohol/nicotine/cannabis group, and non MDMA polydrug group) and the four MDMA groups (less frequent current-MDMA users, frequent-MDMA users, less frequent ex-MDMA users and frequent ex-MDMA users) with the MDMA polydrug groups reporting increased sleep disturbances when compared with the non-MDMA control groups (Figure 5.1). The covariate, cannabis, was non-significantly related to the PSQI scores, $F(1, 991) = 0.05$, $p>0.05$). The covariate, amphetamine, was non-significantly related to the PSQI scores, $F(1, 991) = 0.69$, $p>0.05$). The covariate, cocaine, was non-significantly related to the PSQI scores, $F(1, 991) = 0.87$, $p>0.05$). The covariate, ketamine, was non-significantly related to the PSQI scores, $F(1, 991) = 0.74$, $p>0.05$). There was an overall significant effect of PSQI scores on drug group controlling for the effect of cannabis, amphetamine, cocaine and ketamine, $F(5, 991) = 174.4$, $p<0.01$).

There was a non-significant difference in self-reported scores from the PSQI between current MDMA users and ex-MDMA users (Bonferroni Post Hoc, mean diff=0.43 $p>0.05$; Figure 5.1) with both current and past MDMA polydrug users reporting similar sleep scores.

Between less frequent current-MDMA users and frequent-MDMA users there was a non-significant difference in self-reported scores for the PSOI (Bonferroni Post Hoc, mean

diff=0.45, p>0.05; Figure 5.1) with both frequent and non-frequent MDMA users self-reporting the same scores.

For the past MDMA users, both the frequent and non-frequent users reported identical sleep scores and this mean difference in sleep scores was non-significant between less frequent ex-MDMA users and frequent ex-MDMA users (Bonferroni Post Hoc, mean diff=0.32 p>0.05; Figure 5.1).

Figure 5.1: Mean PSQI scores

*The overall PSQI scores for each drug group (mean ±S.E.M), N=997, where * p<0.05. Non-recreational drug control group (non-drug)=182; alcohol/nicotine control group (alcohol/nicotine)=172; alcohol/nicotine/cannabis control group (alcohol/nicotine/cannabis)=163; non-MDMA polydrug control group (polydrug non-MDMA)=169; current frequent MDMA polydrug group (current frequent MDMA)=87; current less frequent MDMA polydrug group (current less frequent MDMA)=67, ex-frequent MDMA polydrug group (ex-frequent MDMA)=108, ex-less frequent MDMA polydrug group (ex-less frequent MDMA)=49.*

* *denotes a significant difference between non-drug & alcohol/nicotine & nicotine/alcohol/cannabis & non-MDMA polydrug in comparison to the current less frequent MDMA & frequent current MDMA & & ex-less frequent MDMA & ex-frequent MDMA, where p<0.05*

There was a significant positive linear correlation between the level of self-reported sleep disturbance as measured by the PSQI and the amount of self-reported lifetime MDMA consumed ($r=0.45$, $p<0.01$) indicating increased exposure to MDMA results in a positive increase in self-reported sleep disturbance as measured by the Pittsburgh Sleep Inventory.

Regression analysis was performed in order to predict which recreational drugs were more likely to predict the sleep scores, $F(9, 302)=70.8$, $p<0.05$ (table 5.4). The results found that the main predictors of sleep problems was MDMA (Beta=0.36, t-15.7, $sr^2=036$, $p<0.001$); followed by alcohol (Beta=-7.44, $t=-12.33$, $sr^2=0.09$, $p<0.001$) and LSD (Beta=0.37, $t=13.25$, $sr^2=0.062$, $p<0.001$).

Table 5.4 Regression coefficients for each drug of abuse and PSI (N=311)

The table provide details of the regression coefficients for each drug of abuse (MDMA, ketamine, tobacco, heroin, alcohol, amphetamines, cannabis, LSD and cocaine) and the overall PSQI score. The regression was only performed on the past and present MDMA users (n=311).

Drug	% predicts	Beta	t	p
MDMA	45	0.36	15.7	0.000
Ketamine	0	0.008	0.293	0.769 (ns)
Tobacco	1.3	0.17	3.914	0.000
Heroin	2.7	0.17	5.7	0.000
Alcohol	9.6	-7.44	-12.33	0.000
Amp	-2.2	1.26	6.44	0.000
Cannabis	-0.1	-0.09	-1.16	0.244 (ns)
LSD	-7.5	0.37	13.25	0.000
Cocaine	-0.1	-0.069	-2.08	0.038

5.3.4   Sleep, Impulsivity and Depression

Finally the data was further analysed to predict a relationship between sleep, impulsivity and depression.

There was a significant positive linear correlation between the level of self-reported sleep disturbance as measured by the PSQI and the self rated depression as measured by the BDI-II ($r=0.74$, $p<0.01$). Indicating that as sleep quality increases the level of depression decreases.

There was a significant positive correlation between the level of self-reported sleep disturbance as measured by the PSQI and the level of self-reported impulsivity as measured by the BIS ($r=0.71$, $p<0.01$). This suggests that as levels of impulsivity increase the overall sleep quality decreases.

There was a significant positive correlation between the level of self-reported level of depression as measured by the BDI-II and the level of self-reported impulsivity as measured by the BIS ($r=0.62$, $p<0.01$). This result proposes that as the level of depression increases the level of impulsivity increases.

5.4   Discussion

5.4.1   PSQI and MDMA

This study confirmed findings from previous research reporting past and present MDMA polydrug users have increased self-reported sleep disturbance in comparison to other non-MDMA polydrug users; however this study employed larger and more diverse sample sizes including more robust control groups implying MDMA results in acute sleep disturbances (Gouzoulis-Mayfrank et al. 1992; Allen et al. 1993; Cohen, 1995; Parrott, 1997; Soar et al. 2001; Balogh et al. 2004). These findings are further supported by non-human animal studies suggesting that MDMA induces selective 5-HT neuronal damage which adversely affects sleep.

The results found imply present MDMA polydrug users reported similar sleep disturbances as past MDMA polydrug users. This study included participants whom have abstained from MDMA for a mean of 5 years (range 5-11 years). These results are supported by non-animal

studies which suggest MDMDA induces selective 5-HT neuronal toxicity which is long lasting (Schnieder 1973, Levitt et al. 1980, Jonsson et al. 1982, Frankfurt et al. 1984; Gustafson et al. 1987, Fritschy et al. 1992, Ricaurte, 2000; Boot et al. 2000). In non-human primates this MDMA induced damage failed to repair after 9 years (Fisher et al. 1995), suggesting that MDMA causes long lasting sleep disturbances in abstained users.

Finally, past and present occasional MDMA polydrug users whom had only been exposed to MDMA a few times reported similar sleep problems in this study. The findings from this study are supported by non-human animal studies that have found MDMA induced neurotoxicity following small doses of MDMA. These findings contradict some researchers that believe large dosing and frequency of MDMA is needed in order to manifest this neuronal damage. Additional factors need consideration including whether these less frequent MDMA users have frequently used large doses of other recreational drugs including amphetamine, cannabis, alcohol, cocaine and LSD (Croft et al. 2001; Gouzoulis-Mayfrank et al. 2002; Dafters et al. 2004; Daumann et al. 2004; Parrott et al. 2004; Lundqvist et al. 2005; Sala et al. 2005). The sleep disturbance may be a consequence of recreational drugs and not MDMA. Co-using MDMA with other drugs has been demonstrated in non-human animal studies to increase the neurotoxicity of MDMA. Future studies need to investigate sleep disturbances in occasional MDMA polydrug users controlling for co-use of drugs as well as frequency and dosage of other illicit drugs. 5-HT genes have been localised (TPH2, 5-HT1b, 5-HTTLPR, and MAO) which affect serotonergic functioning within the brain. Certain individuals may be more prone to MDMA-induced neurotoxicity due to deficits in these genes.

There was a positive linear relationship between lifetime consumption of MDMA and level of sleep disturbance. MDMA was the main predictor of self-reported sleep disturbance. This relationship suggests that the results were unlikely to be due to other illicit drugs including alcohol, nicotine, cannabis, amphetamine, ketamine, and cocaine. Alcohol has been linked with causing sleep problems (Roehrs & Roth, 2001; Brower, 2003). The figure for the co-morbidity between insomnia and alcoholism is reported as being between 36-72% (Brower, 2003). Literature suggests the relationship between insomnia and alcoholism can be exacerbated by other psychiatric disorders including mood changes as well as a decrease in overall cognitive performance (Roehrs & Roth, 2001; Brower, 2003). Baseline polysomnographic measures correlated alcoholism with increased sleep latency, decreased sleep efficiency and decreased total sleep time, increased REM sleep, and decreased slow wave sleep (Brower, 2003). MDMA users are polydrug users. They are often combining alcohol and MDMA. This cocktail of MDMA and alcohol could elevate the negative

consequences on overall sleep quality.

Global scoring of the PSQI states that a score above 5 suggests sleep disturbance. Findings from the current study show that the non-MDMA groups (non-drug control, alcohol/nicotine control, alcohol/nicotine/cannabis control/ non-MDMA polydrug control) had scores below 5 indicating that they did not have from sleep problems. For the past and present MDMA users irrespective of whether frequent or occasional users the mean score was above 5 indicating sleep deficits. The PSQI is a validated and reliable measurement of sleep dysfunction; often used in the clinical setting and for research purposes (Buysee et al. 1998).

5.4.2 Sleep, Depression and Impulsivity

The results found a positive association between sleep and depression. The relationship between sleep and depression has long been established with health professionals and researchers suggesting figures could be as high as 80% of individuals suffering from depression having sleep related problems. Depression can lead to too much sleep alternatively it can result in too little sleep. Figures suggest that around 15% of depressed individuals will over sleep. Research states the lack of sleep alone is not the reason for the onset of depression however it can be a contributing factor. Sleep studies suggest that individuals with depression often complain of a difficulty in falling asleep, frequently waking up in the night, and waking up early in the morning being unable to fall back asleep. Case studies suggest that individuals with depression who are able to sleep often complain they are constantly tired throughout the day and their sleep was restless. Physiologically depressed individuals have little or no deep sleep (stages 3 and 4). REM sleep will occur earlier in the night. This restlessness could be explained by anxiety being a contributing factor and requires further exploration. Future detailed studies are required to investigate whether MDMA polydrug users are falling asleep, remain asleep during the night, experience disruptions in the night, and wake early. The amount of REM sleep needs to be recorded as well as the level of deep sleep (stage 3 and 4). This will help to decide whether the problem is due to the sleep cycle and/or pattern or if it is down to anxiety and/or restlessness (Buysee et al. 1998; Monk et al. 2000; Colbron et al. 2002; Roman et al. 2005).

Current theories have clearly suggested a link between sleep disturbance and depression (Allen et al. 1993; Cohen, 1995; Parrott, 1997; Soar et al. 2004). In all of these studies participants reported increased depression and sleep problems which authors attributed to MDMA use. Davisions and Parrot reported that 85% of MDMA users associated MDMA use with moodiness and 85% reported MDMA was associated with insomnia (Parrott, 1997).

Cohen reported slightly lower figures stating that 38% of MDMA users associated MDMA with insomnia and 38% associated it with depression (Cohen, 1995). In the case study reported by Soar and co-workers, the patient presented suffered from depression, suicidal thoughts and severe sleeping problems that he attributed to MDMA (Soar et al. 2004). The current findings clearly state that there is a relationship between self-reported depression and sleep.

This study found a positive correlation between sleep and impulsivity. This relationship supports research stating that substance users are high sensation seekers (Everitt & Robbins, 2005). However, there is still considerable debate concerning the route of these psychopathological disturbances. Are they a consequence of drug abuse or a predisposing factor (Everitt & Robbins, 2005; Blanchard et al. 2009)? These high sensation seekers will use many illicit and licit substances. A consequence of using these substances will include sleep deficits. Substance users may try to self-medicate to overcome sleep disturbances using drugs such as sedatives, which may worsen the problem. This pattern of use of illicit drugs will complicate treatment and rehabilitation. Research has found that the use of caffeine can disrupt sleep. Caffeine use may need to be controlled in future studies. MDMA tablets are often mixed with caffeine and this may need to be considered in future research (Parrott, 2001).

An association was found between impulsivity and depression nevertheless this connection was relatively weak in comparison to the other relationships found between sleep/depression and sleep/impulsivity. Studies comparing the BIS with patients with diagnosed depression/mania have found that motor impulsiveness is related to mania episodes, non-planning impulsiveness is connected to depressive episodes and attentional impulsiveness is linked with both mania and depression. Peluso et al (2007) predict that non-planning is a state-dependent symptom of depression. This should be investigated further in future studies.

5.4.3 Limitations and future studies

An area that needs attention is the link between anxiety, depression and MDMA. There have been a considerable number of reports linking MDMA use with occurrence of anxiety and depression. In the case study of a 26 year old reported to have taken 750 MDMA tablets, the individual was diagnosed with anxiety, phobia disorder, panic attacks as well as depression (Soar et al. 2004). Cohen reported that 16% of MDMA users associated MDMA with anxiety related problems in comparison to the 38% reporting depression (Cohen, 1995). Davison and Parrott reported rates as high as 40% for anxiety, 35% for paranoia and 55% for depression

(Parrot, 1997). This association could potentially be even more alarming as current research is suggesting that depression and anxiety co-exist, thus prognosis is more severe with an increased morbidity, elevated suicide risk and increased resistance to treatment (Lydiard & Brawman-Mintzer, 1998).

Criticism of the current study includes the methodology used to determine sleep disturbance. Self-reported measures are considered to be very unreliable (refer to chapter 8 for further discussion). A more accurate measure would be to ask participants to keep a sleep diary. Regrettably these methods can be very costly and time consuming for the participants' as well as the researcher. Even more accurate measures would include polysomnographic and actigraphic sleep measures (Monk et al. 1994). On the other hand studies suggest that there is a significant correlation (r=0.56-0.81) between scores on the PQSI and polysomnographic sleep measures (Monk et al. 1994). The PQSI gives an overall index of sleep quality rather than an index for a particular night using polysomnographic measures. This has its own advantageous and disadvantageous. The PSQI is a respected clinical tool.

Colbron and co-workers exposed hamsters to MDMA to investigate the ability of the SCN to phase shift to a photic stimulus after MDMA exposure. MDMA was administered on successive days. The results demonstrated that repeated exposure of MDMA resulted in altering the circadian clocks and the ability to phase shift to photic stimuli. This suggested that MDMA may cause a disruption to the normal functioning of the circadian clock and its resetting. This disruption could result in sleep disorders, increased mood, and a lack of concentration as seen in both jetlag and shift workers (Colbron et al. 2002). Future non-human animal studies are needed to confirm and identify the exact anatomical damage caused by MDMA particularly target the SCN and/or the pineal gland. In addition, studies need to target whether 5-HT directly disrupts the SCN or whether 5-HT indirectly affects another chemical like GABA. Secondly, future studies need to investigate the role of MDMA and its affect on melatonin. Non-human animal studies have indicated that 5-HT is synthesised to melatonin. If past and present MDMA users have a lack of available 5-HT it could consequently result in less melatonin and effect sleep onset and/or sleep quality.

Future investigation would be to investigate past and present MDMA users for other health issues such as headaches, pain and migraines as these health issues are highly linked with sleep disturbances.

Sleep disorders are vast with each one having its own aetiology. The most common sleep disorders include insomnia, sleep apnoea, restless leg syndrome (RLS), narcolepsy and

daytime sleepiness. Insomnia affects everyone at some point. Insomnia can be caused predominantly by stress, illicit drugs, jet lag and diet. Insomnia increases with age. Around 40% are affected by insomnia in comparison to 30% of men. Sleep apnoea is caused by interruption of breathing during sleeping. Narcolepsy involves sudden onset of sleep known as 'sleep attacks'. These attacks can last from 30 seconds to 30 minutes. Narcolepsy is considered to be related to a dysfunction of sleep regulation. Narcolepsy has been associated with head injury and neurological disorders. Narcolepsy is considered to be hereditary and research is currently trying to locate genes. Further MDMA experiments are needed including more polysomnography, and brain imaging to try and localise the exact nature of the MDMA induced sleep dysfunction (Buysee et al. 1998; Monk et al. 2000; Colbron et al. 2002; Roman et al. 2005).

Current treatment for sleep dysfunction includes older antidepressants including sedatives like amitriptyline and dosulepin. Other pharmaceutical treatments include methylphenidate, antipsychotic drugs and benzodiazepines. Antidepressants decrease REM sleep percentage, and increase total sleep time in stages 3 and 4. Antipsychotic drugs increase stages 3 and 4 as well as decreasing REM sleep. Benzodiazepines increase stages 2, 3, and 4 additionally decreasing REM. Other possible treatments may include 5-HTP and melatonin which increase REM sleep. In addition, non-human animal and human studies are needed to test the efficacy for possible treatments for MDMA induced neurotoxicity. There may be an excess of individuals with MDMA induced sleep dysfunction in the future and appropriate treatments will be needed. Each therapy affects different sleep stages. It is essential that the sleep physiology and stages affected by possible MDMA neurotoxicity are understood so appropriate treatment can be administered (Buysee et al. 1998; Monk et al. 2000; Colbron et al. 2002; Roman et al. 2005).

Sleep alters with the aging process. Older individuals report more sleep related disturbances. Levels of melatonin will be reduced as individuals age as part of the normal aging process. Individuals using MDMA at a young age may produce problems later in life. A combination of the normal reduction in melatonin due to the aging process and MDMA induced neurotoxicity causing further possible reductions in melatonin levels could consequently result in premature aging process in terms of sleep problems (Buysee et al. 1998; Monk et al. 2000; Colbron et al. 2002; Roman et al. 2005).

5.4.4   Summary

Even though the hypothesis for this study was formulated in 2001, it is still to date the largest single study investigating the association between sleep and MDMA use, which includes a sample that is a true 'real-life' representation of the general population, including a diverse range of ages and a large selection of educated individuals. This is the only study to date that robustly controls the use of other recreational drugs of abuse: amphetamine, cocaine, cannabis, heroin and alcohol. Previous studies are predominantly based on student samples and/or younger adults. This study includes a larger representation of the population of MDMA polydrug users during the period 2002-2007. Secondly, this is the first study to date to investigate the association between depression, sleep, impulsivity and MDMA.

The results from this study found that and present MDMA polydrug users self report enhanced sleep disturbances in comparison to non-MDMA polydrug users. These findings provide further support suggesting that this deficit in sleep is maintained even after abstinence in past MDMA users. These results support non-human animal studies suggesting MDMA may induce selective neurotoxicity to 5-HT neurons resulting in sleep problems that is non-repairable and long lasting. These results are further supported by evidence from non-human animal and human studies which link sleep dysfunction with 5-HT. More studies are needed to investigate this sleep disturbance found in MDMA polydrug users. Such investigations need to include more physiological studies using EEGs as well as measuring sleep patterns and alterations. Sleep disturbance is a common disorder affecting a large percentage of the normal population. MDMA users maybe more prone to sleep disorders incurring substantial costs for health services as well society due to loss of productivity. Full sleep history and sleep examination should be taken in past, present and future MDMA polydrug users.

This is the first study to find an association between MDMA, depression, sleep and impulsivity. These functions seem to be correlated to each other in previous research suggesting 5-HT plays a substantial role in maintaining normal psychological and physiological baseline levels. Further explorations of the association between sleep, impulsivity and depression are required. These psychological functions need to be controlled in future studies.

Chapter 6 - Memory

6.1 Introduction

This section will provide a brief introduction and definition of memory. It will evaluate the evidence supporting the role of 5-HT in memory functioning. Finally, it will evaluate both non-human animal studies and human studies concerning MDMA exposure and memory deficits.

6.1.1 The description of memory

To begin it is necessary to provide a brief description of memory, which will provide an outline of what will be measured in this chapter.

Figure 6.1 provides an outline of the structure of memory. Memory has often been referred to as a scheme that involves sensory information (verbal and visual) that can be stored into short-term memory (working memory), intermediate memory, and long-term memory. Information can be further classified into implicit and episodic memory (Fuster et al. 1971; Markowitsch, 1994; Frisk et al. 1990; Passchier et al. 2001; Smith et al. 2006; LaBar et al. 2006).

Episodic memory refers to remembering things that have happened in ones life experience in comparison to general memory, which is not associated to an individual's personal experience and known as semantic memory (Figure 6.1). In contrast, implicit memory involves remembering something with the lack of awareness of recollection. It is defined as an automatic or subconscious form of memory (Schacter, 1987; Toates, 2001).

Short-term memory is information being stored for a brief period of time (Fuster et al. 1971; Markowitsch, 1994; Frisk et al. 1990; Passchier et al. 2001; Smith et al. 2006; LaBar et al. 2006). On the contrary, information might be stored for a longer time by rehearsal. Only a limited amount of information may be stored in short-term memory (Figure 6.1).

Long-term memory deals with information that is relatively permanent (Fuster et al. 1971; Markowitsch, 1994; Frisk et al. 1990; Passchier et al. 2001; Smith et al. 2006; LaBar et al. 2006). Long-term memory is further divided into declarative and non-declarative memory.

Declarative memory referred to as 'explicit memory' is subdivided into memory for facts and memory for events. Non-declarative memory known as 'implicit memory' can be further broken down into memory for skills and habits, priming, basic associative learning and non-associative learning (Figure 6.1).

Research indicates different anatomical brain systems and neurons play particular roles in memory thus different types of brain neurons and synapses are involved in these types of memory (Fuster et al. 1971; Markowitsch, 1994; Frisk et al. 1990; Passchier et al. 2001; Smith et al. 2006; LaBar et al. 2006). These anatomical regions include the cortex, hippocampus, thalamus, striatum, medial temporal lobe, and amygdala (Figure 6.1).

Of particular interest is the hippocampus, which receives sensory input from various brain regions with many researchers agreeing that the role of the hippocampus is for the consolidation of memory from short-term to long-term memory (Olton, 1979; Squire, 1994; Eichenbaunm, 2001). A further role for the hippocampus involves the storage of episodic memory primarily for spatial information (Rolls, 1996; Kesner, 1998; Jenkins et al. 2004; Lee & Kesner, 2004).

Figure 6.1 – Structure of memory

The diagram provides the different divisions of memory and their anatomical associations (Toates, 2001)

Memory
Sensory and/or Verbal information

Short-term memory
Cortex

Intermediate memory
Thalamus

Long-term memory

Non-declarative
(Implicit)

Declarative
(Explicit)

Skills
Striatum

Priming
Cortex

Associative learning
Cerebellum

Facts   Events
Medial temporal lobe
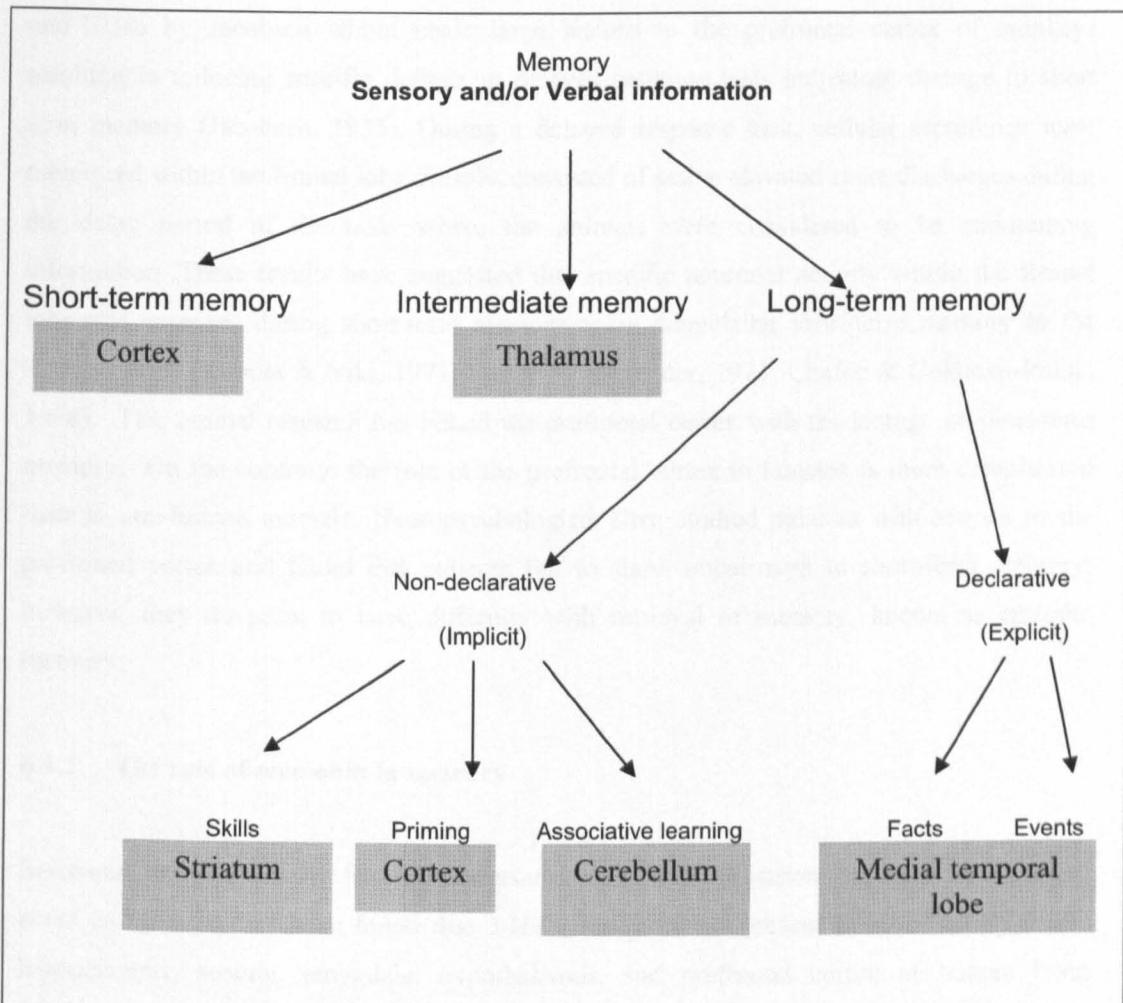
Emotion can play a role in memory resulting in emotional events being stored. Research suggests that the brain region the amygdala plays a pivotal role in the retention of emotional information. Evidence suggests that the amygdala facilitates the storage of emotional information via the prefrontal cortex and hippocampus (LaBar & Cbeza, 2006). Neuroimaging techniques have found a link between the amygdala, hippocampus and emotional memory retrieval. Studies have found that during emotional retrieval of information there was an increase in connectivity between the amygdala and the hippocampus (Smith et al. 2006). The study suggests that the amygdala is involved in emotional memory retrieval and accomplishes this via the hippocampus. Patients with the rare Urbach-Wiethe

syndrome who have selective bilateral lesions to the amygdala show deficits in the long-term recall/recognition of emotional pictures, words and stories (Markowitsch, 1994).

The involvement of the frontal cortex in short term memory was originally suggested in the mid-1930s by Jacobsen whom made large lesions to the prefrontal cortex of monkeys resulting in inducing specific deficits in delayed response tests indicating damage to short term memory (Jacobsen, 1935). During a delayed response task, cellular recordings were monitored within the frontal lobe. Results consisted of active elevated spike discharges during the delay period of the task, where the animals were considered to be maintaining information. These results have suggested that specific neuronal activity within the frontal lobe was essential during short-term memory again connecting short-term memory to the frontal cortex (Kubota & Niki, 1971; Fuster & Alexender, 1971; Chafee & Goldman-Rakic, 1998). This animal research has linked the prefrontal cortex with the storage of short-term memory. On the contrary, the role of the prefrontal cortex in humans is more complicated than in non-human animals. Neuropsychologists have studied patients with lesions to the prefrontal cortex and found that patients fail to show impairment to short-term memory; however, they do seem to have difficulty with retrieval of memory, known as episodic memory.

6.1.2   The role of serotonin in memory

Serotonin receptor density has been measured using PET (Positron emission tomography) scans *in vivo*. Studies have found that $5-HT_{1A}$ receptors are present in high density in the hippocampus, septum, amygdale, hypothalamus, and prefrontal cortex of human brain (Passchier et al. 2001). Furthermore $5-HT_{2A}$ receptors are present in the prefrontal cortex of the human brain. Conversely there are lower $5-HT_{2A}$ receptors densities in the hippocampus, basal ganglia and thalamus (Passchier et al. 2001).

Areas that are important in the role of memory: the hippocampus, amygdala, hypothalamus, thalamus and the prefrontal cortex, are associated with 5-HT receptor. This suggests that in humans it maybe the 5-HT neurotransmitter involved in memory (Fuster et al. 1971; Markowitsch, 1994; Frisk et al. 1990; Passchier et al. 2001; Smith et al. 2006; LaBar et al. 2006) and subsequently disrupted by MDMA consumption.

6.1.3   The role of MDMA and memory

It is clear that memory is related to the activity of 5-HT. As MDMA is a possible 5-HT neurotoxin, the non-human animal and human data suggesting that MDMA affects memory will be evaluated in this section.

As the acute effects of MDMA are similar between non-human animals and humans it is likely the neurotoxic effects of MDMA are comparable (Bolla et al. 1998; Parrott et al. 1998; Fox et al. 2001; Wareing et al. 2000). Non-human animal research suggests that MDMA initially causes an increase in 5-HT followed by a decrease it seems plausible to suggest that this decrease in 5-HT may occur in the frontal cortex, amygdala and hippocampus and affect memory (Fuster et al. 1971; Markowitsch, 1994; Frisk et al. 1990; Passchier et al. 2001; Smith et al. 2006; LaBar et al. 2006).

Non-human animal studies have shown that MDMA induced neurotoxicity affects the hippocampus suggesting that MDMA may cause disruptions to the recall of spatial memory (Frisk et al. 1990; Passchier et al. 2001; Smith et al. 2006; LaBar et al. 2006).

Consolidating information from short-term memory into long-term memory involves the limbic system including the hippocampus. MDMA is known to have acute effects on the hippocampus and other limbic structures resulting in behavioural changes in non-human animal studies. As non-human animal studies indicate that following the initial increase in serotonin, MDMA is selectively neurotoxic causing a depletion of 5-HT (Bolla et al. 1998; Parrott et al. 1998; Fox et al. 2001; Wareing et al. 2000). It is therefore plausible that MDMA may have a detrimental effect on consolidating information from the short-term to long-term memory store in MDMA users.

6.1.3.1   The role of MDMA on memory in non-human animals

Rats were administered either a high dose (4*5 mg/kg) of MDMA every four hours for two consecutive days, a moderate dose (1*5 mg/kg) of MDMA every four hours for two consecutive days, D-amphetamine (4*1 mg/kg) every four hours for two consecutive days, and finally vehicle injections. Fourteen weeks later, the rats were tested on a recognition memory task. The high MDMA group demonstrated memory impairment relative to all other groups (Morley et al. 2001). This study suggests that binging on moderate to heavy amounts of MDMA over a period of 48 hours may lead to memory recall impairment lasting up to

three months following abstinence.

Marston's group found impairment in a delayed matching to position working memory task in rats for up to 19 days following MDMA exposure (Marston et al. 1999). On the contrary, not all studies have found such results for example Ricaurte et al (1993) found that the choice accuracy of rats in a T-maze delayed in alternation task was generally unaffected following exposure to neurotoxic doses of MDMA.

Daza-Losada and co-workers (2009) gave MDMA alone or with cocaine to rats. The study found that MDMA alone failed to produce significant changes in brain monoamines. However, MDMA and cocaine showed a decreased level of DA in the striatum followed by an increase in 5-HT in the striatum and cortex. The study only observed the acute effects of MDMA. It is predicted that this increase in 5-HT in the cortex and striatum would decrease as has been demonstrated in other non-human animal studies (Daza-Lasada et al. 2009).

Camarasa et al. (2008) administered MDMA alone or MDMA with memantine, to rats. Memantine is an antagonist on several receptors: 5HT3, NMDA, D2, and nicotinic acetylcholine receptors. Rats were required to perform cognitive tasks. MDMA alone resulted in spatial memory impairment. On the other hand, MDMA pre-treated with memantine improved performance on the memory task. This finding suggests that MDMA may work via 5HT3, NMDA, D2, and/or acetylcholine nicotinic receptors. Further research investigating these nicotinic receptors in MDMA is required (Camarasa et al. 2008).

6.1.3.2   The role of MDMA on memory in humans

Over the last 10 years there has been a substantial amount of research investigating the effects of MDMA on memory performance using clinical trials, imaging and cohort experiments (Table 6.1).

An 18-month longitudinal fMRI study investigated the effects of MDMA on working memory processing (Daumann et al. 2004). A sample of 21 MDMA users was scanned, whilst performing on the n-back task, with increasing memory load. Participants were re-tested 18 months later. At 18 months, the initial 21 MDMA users were further spilt into those that had continued to use MDMA (n=9) and those that had abstained from MDMA (n=8). The results found that there was a non-significant difference in brain activity for both current and abstained MDMA users at baseline and/or on the n-back task. However, after 18 months the

current MDMA users showed an increase in activation of the parietal region in comparison to their baseline activity, this was not observed after abstinence. The authors concluded that MDMA could cause damage to the neuronal activity to a particular brain region resulting in adjacent areas of the brain having to compensate. The imaging study found no abnormal cortical activity in the prefrontal, parietal, occipital, and cingulate brain regions for those that had abstained from MDMA. The authors concluded that abstinence from MDMA needed to be longer than 18 months in order to see altered cerebral activation (Daumann et al. 2004). This study suggests that if MDMA causes a problem to memory functions, the participant needs to have abstained from MDMA for a period of 18 months or longer.

A study by Reneman et al (2000) investigated the long lasting effects of MDMA. The pilot study involved measuring the relationship between 5-HT neuronal activity and memory impairment as recorded by the Rey Auditory Verbal Learning Test (RAVLT). Serotonin activity was measured via $[^{123}I]$-5-I-R91150 SPECT (5-HT$_{2A}$ receptor densities). The study investigated five ex-MDMA users (abstained for a mean of 4 months) and nine healthy non-MDMA controls. The results found that ex-MDMA users demonstrated significantly higher binding ratios in the occipital cortex in comparison to the controls during the memory task, indicating up-regulation. The area of the occipital cortex has been shown in non-human primates to demonstrate high 5HT$_{2A}$ receptor binding sites due to a reduced 5-HT available (Heal et al. 1985; Scheffel et al. 1998). Mean 5-HT receptor binding correlated positively with memory performance. The authors concluded MDMA might cause long lasting alterations to 5-HT activity subsequently affecting memory performance (Reneman et al. 2000).

Reneman et al (2006) continued this work by doing a similar study using larger samples and better controls investigating the relationship between MDMA and memory by means of Single photon emission computed tomography (SPECT) using iodine labelling to quantify the density of brain 5-HT transporter in current and ex-MDMA users. Verbal memory was assessed using the RAVLT. The main study included 22 current MDMA users, 16 ex-MDMA users (abstained for more than 1 year) and 13 non-MDMA controls. The results found that the two MDMA groups were significantly impaired on the immediate recall and delayed recall tasks in comparison to the non-MDMA control group. However, the mean cortical 5-HT transporter density was only significantly lower in recent MDMA users and not ex-MDMA users. The study suggests that MDMA is neurotoxic to 5-HT neurons, which is reversible in humans, however MDMA induced disruptions in memory performance in non-human animals may not be reversible (Reneman et al. 2006).

Gouzoulis-Mayfrank et al (2003) investigated memory impairment in abstained MDMA users. This study consisted of 60 MDMA users that had taken MDMA on more than 20 occasions, and 30 healthy non-MDMA controls that had no previous history of alcohol or drug use other than moderate cannabis use. The MDMA group was further split into moderate users (taken MDMA less than 80 occasions) and heavy users (taken MDMA on more than 80 occasions). Working memory performance was measured using the digit span task from the WAIS-R and the 2-back task from the 'Testbatterie zur Aufmerksamkeitsprüfung' (TAP - German assessment of attentional functions). General memory tests included the four subtests from the German learning and memory test (Baumler, 1974). The results revealed a correlation between the amount of MDMA consumed and memory performance indicating that the heavier the patterns of MDMA use the increased likelihood of memory deficits. There was no significant difference between the moderate MDMA group and the control group (Gouzoulis-Mayfrank et al. 2003). The authors' concluded that MDMA maybe a risk factor for an earlier onset of age-related memory problems or a risk of more severe memory deficits later on in life.

A study by Wareing et al (2005) further investigated the link between MDMA and verbal working memory deficits. The study included 42 current MDMA users, 17 previous MDMA users (that had abstained from MDMA for more than 6 months) and 31 non-MDMA users. The study involved two parts: reading span and arithmetic span. The reading span involved answering simple multiple choice comprehension questions. Secondly, they had to recall the final word of a sentence after they had answered the question. The computation span part was similar; except the participant was required to uses arithmetic processing instead of sentence comprehension. Participants were presented with an arithmetical problem and had to solve it. Finally, they were required to recall the second digit of the problem (Frisk et al.1990). Both MDMA user groups were impaired on the computation digit span, with the current users only impaired on the comprehension span. The use of other recreational drugs was controlled using statistical analysis only (Wareing et al. 2005).

A study by Parrott et al (1998) investigated the effects of MDMA on a battery of cognitive tasks: verbal recall and visual scanning. Participants completed the task four times: initial drug-free baseline, at a Sat night club whilst on a drug, 2 days later and 7 days later. The study included 15 MDMA users whom reported taking MDMA on more than 10 occasions, 15 novice MDMA users whom reported taking MDMA on less than 10 occasions, and 15 controls whom had never taken MDMA. Overall the regular MDMA users recalled significantly less words on the verbal recall and the visual scanning recall in comparison to the other groups: novice MDMA and controls.

Daumann et al. (2003) used fMRI to investigate cerebral activation during a memory task in eleven heavy current MDMA users (used MDMA on more than 80 occasions), eleven moderate current MDMA users (used MDMA on less than 80 occasions) and eleven non-MDMA users (that had no previous history of regular drug use). The findings found no difference in overall performance in working memory scores between the three groups and there was no difference in cortical activation during the memory task. However, the two MDMA groups showed significantly more activation of the right parietal lobe during the memory task (Daumann et al. 2003). The study controlled for other drugs of abuse including amphetamine and cannabis. However, the study failed to have separate control groups for these different recreational drugs. The authors did suggest that MDMA users might demonstrate an altered brain function. However, investigations are required before any conclusions can be reached as the results could be explained by differences in motivational levels or different cognitive strategies between the moderate and heavy users.

Morgan (1999) investigated memory impairment and MDMA use by comparing 25 polydrug MDMA users that had reportedly taken more than 20 ecstasy tablets, 22 polydrug users that had used illegal recreational drugs however had never taken MDMA and finally 19 non-recreational control group. All participants were matched for age, gender, education, height and weight. Memory was measured using the behavioural evaluation test - Rivermead Behavioural Memory (RBM) test that measures both immediate and delayed recall. The results found that MDMA users recalled significantly fewer items in the immediate and delayed conditions in comparison to the two non-MDMA groups (Morgan, 1999).

Parrott et al (2002) asked MDMA users to self-report psychobiological problems that they associated with the use of MDMA. The participants included novice (used MDMA on less than 9 occasions); moderate (use of MDMA between 11-99 occasions) and heavy users (used MDMA on more than 100 occasions). The results found memory problems were reported by 19% of the novice users, 52% of the moderate users and 73% of the heavy users. This study attempts to suggest that psychological damage caused by MDMA use is directly related to lifetime MDMA exposure (Parrot et al. 2002).

Hasler et al. (2008) employed a double blind study on males. The study involved participants being administered MDMA alone or in combination with pindolol. Pindolol is a beta-adrenoreceptor and a weak 5-HTIA antagonist (Isaac, 2004). Participants were assessed on cognitive performance. Findings found that MDMA only users were significantly impaired on attention and visual-spatial memory. The pre-treatment with pindolol did not alter the

MDMA-induced impairment. The authors concluded that MDMA differentially affects selective memories which are not mediated by the 5-HT1A receptor system (Hasler et al. 2008).

Simon and Mattick (2002) investigated 40 regular MDMA users and 37 regular cannabis users using the Wechsler Memory Scale (WMS). The results from the study found that the lifetime exposure of MDMA and cannabis predicted memory ability. This study suggests that more robust control groups are required when investigating drug related research including separate MDMA and cannabis groups (Simon and Mattick, 2002).

Not all studies have found a strong link between MDMA and memory deficits. A similar study investigating neuronal activity during a working memory task using fMRI techniques compared eight pure MDMA users, eight polydrug control MDMA users and eight non-polydrug user controls. The results found that pure MDMA users demonstrated a lower activation than the other two control groups in the inferior temporal regions, the angular gyrus and the striate cortex. There was a non-significant difference between polydrug MDMA users and non-drug controls. The study suggests that altered brain activity may occur during cognitive tasks in MDMA users; however the use of other recreational drugs may mask this effect or help to prevent it occurring (Daumann et al. 2003).

A cohort study investigated 15 regular MDMA users, 15 regular cannabis users excluding the use of MDMA, 15 control non-recreational drug users. The participants were tested on the WMS (Revised) on a day that all participants reported to be drug free. Performance was similar between all groups for measures of visual reaction time, auditory reaction time, complex reaction time, visual memory, attention, and concentration (Rodgers, 2000). The current MDMA/cannabis group had significantly impaired scores on general memory and the verbal memory task. The only task that the current MDMA users were significantly impaired in comparison to the cannabis and control group was delayed memory.

6.1.3.3   Summary of non-human animal and human studies (2009 – 2011)

This section will summarise the non-human animal and the human evidence supporting the role of MDMA in memory deficits during the period 2010-2011.

Morini et al. (2011) investigated the role of MDMA in disrupting long-term potentiation (LTP) in the CA1 cells of the hippocampus. A neurotoxic dose of MDMA was administered

to rats. Slices of hippocampus were examined a week later to find 53% reduction in 5-HT content, demonstrating 5-HT neurotoxicity. However, in these reduced 5-HT rats, the LTP was 46% greater than controls. They concluded there is a positive correlation between reduced 5-HT and enhanced synaptic plasticity (Morini et al. 2011). Form this study it suggests that MDMA induced learning and memory deficits are not a consequence of disruption to LTP.

Blagrove et al. (2010) studied procedural and declarative memory in MDMA users. The participants were tested on two consecutive sessions. The groups consisted of drug-naïve control (n=24), recent MDMA whom had taken MDMA within 3 days of the study (n=25), abstinent whom had abstained for 8 days prior to the study (n=17). The results concluded that greater lifetime exposure to MDMA resulted in poorer procedural memory whereas MDMA and cocaine lifetime use was associated with deficits in declarative memory (Blagrove et al. 2010). This study highlights the need to control for other recreational drugs of abuse. A similar study reported that lifetime use of MDMA caused deficits to spatial span and spatial working memory tasks; however they also found that lifetime use of cannabis was problematic for verbal learning and overall memory performance (Hanson and Luciana, 2004).

During the period 2000-2011, there have been limited studies investigating exposure to MDMA and memory impairment; however results from such studies have reported contradictory findings (Table 6.2). Studies now need to take into account lifetime use of other recreational drugs which may affect memory performance including alcohol, cannabis, cocaine, and amphetamine. In some of the previous MDMA/memory studies, for example Morgan (1999), they did try to exclude other recreational drugs by including them as a covariate in the analysis. There are many issues with this statistical analysis. In addition, using separate control groups for these recreational drugs would have been beneficial and more robust (Gouzoulis-Mayfrank et al. 2003; Wareing et al. 2005; Morga., 1999; Parrott et al. 2002; Parrot et al. 1998; Daumann et al. 2003; Rodgers, 2000). Previous studies have failed to investigate the deficits caused by MDMA on memory and its effect on the normal aging process. The majority of studies have investigated the short-term consequences of MDMA and memory only. Finally, there is debate with the methodology employed in these studies as it is argued that in order to identify memory deficits the memory task needs to be complex (Brown et al. 2010). Not all studies have employed complex tasks.

Table 6.2   Summary of previous research investigating MDMA and memory

Provides a summary of some studies investigating the link between MDMA and memory during the period 2005 – 2009. The table provides details of authorship, test employed, the control groups included, whether long lasting effects were investigated and finally if they found a significant result

Author	Test	Groups	Long lasting effects	Result
Ramaekers et al. 2009	Double-blind fMRI	12 MDMA	No	Less activity in MDMA vs control
Cowan et al. 2009	MRI	12 MDMA	No	No difference (Non sig)
Kuypers et al. 2009	Double blind	14 MDMA	No	MDMA worse
McCann et al. 2009	PET/WMS-11	16 ex-MDMA polydrug	Yes	ex-MDMA worse on WSM
Indlekofer et al. 2009	WMS-11	284 polydrug users	No	MDMA worse on WSM
Nifosi et al. 2008	fMRI/MRI	Case study	Yes	MDMA caused problems
Bedi et al. 2009	WSM-11	45 MDMA 48 cannabis groups 40 alcohol/nicotine	Yes	No difference between (Non- sig)
De Sola Llopis et al. 2008	WSM-11	37 MDMA 23 cannabis 34 non-drug	No	MDMA worse on WSM

Author	Test	Groups	Long lasting effects	Result
Schilt et al. 2009	WSM	67 polydrug users	No	MDMA worse on WSM
Rendell et al. 2007	Prospective memory	27 MDMA 34 controls	No	MDMA worse on WSM
Montgomery et al. 2007	CFQ/EMQ/PMQ	28 MDMA 35 non-MDMA control	No	No difference between groups (Non-sig)
Hoshi et al. 2007	WSM	25 current MDMA 28 ex-MDMA 29 polydrug 27 non-drug control	Yes	No difference between groups (Non-sig)
Schilt et al. 2007	Verbal Memory	58 MDMA 60 controls	No	MDMA worse
Golding et al. 2007	WSM	20 MDMA 20 ex-MDMA 20 controls	Yes	No difference (Non sig)
Groth-Marnat et al. 2007	WMS	26 MDMA 26 controls	No	No difference between groups (Non-sig)

Author	Test	Groups	Long lasting effects	Result
Ward et al. 2006	WMS-11	31 current MDMA 30 ex-MDMA	Yes	MDMA current and ex worse WMS
Quednow et al. 2006	RAVLT	19 MDMA 19 cannabis 19 controls	No	MDMA worse on RAVLT
Zakzanis et al. 2006	Cogn tests	7 MDMA 8 ex-MDMA	Yes	MDMA worse on cognitive tests
Gouzoulis-Mayfrank et al. 2005	WSM	17 ex-MDMA 21 current MDMA	Yes	MDMA current and ex worse on WSM
Wareing et al. 2005	Visuo spatial working memory	36 MDMA 12 ex-MDMA 31 polydrug	Yes	MDMA worse on visuo-spatial task
Daumann et al. 2005	fMRI	12 MDMA 12 controls	No	MDMA less activation frontal lobe

The Wechsler Memory Scale – Revised (WMS-R) provides a measure of various aspects of memory (Wechsler, 1987). The WMS-R measures several subscales: general memory, attention/concentration, verbal memory, visual memory, delayed recall, logical memory, and visual reproduction. Two of the subscales are repeated during the task: logical memory and visual reproduction. Verbal and visually material is alternated during the task in order to maintain the participant's concentration and interest (Wechsler, 1987).

The WMS-R test has undergone reliability tests (test-retest) for five of the subscales. Scoring for internal consistencies ranges from 0.41 to 0.88. The WMS-R has strong correlations with the California Verbal Learning test (CVLT) (0.79) (Delis et al. 1988). The CVLT was compared with the RAVLT. Factor analysis yielded a five-factor model between the WAIS-R, RAVLT and WMS-R including verbal comprehension, perceptual organisation, attention, learning and retention (Smith et al. 1992).

The WMS-R has been used on a number of different patient groups with learning and memory disorders including Alzheimer's disease (Butters et al. 1988; Troster et al. 1993), Huntington's disease (Troster et al. 1993), multiple sclerosis, head injuries (Crossen et al. 1988; Janowsky et al. 1989), Korsakoff's syndrome, alcoholism, cerebral aneurysms, exposure to neurotoxins, schizophrenia (Gold et al. 1992), and depression (Wechsler, 1987; King et al. 1995).

Standardised scores are available for the WMS-R based on a sample from the US that is considered to be representative of the general population. The manual provides norms for individuals aged 16-74 years old, being divided into six age groups (Wechsler, 1987). These norms are based a sample size of about 50 for each age group.

6.1.5   The objectives of the study

Experimental studies have linked brain 5-HT with memory functioning. Studies have indicated that lowered levels of 5-HT can result in memory disturbance. Non-human animal research has demonstrated that MDMA may cause a long lasting depletion of CNS 5-HT, in specific areas of the brain. The long lasting consequences of MDMA on humans are still unknown. It is plausible to suggest that MDMA may cause memory disturbances in humans. Several studies have already investigated the effect of MDMA on memory however, such studies have failed

to control for other recreational drugs, employed small sample sizes thus reducing the power of the study and failed to investigate the long lasting effects of MDMA on memory on an aged sample.

Based on previous research in related areas, the main hypothesis of this study includes: 1) MDMA users will demonstrate memory disturbance as measured by the WMS-R in comparison to non-MDMA polydrug users, 2) There will be a non-significant difference in memory scores as measured by the WMS-R between present and past MDMA polydrug users, 3) There will be a negative correlation between memory deficits as measured by the scores of the WMS-R and lifetime exposure to MDMA, it is predicted increased lifetime exposure to MDMA will result in decreased memory scores.

6.2   Methodology

6.2.1   Participants

997 of the original 1399 participants were involved in this part of the study, based on a power calculation, where N=432 (Power calculation; minimum of 72 per group, power=0.80, δ=2.80 – Cohen, 1992; Faul et al. 2007; Faul et al. 2009; minimum of 72 per group, power=0.80, δ=2.80). Refer to chapter 3 for full demographic details of the participants.

The participants were further divided into four control groups and two MDMA groups (non-recreational drug control group n=182; alcohol/nicotine control group n=172; cannabis/alcohol/nicotine control group n=163; non MDMA polydrug control n=169; current MDMA polydrug group n=154; ex-MDMA polydrug group n=157).

6.2.2 Measures

All participants were administered with a DHQ (Chapter 2, Appendix 2.2).

Secondly, participants were further required to complete the Weschler Memory Scale - Revised. Instructions for the test were followed from the manual. The approximate time of test administration was 45 minutes. The test was made up of eight subscales (Wechsler, 1987). These included: figural memory, logical memory, visual paired associates, verbal paired associates, visual reproduction, digit span, mental control and visual memory span. Four of the eight subtests are repeated after a 30 minute period to assess delayed recall (visual paired

associates, verbal paired associates, visual reproduction and logical memory). Scoring involved a raw score to be obtained for each subscale, resulting in a final total of 8 raw scores. Each raw score was multiplied by a value provided on the record sheet to provide a new weighted score. This weighted score was transformed into an index score by an age-graded table, which can be found in the manual. Each index score has a mean of 100 and SD of 15.

The eight index scores produce five overall scores including:

- General memory (formed from five of the sub tests – logical memory, verbal paired associates, figural memory, visual paired associates and visual reproduction).
- Verbal memory (formed from verbal paired associates and logical memory).
- Visual memory (formed from figural memory, visual paired associates, and visual reproduction).
- Attention/concentration (formed from mental control, digit span and visual memory span).
- Delayed recall (formed from the second attempt at logical memory, visual paired associates, verbal paired associates, and visual reproduction).

6.2.3   Ethical Issues

All participants provided written consent. Participants were able to withdraw at any point throughout the study. All data was anonymous. The study was approved by the local Ethics Committee, London Metropolitan University formally known as London Guildhall University, 2001. Participants were given a briefing and debriefing (Appendix 2.3).

6.2.4   Statistical Analysis

Data was analysed using Statistical Package for the Social Sciences (SPSS) version 16. Five one-way ANCOVAs were run; the outcome variable was the subscales of the WSM – Revised test; the predictor variable was the drug group (non-recreational drug control group n=182; alcohol/nicotine control group n=172; cannabis/alcohol/nicotine control group n=163; non MDMA polydrug control n=169; current-MDMA polydrug group n=154; ex-MDMA polydrug group n=157) and the covariate was the lifetime use of cannabis, amphetamine, cocaine and ketamine. The results were further analysed using the Bonferroni test where required.

The ANOVAs and ANCOVAs were checked for normality using the Kolmogorov-Smirnov and Shapiro-Wilk test. As the tests were significant, the data was transformed to logs and the normality test re-checked. The log transformed data was non-significant, suggesting the data was normally distributed. The kurtosis and skewness were checked for values between -2 and 2. The log transformed data was plotted using the output of a quantile-quantile (Q-Q) plot. As the data did not stray from the predicted line, the data was linear and normally distributed. The covariate in the analysis was checked for its independence from the experimental manipulation; an ANOVA with the covariate as the outcome and the drug group as the predictor was run for all of the covariates (cannabis, amphetamines, cocaine and ketamine).

For the five ANCOVAs the Levene's test of the homogeneity of variance assumption was checked for non-significance relating to the homogeneity of residuals. The residual plot was checked for assumption of equality of variance. The spread vs. level plot was used to check there was no relationship between the mean and standard deviation. The homogeneity of regression slopes was checked by customising the ANCOVA model in SPSS to look at the independent variable * covariate interaction. The interaction term was tested in addition to the main effects. The log transformed interaction term (independent variable * covariate interaction) was non-significant; the assumption of homogeneity of regression slopes was not broken.

Log transformed self-reported sub-domain memory scores were correlated with log transformed self-reported lifetime MDMA exposure using the Pearson correlation coefficient.

Multiple regression analysis was performed on the sub-domain memory scores with the log transformed lifetime exposure to recreational drugs (alcohol, cannabis, nicotine, amphetamine, cocaine, LSD and ketamine) as the predictor variables. Using SPSS, the variance inflation factor (VIF) and tolerance statistics were checked. The VIF values were below 10 and the tolerance statistics were all above 0.2. The residual statistics was checked for extreme cases. The standardised residuals were all between -2 and 2. The Cook's distance was checked and all values were below 1. 5. The DFBeta statistics was checked to make sure no value was greater than 1. Examination of the residual plots demonstrated the data did not stray from the predicted line; the data was linear and normally distributed. The Levene's test was checked; it was non-significant thus homogeneity of variance was assumed. Homoscedasticity and hetroscedasticity were checked visually by plotting the standardised residuals (the errors) by the regression standardised predicted value. The residuals were randomly scattered around the horizontal line (0) (Tabachnick and Fidell, 2001).

6.3 Results

6.3.1 Demographics

For an account of the demographic details and a full drug history of the participants, refer to chapter 2.

6.3.2 Subdivisions of the WMS-R

The ANOVA was non-significant demonstrating independence between the predictor variables and the covariates. The homogeneity of residuals, normality, equality of variance and the homogeneity of the regression slopes were all checked for the ANCOVA.

For the multiple regression, the data was checked for multicollinearity, curvilineraity, hetroscedasticity and homogeneity of variance, and finally normality.

6.3.2.1 Verbal Memory Test

An overall significant difference was found on the verbal memory index score between the MDMA groups and non-MDMA control groups, where the mean verbal memory score was less for the MDMA groups in comparison to the non-MDMA control groups (Table 6.3). The covariate, cannabis, was non-significantly related to the verbal memory scores, $F(1, 991) = 1.22, p>0.05$. The covariate, amphetamine, was non-significantly related to the verbal memory scores, $F(1, 991) = 0.65, p>0.05$. The covariate, cocaine, was non-significantly related to the verbal memory scores, $F(1, 991) = 0.37, p>0.05$. The covariate, ketamine, was non-significantly related to the verbal memory scores, $F(1, 991) = 2.29, p>0.05$. There was an overall significant effect of verbal memory scores on drug group controlling for the effect of cannabis, amphetamine, cocaine and ketamine, $F(5, 991) = 176.4, p<0.01$.

Further analysis using post-hoc analysis found a significant difference between all four control groups (non-drug, alcohol/nicotine group, alcohol/nicotine/cannabis group, and non MDMA polydrug group) and the two MDMA groups (current-MDMA users and frequent ex-MDMA users), where the MDMA groups mean score was less than that of the non-MDMA control groups (Bonferroni Post Hoc, $p<0.01$). There was a non-significant difference between the current and ex-MDMA polydrug groups, with all groups scoring similar mean scores (Bonferroni Post Hoc, $p>0.05$).

6.3.2.2 Visual Memory Test

For the visual memory index there was a difference in mean scores between drug groups (Table 6.3). The covariate, cannabis, was non-significantly related to the visual memory scores, $F(1, 991) = 0.048$, $p>0.05$. The covariate, amphetamine, was non-significantly related to the visual memory scores, $F(1, 991) = 0.73$, $p>0.05$. The covariate, cocaine, was non-significantly related to the visual memory scores, $F(1, 991) = 0.83$, $p>0.05$. The covariate, ketamine, was non-significantly related to the visual memory scores, $F(1, 991) = 0.94$, $p>0.05$. There was an overall significant effect of visual memory scores on drug group controlling for the effect of cannabis, amphetamine, cocaine and ketamine, $F(5, 991) = 55.2$, $p<0.01$.

Further analysis found a significant difference between the four control groups (non-drug, alcohol/nicotine group, alcohol/nicotine/cannabis group, and non MDMA polydrug group) and the two MDMA groups (current-MDMA users and frequent ex-MDMA users) (Bonferroni Post hoc, $p<0.01$), where the mean scores for the MDMA groups was less than the mean scores for the non-MDMA control groups. There was a non-significant difference between the current MDMA users and the ex-MDMA users, with the MDMA groups scoring alike scores (Bonferroni Post hoc, $p>0.05$).

6.3.2.3 General Memory Test

Overall there was a difference on the general memory index scores between the drug groups (Table 6.3). The covariate, cannabis, was non-significantly related to the general memory scores, $F(1, 991) = 0.007$, $p>0.05$. The covariate, amphetamine, was non-significantly related to the general memory scores, $F(1, 991) = 0.14$, $p>0.05$. The covariate, cocaine, was non-significantly related to the general memory scores, $F(1, 991) = 0.15$, $p>0.05$. The covariate, ketamine, was non-significantly related to the general memory scores, $F(1, 991) = 0.006$, $p>0.05$. There was an overall significant effect of general memory scores on drug group controlling for the effect of cannabis, amphetamine, cocaine and ketamine, $F(5, 991) = 187.3$, $p<0.01$.

Further analysis found a significant difference between the two MDMA groups (current-MDMA users and frequent ex-MDMA users) and the four control groups (non-drug, alcohol/nicotine group, alcohol/nicotine/cannabis group, and non MDMA polydrug group) for the general memory index, where the mean scores for the non-MDMA control groups were greater than the past and present MDMA groups mean scores (Bonferroni Post hoc, $p<0.05$). There was a non-significant difference between the current and ex-MDMA group on the

general memory index (Bonferroni Post hoc, p>0.05), with both the MDMA groups scoring similar mean scores. There was a significant difference in general memory index between the non-drug control/nicotine alcohol group and the alcohol/nicotine/cannabis and non-MDMA poly drug groups (Bonferroni Post hoc, p<0.05), where the non-drug control/nicotine alcohol groups mean scores were greater than that of the alcohol/nicotine/cannabis group and non-MDMA polydrug group. There was a significant difference between the alcohol/nicotine/cannabis and non-MDMA poly drug groups and the current and ex-MDMA groups (Bonferroni Post hoc, p<0.05), where the mean scores of both the current and present MDMA groups mean scores were less than that of the alcohol/nicotine/cannabis group and non-MDMA polydrug group (Table 6.3).

6.3.2.4   Delay Memory Test

There was a difference on the delay memory index score between the different drug groups, where the mean scores differed between all the drug groups (Table 6.3). The covariate, cannabis, was non-significantly related to the delayed memory scores, $F(1, 991) = 0.448$, p>0.05. The covariate, amphetamine, was non-significantly related to the delayed memory scores, $F(1, 991) = 0.449$, p>0.05. The covariate, cocaine, was non-significantly related to the delayed memory scores, $F(1, 991) = 0.618$, p>0.05. The covariate, ketamine, was non-significantly related to the delayed memory scores, $F(1, 991) = 0.261$, p>0.05. There was an overall significant effect of delayed memory scores on drug group controlling for the effect of cannabis, amphetamine, cocaine and ketamine, $F(5, 991) = 236.1$, p<0.01.

Further analysis found a significant difference between the four control groups (non-drug, alcohol/nicotine group, alcohol/nicotine/cannabis group, and non MDMA polydrug group) and the two MDMA groups (current-MDMA users and frequent ex-MDMA users), where the two MDMA groups scored less in terms of mean scores in comparison to the non-MDMA control groups (Bonferroni Post hoc, p<0.01) (Table 6.3).

6.3.2.5   Attention Test

Finally, there was no overall difference on the attention index score between the drug groups (Table 6.3), where the mean scores between the MDMA groups and the four non-MDMA control groups were similar (Table 6.3). The covariate, cannabis, was non-significantly related to the attention scores, $F(1, 991) = 0.001$, p>0.05. The covariate, amphetamine, was non-significantly related to the attention scores, $F(1, 991) = 0.005$, p>0.05. The covariate, cocaine, was non-significantly related to the attention scores, $F(1, 991) = 0.004$, p>0.05. The covariate,

ketamine, was non-significantly related to the attention scores, $F(1, 991) = 0.408$, $p>0.05$. There was a non-significant effect of attention scores on drug group controlling for the effect of cannabis, amphetamine, cocaine and ketamine, $F(5, 991) = 6.52$, $p>0.05$.

Table 6.3   Mean (SD) index score for five subscales of the WMS-R

*The overall index scores for the WMS-R (verbal, visual, general, attention and delayed memory) for each drug group (mean ± SD), N=997, where * p<0.05, (non-drug, alcohol/nicotine group, alcohol/nicotine/cannabis group, non-MDMA polydrug group, current MDMA users and frequent ex-MDMA users).*

Measure	Non-drug	Alcohol/ Nicotine	Alcohol/ Nicotine/ Cannabis	Non- MDMA Poly Drug	Current MDMA	Ex- MDMA
Verbal Memory	108.5	109.5	99.2	98.5	87.5 *	88.3 *
Visual Memory	111.8	110.4	111.1	111.0	99.4 *	98.2 *
General Memory	115.7	113.2	98.7 **	97.8 **	82.5 **	86.2 **
Attention	119.4	116.4	111.2	110.1	115.7	112.3
Delayed Memory	110.1	108.7	108.6	107.9	89.2 *	86.7 *

* Indicates significance during analysis at p<0.05 between current/ex MDMA polydrug group versus non-MDMA control groups (non-drug group, alcohol/nicotine group, alcohol/nicotine/cannabis group, and non-MDMA polydrug group)

** Indicates a significant difference (p<0.05) between current/ex MDMA polydrug group versus alcohol/nicotine/cannabis group, and non-MDMA polydrug group

*** Indicates a significant difference (p<0.05) between alcohol/nicotine/cannabis group, and non-MDMA polydrug group versus non-drug group, alcohol/nicotine group

6.3.3   Correlations

The results found a significant negative linear correlation between the verbal memory index and the amount of self-reported lifetime MDMA consumed, indicating the greater exposure to MDMA the less the mean verbal memory index score (r=-0.43, p<0.05, Table 6.4).

In addition, a significant negative linear correlation between the visual memory index and the amount of self-reported lifetime MDMA consumed, indicating the less exposure to MDMA the greater the mean visual memory index score (r=-0.47, p<0.05, Table 6.4).

A negative linear correlation was found between the delayed memory index score and the

amount of self-reported lifetime MDMA consumed, suggesting the more the delayed memory index score the less MDMA consumed (r=-0.51, p<0.05, Table 6.4).

Table 6.4   **Correlation scores for the WMS-R**

Correlation scores between total lifetime use of MDMA and index scores from the WMS (verbal memory, visual memory, general memory, attention, and delayed memory), where n=311.

	MDMA use
Verbal memory	-0.43*
Visual memory	-0.47*
General Memory	-0.35
Attention	-0.22
Delayed memory	-0.51*

* Indicates a significant negative correlation (p<0.05) between MDMA use and delayed, visual and verbal memory.

6.3.4   Regression

Regression analysis was performed on the MDMA polydrug group only in order to predict which of the recreational drugs (MDMA, ketamine, nicotine, heroin, alcohol, amphetamine, cannabis, LSD, and cocaine) were more likely to predict the verbal memory scores, $F_{(9, 302)}=29.27$, p<0.05 (Table 6.5a). The results found that the main predictors of verbal memory scores were MDMA (Beta=3.62, t=17.1, sr^2=0.41, p<0.00); followed by cannabis (Beta=1.09, t=2.77, sr^2=0.039, p<0.000) and alcohol (Beta=2.68, t=4.32, sr^2=0.034, p<0.000) (Table 6.5a).

Table 6.5a Regression coefficients for each drug of abuse and verbal memory (N=311)

The table provide details of the regression coefficients for each drug of abuse (MDMA, ketamine, tobacco, heroin, alcohol, amphetamines, cannabis, LSD and cocaine) and the overall verbal memory index score. The regression was only performed on the past and present MDMA users (n=311).

Drug	% predicts	Beta	t	p
MDMA	43	3.62	17.1	0.000
Ketamine	1.3	1.8	0.94	0.000
Tobacco	0.3	1.15	6.94	0.000
Heroin	2.9	2.27	8.8	0.000
Alcohol	3.6	2.68	4.32	0.000
Amp	1.2	11.6	6.45	0.000
Cannabis	4.1	1.09	2.17	0.000
LSD	0.5	0.17	0.39	0.000
Cocaine	2.1	1.069	1.004	0.000

Regression analysis was performed on the MDMA polydrug group only in order to predict which of the recreational drugs (MDMA, ketamine, nicotine, heroin, alcohol, amphetamine, cannabis, LSD, and cocaine) were more likely to predict the visual memory scores, $F_{(9, 302)}=3.36$, $p<0.01$ (Table 6.5b). The regression results found that the main predictors of visual memory scores were MDMA (Beta=0.56, t=15.7, $sr^2=0.463$, $p<0.00$); followed by cannabis (Beta=6.02, t=3.6, $sr^2=0.048$, $p<0.000$) and alcohol (Beta=6.44, t=11.9, $sr^2=0.0377$, $p<0.000$) (Table 6.5b).

Table 6.5b Regression coefficients for each drug of abuse and visual memory (N=311)

The table provide details of the regression coefficients for each drug of abuse (MDMA, ketamine, nicotine, heroin, alcohol, amphetamines, cannabis, LSD and cocaine) and the overall visual memory index score. The regression was only performed on the past and present MDMA users (n=311).

Drug	% predicts	Beta	t	p
MDMA	47	0.56	15.7	0.000
Ketamine	2.1	1.28	1.31	0.000
Nicotine	0.3	2.12	4.4	0.000
Heroin	1.7	1.27	5.9	0.000
Alcohol	4.0	6.44	11.9	0.000
Amp	3.1	1.60	6.04	0.000
Cannabis	5.1	6.02	3.6	0.000
LSD	0.5	1.37	14.5	0.000
Cocaine	3.1	1.019	3.12	0.000

Regression analysis was performed on the MDMA polydrug group only in order to predict which of the recreational drugs (MDMA, ketamine, nicotine, heroin, alcohol, amphetamine, cannabis, LSD, and cocaine) were more likely to predict the delayed memory scores, $F_{(9, 302)}=11.46$, $p<0.05$ (Table 6.5c). The results found that the main predictors of delayed memory scores were MDMA (Beta=0.59, t=18.4, $sr^2=0.49$, $p<0.00$); followed by cannabis (Beta=1.06, t=1.24, $sr^2=0.057$, $p<0.000$) and nicotine (Beta=0.22, t=1.18, $sr^2=0.031$, $p<0.000$) (Table 6.5c).

Table 6.5c Regression coefficients for each drug of abuse and delayed memory (N=311)

The table provide details of the regression coefficients for each drug of abuse (MDMA, ketamine, nicotine, heroin, alcohol, amphetamines, cannabis, LSD and cocaine) and the delayed index score. The regression was only performed on the past and present MDMA users (n=311).

Drug	% predicts	Beta	t	p
MDMA	51	0.59	18.4	0.000
Ketamine	1	0.308	0.69	0.000
Nicotine	3.3	0.22	1.18	0.000
Heroin	1.5	0.71	5.9	0.000
Alcohol	2.6	6.41	2.39	0.000
Amp	0.2	1.62	5.34	0.000
Cannabis	6.0	1.06	1.24	0.000
LSD	0.2	2.37	11.7	0.000
Cocaine	3.1	0.39	3.8	0.000

6.4   Discussion

6.4.1   Main overall findings

Even though this hypothesis was formulated in 2001, to date this is the most stringent study investigating MDMA and memory; including a robust control of illicit drugs, comparing scores on the different subscales of memory investigating past and present MDMA polydrug users.

The overall findings found that MDMA polydrug users demonstrate lower performance in four of the five tests of memory including delayed memory tasks, general memory tasks, visual memory tasks and verbal memory tasks in comparison to other recreational drug users. These findings support non-human animal studies suggesting that MDMA induces selective neuronal damage to 5-HT subsequently causing memory disturbance (Parrott et al. 1998; Morgan, 1999; Rodgers, 2000; Parrott et al. 2002; Gouzoulis-Mayfrank et al. 2003; Daumann et al. 2003; Wareing et al. 2004). However, taking into consideration the correlation and regression scores it seems more likely that MDMA causes disruption to verbal, visual and delayed memory only.

The results failed to find a significant difference on performance between present and past MDMA polydrug users on verbal, visual, general and delay memory. These findings support primate studies suggesting that MDMA induces long lasting selective neuronal damage to 5-HT (Parrott et al. 1998; Morgan, 1999; Rodgers, 2000; Parrott et al. 2002; Daumann et al. 2003; Gouzoulis-Mayfrank et al. 2003; Wareing et al. 2005). This study compared users that had abstained for up to a mean of 60 months ranging from 55 months up to 132 months. These findings suggest the damage caused by MDMA is long lasting and possibly permanent to 5-HT neurons. This is the first reported study to investigate the long lasting consequences of MDMA on memory functioning in humans.

A study by Gouzoulis-Mayfrank (2005) investigated the link between MDMA use, memory and whether a following a period of abstinence from MDMA if there is any improvement in memory performance. 38 MDMA users were followed up over a period of 18 months. After the initial baseline examination 17 of the MDMA users stopped taking MDMA however 21 continued to use it. After 18 months of monitoring memory performance, the results found that for those participants that stopped using MDMA after the initial baseline examination their memory performance failed to improve 18 months later. For those MDMA users that continued to use MDMA their performance on the memory task remained the same. This study suggests that a period of abstinence of 18 months from MDMA is not long enough to detect an

improvement in memory ability and secondly that there is no continual decline in memory performance over an 18 month period if MDMA use is continued. However, this study does not rule out the fact that MDMA causes memory deficits however it does suggest that the time interval needs to be longer than 18 months (Gouzolis-Mayfrank et al. 2005); or exposure to MDMA needs to be increased. The current study found that past and present MDMA users demonstrated significantly worse scores on the delayed memory test, general memory test, visual memory test and verbal memory test confirming the results found by Gouzolis-Mayfrank et al. (2005). The current study used more stringent control groups in comparison to other studies.

The current study did find that cannabis predicted general memory scores. The regression analysis found that cannabis seemed play a role in memory performance second to MDMA. Previous research has suggested that cannabis and cannabinoids can affect memory performance (Croft et al. 2001; Gouzoulis-Mayfrank et al. 2002; Dafters et al. 2004; Parrott et al. 2004; Daumann et al. 2004; Lundqvist et al. 2005; Sala et al. 2005). Studies have demonstrated that cannabis can cause disruption to short-term memory. In addition, studies have found that cannabis may interrupt the transfer of information from short-term to long-term storage. Secondly, studies indicate cannabis disrupts attention and concentration. The duration of these disruptions caused by cannabis after abstinence, has been disputed within the research field, however some reports suggest disruptions can last up to 24 hours (Chait et al. 1985). Some researcher state cannabis may have longer lasting consequences on memory; however, this is still questionable. In this study, participants were not required to abstain from cannabis before partaking in the experiment. Future, MDMA studies need to control for cannabis as well as investigating the role of MDMA on possible disruption to short-term memory, and the transfer of memory from short-term to long-term storage.

The present study included several separate control groups controlling for other recreational drugs like alcohol, cocaine, and nicotine, which have also been associated with affecting memory performance (Sahakian et al. 1989). Nicotine has been associated with improving attention and short-term memory, providing a possible protection (Rezvani et al. 2001). Studies have identified that cotinine, a nicotine metabolite, may provide protection to nerve cells preventing diseases: Alzheimer's disease and Parkinson's disease. Future studies need to investigate the protective nature of nicotine in MDMA users. In comparison, alcohol and cocaine, decrease memory performance and attention (Heishman et al. 1997; Bolla et al. 1998). This study does seem to identify that other recreational drugs may indeed have an effect on general memory performance including cannabis however, these results seem to suggest that

the use of MDMA alone or in combination with other illicit drugs results in far more impairments on memory performance.

This study to date is the largest study investigating the current and long lasting effects of MDMA on memory. It is the only study investigating MDMA and its effect on memory performance that compares past MDMA polydrug users that have abstained for a period of more than 5 years (range 5-11 years). Previous studies have compared abstained MDMA polydrug users for period ranging from 6-36 months maximum. It has been difficult from previous studies to clarify whether deficits in memory performance are permanent or reversible. The current study confirms that after abstaining from MDMA for a mean period of 60 months (ranging between 55 months to 132 months) memory performance is still poor in past MDMA polydrug users in comparison to other non-MDMA recreational drug users. Suggesting MDMA induced memory deficits are long lasting and possibly permanent as has been shown in non-human primates (Parrott et al. 1998; Morgan, 1999; Rodgers, 2000; Parrot et al. 2002; Daumann et al. 2003; Gouzoulis-Mayfrank et al. 2003; Wareing et al. 2005).

6.4.2 Future studies and limitations

Previous research has linked serotonin to memory consolidation, the storage of spatial episodic memory, the storage and retrieval of emotional memory, as well as the storage and retrieval of short-term memory (Dixon, 1999; Smith et al. 2006). Results from the present study clearly demonstrate that MDMA effects memory, however it is specific to various aspects of memory. Future studies need to target these specific areas of memory related to 5-HT. This future research would include measuring memory performance (spatial episodic memory, emotional memory and short-term memory) in addition to investigating the brain areas effected using fMRI, including the limbic system and the frontal lobe.

The results from the present study are consistent with previous research in the area using alternative methodologies. The WMS-R is a validated and reliable measure of memory performance. On the other hand, other methodologies need to be used on MDMA polydrug users providing further insight into MDMA memory induced problems. A study using fMRI techniques investigated 17 MDMA users and monitored them for a period of 18 months (Daumann et al. 2004). The participants were divided into those that had stopped taking MDMA after the initial recruitment into the study (abstained MDMA group) and those that continued to use MDMA throughout the study (current-MDMA group). The results found that at baseline, the two groups had similar performance on a working memory tasks, however after 18 months the current users demonstrated an MDMA dose-dependent increase in parietal

activation during the memory task in comparison to the abstained group. The authors conclude that changes in neuronal activity may occur before changes in cognitive performance are noticeable, however further investigation is warranted. The study concludes that areas of the brain may need to become active during certain tasks to compensate for neuronal damage in other areas. This may mean that using standard tests to measure memory performance may not flag up early memory disturbance in comparison to other methods like fMRI. fMRI may provide a method of early diagnosis of MDMA induced memory problems. Further evidence is required using techniques like fMRI comparing current and past MDMA poly drug users with matched recreational control users on memory performance to identify particular neuronal areas that show increased or decreased neuronal activity and/or compensatory anatomical alterations. Future longitudinal studies would be beneficial to investigate the anatomical changes during memory performance in MDMA polydrug users.

A study looked at the relationship between MDMA users and its effect on verbal working memory performance (Jacobsen et al. 2004). The study consisted of six adolescent MDMA users (mean age 17 years old) and six adolescent non-MDMA users (mean age 17 years old). Participants were matched for age, IQ, and previous recreational drug use. During the performance of the working memory task, fMRI, was employed to picture brain activity. The results found that MDMA users failed to activate the left hippocampus during the verbal memory task in comparison to the non-MDMA controls (Jacobsen et al. 2004). The authors concluded that the study highlighted early exposure to MDMA might cause selective damage to the hippocampus confirming non-human animal studies. More studies are required using humans to monitor if this lack of use of the left hippocampus changes later in life, whether it is used in the future or whether this lack of use persists and is a long lasting consequence. Results from the Jacobsen study could be interpreted as MDMA being a selective neurotoxin to the left side of the brain. More studies are needed to be done using fMRI on present and past MDMA polydrug users comparing them to matched recreational non-MDMA users on lateralisation of the brain and performance on memory tasks. It is widely accepted that males will rely on the left hemisphere of the brain during language tasks in comparison to females whom are more bilateral (Kulynych et al. 1994). Future studies need to investigate the differences in the long lasting effects between males and females paying particular attention to lateralisation of the brain. Males may have more problems due to relying on a damaged left hemisphere in comparison to females.

A study investigated the association between MDMA use, personality, cognitive and emotional processes (Hanson and Luciana, 2004). Fifty-two participants were recruited and divided into two groups: MDMA and a non-MDMA control group. The control group were excluded for a

history of psychiatric illness or previous substance abuse. The results found that MDMA users performed significantly worse in the memory tests in comparison to the non-MDMA group. These deficits included spatial memory task (memory load), working memory and verbal recall. A criticism of this study was that half of the MDMA group met the diagnostic criteria for severe psychiatric disorders including substance abuse, anxiety disorder, and specific phobias (Hanson and Luciana, 2004). In another study, 45% of psychiatric in-patients over 60 years of age and 29% of younger psychiatric in-patients had severe memory problems (Chandler et al. 1988). It seems that MDMA users need to be screened for psychiatric disorders as they may be a confounding variable in drug research. Future MDMA-related studies need to investigate psychiatric disorders and memory as a distinct group. The current study excluded anyone with a history of a psychiatric disorder.

One region of the brain where neurons develop throughout life is the hippocampus. A novel case study investigated a 16 year old girl that had used been exposed to low amounts of MDMA. The girl was suffering from memory problems. The study found that after 18 months of cognitive rehabilitation her memory performance improved and this correlated with structural and metabolic changes; particularly remarkable hippocampal remodelling (Nifosi et al. 2009). This study provides possible evidence for cognitive rehabilitation as a future treatment for MDMA induced memory problems. This needs extensive investigation.

The hippocampus plays a vital role in long-term potentiation, which is vital for long-term memory formation via glutamate (Bliss and Collingridge, 1993). MDMA research needs to investigate the role of glutamate in possible long lasting memory problems. Studies have demonstrated that memory formation involves changes in the glutamate neurons and synaptic alterations in hippocampus (Matthies et al. 2000). Further studies are required investigating the indirect or direct effect of MDMA on glutamate neurons and synapses. Secondly, tetrahydrocannabinol (THC) the active compound in cannabis interferes with long-term potentiation in the hippocampus. THC can cause short-term memory lapse (Piomelli et al. 1997). The combined role of MDMA and THC needs further investigation.

The role of the amygdala is emotional recall of memory. Non-human animal studies link neuronal damage to MDMA within the amygdale and this damage could potentially be long lasting. Further studies are needed to investigate emotional recall in past and present MDMA users including tests like the Stroop (Fuster et al. 1971; Markowitsch, 1994; Frisk et al. 1990; Passchier et al. 2001; Smith et al. 2006; LaBar et al. 2006).

Many other contributory factors can affect memory including caffeine. The effects of caffeine

on memory are controversial with research suggesting it can affect short-term memory and long-term memory (Erikson et al. 1985). Stress and diet play a role in memory performance (Bremner et al. 1995). In addition, further studies are required investigating levels of cortisol, memory and MDMA exposure.

6.4.3   Summary

The hypothesis for this study was formulated in 2001, but the largest single study investigating the association between memory and MDMA use, which includes a sample that is a true 'real-life' representation of the general population, including a diverse range of ages and a large selection of educated individuals. This is the only study to date that robustly controls the use of other recreational drugs of abuse (amphetamine, cocaine, cannabis, heroin and alcohol) when investigating memory deficits. Previous studies are predominantly based on student samples and/or younger adults. This study includes a larger representation of the population of MDMA polydrug users during the period 2002-2007. This is the first study to compare past MDMA users (abstained for 5 years) to investigate the long lasting consequences of memory problems.

This study found that MDMA polydrug users past and present demonstrate decreased performance in selective memory functions: visual memory, verbal memory, and delayed memory. These findings are consistent with previous studies suggesting MDMA induces neurotoxicity to selective brain neurons consequently affecting memory performance. This may be the result of damage to 5-HT directly or indirectly effecting other neurotransmitters like glutamate and acetylcholine. Additional research is required to investigate the role of neurotransmitters in this memory impairment. This study suggests that this deficit found in memory performance in past and present MDMA users is not a result of cannabis alone. It cannot rule out the fact that MDMA and cannabis consequently caused this impairment. The outcome of this memory impairment in MDMA users is noteworthy, as this would result in past and present MDMA users facing problems in their everyday life. Future studies need to target specific domains of memory in terms of MDMA exposure: short-term memory, spatial episodic memory and emotional memory, as well as relating these to areas of the brain including the frontal lobe, and limbic system.

Chapter 7 – Executive functioning

7.1   Introduction

This section will provide a brief introduction and definition of executive functioning. It will evaluate the evidence supporting the role of 5-HT in executive functioning. Finally, it will evaluate both non-human animal and human studies concerning MDMA exposure and executive functioning deficits.

7.1.1   Description of Executive functioning

Executive functioning is the ability to organise and synchronise all cognitive abilities. It involves how we plan and organize our lives, and how we execute these plans (Shallice, 1982; Morris et al. 1993; Park et al. 1994; Cockburn, 1995; Nagahama et al. 1996; Stuss et al. 2000; Carlin et al. 2000).

Planning requires the synchronisation of numerous cognitive processes (Shallice, 1982; Morris et al. 1993; Park et al. 1994; Cockburn, 1995; Nagahama et al. 1996; Stuss et al. 2000; Carlin et al. 2000). The process of planning includes an ability to plan, in order to create multiple sequences of hypothetical events, and their consequences. Secondly, planning is an ability to mentally structure movements in abstract form from an initial state to a goal state. Finally, planning is the ability to anticipate future events mentally (Table 7.1). Executive functioning involves a host of complex processes (Grafman, 1995; Roberts et al. 1998 & 2010).

Executive functions can be broken down into two main groups, organisation and regulation. Organisation deals with attention, planning, sequencing, problem solving, working memory, cognitive flexibility, abstract thinking, rule acquisition, and selecting relevant sensory information. Regulation involves initiation of action, self-control, emotional regulation, monitoring external and internal stimuli, initiating and inhibiting context specific behaviour, moral reasoning and decision-making (Shallice, 1982; Morris et al. 1993; Park et al. 1994; Cockburn, 1995; Nagahama et al. 1996; Stuss et al. 2000; Carlin et al. 2000).

Table 7.1   Summaries the major processes included in executive functioning

The table summaries the major processes associated with the term 'executive functioning'. The table provides a brief description of each of these functions.

Executive Function	Function
Planning	Foresight into devising multiple step strategies
Flexibility	Capacity for quick switching to the appropriate mental mode
Inhibition	Ability to withstand distraction and internal urges
Anticipation	Prediction based on pattern recognition
Critical evaluation	Logical analysis
Working memory	Capacity to hold and manipulate information in 'our minds' for a period of time
Fuzzy logic	Capacity to chose with incomplete information
Divided attention	Ability to pay attention to more than one thing at a time
Decision-making	In terms of quality and speed

7.1.2   Neuropharmacology and neuroanatomy of executive functioning

The anatomical region of the brain largely implicated in executive functioning is the forward section of the frontal lobe or prefrontal cortex (Reuter et al. 2008). Additional neuroanatomical regions implicated in executive functioning consist of the basal ganglia and thalamus. The frontal lobe is the most recent region of the brain to evolve (Robbins & Roberts, 2007). It is substantially larger in humans in comparison to other non-human primates and accounts for approximately 40% of the total volume of the human brain. The frontal lobe is innervated with many monoamines: dopamine, serotonin, noradrenaline and acetylcholine (Robbins & Roberts, 2007).

Evidence for the role of the frontal lobe in executive functioning has been confirmed using neuroimaging (Shallice, 1982; Morris et al. 1993; Park et al. 1994; Cockburn, 1995; Nagahama et al. 1996; Stuss et al. 2000; Carlin et al. 2000). These scans consist of case studies involving brain injury, tumour to the frontal lobe, and epilepsy. Additional experiments consist of imaging studies correlating 5-HT levels and performance in cognitive tasks for non-psychiatric individuals (Reuter et al. 2008).

Executive functioning abnormality has been observed in many psychiatric disorders including OCD (obsessive compulsive disorder), depression, schizophrenia, Tourette's disease, ADHD (attention deficit hyperactivity disorder), autism and drug addiction (Shallice, 1982; Morris et al. 1993; Park et al. 1994; Cockburn, 1995; Nagahama et al. 1996; Stuss et al. 2000; Carlin et al. 2000). As executive functions, integrate various skills and subordinate cognitive processes,

damage to the executive functions results in a cluster of abnormalities in many skills as well as encroaching on lasting personality changes (Table 7.2).

Additional evidence for the role of the frontal lobe in executive functioning consists of studies examining behavioural frontal lobe dementia (bvFTD). The progressive shrinking of the tissue in the frontal lobe and anterior temporal lobe causes this brain malfunction. Cognitive adaptations associated with bvFTD include loss of social skills, lack of empathy, disinhibition and antisocial behaviours, poor moral reasoning, lack of initiation, inappropriate humour, trouble making plans, with some developing eating disorders and addictions. These cognitive deficiencies as measured using executive functioning tests have been correlated with levels of brain 5-HT (Shallice, 1982; Morris et al. 1993; Park et al. 1994; Cockburn. 1995; Nagahama et al. 1996; Stuss et al. 2000; Carlin et al. 2000). There is a negative correlation between 5-HT levels and executive dysfunction. Non-human animal studies have demonstrated that depletion of prefrontal 5-HT results in the disruption of executive functioning processes and perseverative inflexible behaviour including failure in error detection, altered responsiveness to punishment or loss of reward, and a deficit in inhibitory control (Evers et al. 2005; Robbins and Roberts, 2007).

Table 7.2   Consequences of damage to the executive system on personality

The table provides a brief summary of the processes disrupted during frontal lobe dysfunction (Toates, 2001)

Personality affected due to frontal lobe damage
Socially inappropriate behavior
Inability to apply consequences from past actions
Difficulty with abstract concepts (the inability to make the leap from the symbolic to the real world)
Difficulty in planning and initiation (getting started)
Difficulty with verbal fluency
Inability to multitask
Difficulty processing, storing, and/or retrieving information
Frequent "policing" by others to monitor the appropriateness of their actions
Loss of fine motor skills
Moody or "roller coaster" emotions
Lack of concern toward people and animals
Loss of interest in activities
Unawareness or denial that their behavior is a problem
Antisocial behavior associated with disinhibition
Trouble planning for the future

7.1.3 The role of serotonin in executive functioning

Early research has linked 5-HT to cognitive functioning; specifically learning and attention processes (Riedel, 2003). Experiments investigating healthy participants inflicted with acute tryptophan depletion resulted in deficits in learning and cognitive ability (Park et al. 1994; Riedel et al. 2003; Klaassen et al. 2002; McAllister-Williams et al. 2002).

Serotonin-related deficient disorders consisting of schizophrenia (Laurent et al. 2000), patients with frontal lobe dementia (Carlin et al. 2000) and frontal lobe lesions (Carlin et al. 2000) have correlated reduced levels of 5-HT to a decline in certain executive and/or attentional measures. These deficits in 5-HT levels have been associated with less frontal lobe activity using imaging and brain scans. Individuals with frontal lobe brain damage are constantly reporting impairments in plan development and executive functioning with these deficiencies corresponding to marked deficiencies in 5-HT (Shallice, 1982; Morris et al. 1993; Park et al. 1994; Cockburn, 1995; Nagahama et al. 1996; Stuss et al. 2000; Carlin et al. 2000).

The role of 5-HT in executive functioning has recently focused on hereditability and genes. One gene of interest is the TPH2 (tryptophan hydroylase 2) gene. TPH2 is the rate limiting enzyme of brain 5-HT. Various polymorphisms of this gene have led to alterations in cognitive performance in animal studies (Osinsky et al. 2009). Polymorphism of the TPH2 gene has demonstrated to impair working memory (Reuter et al. 2008). Working memory affects performance on executive functioning and some scientists argue it is part of the executive functions.

Experimental studies have demonstrated that the frontal cortex contains a high density of 5-HT2A and 5-HT3 receptors (Clarke et al. 2006). The blocking of these receptors in lesioned monkeys, results in significant deficits within executive functioning ability. This blocking of receptors specifically targets information processing, inhibition and an increase in preservative errors (Clarke et al. 2006).

Further evidence for the role of 5-HT in executive functioning consists of a study on rats comparing 5-HT1A and 5-HT2A receptors. The findings from the study demonstrated that 5-HT1A antagonist resulted in more errors on an executive functioning task whilst the 5-HT2A antagonist affected attention and inhibition in the executive functioning task (Mirjana et al. 2004; Carli et al, 2006). This suggests that executive functioning is a complicated function and different receptors may be involved in the different domains.

7.1.4 The link between MDMA and executive functioning

It is clear that executive functioning is correlated to the activity of 5-HT. As MDMA is a possible 5-HT neurotoxin, evidence from non-human animal and human data suggesting that MDMA effects executive functioning will be evaluated.

Non-human animal studies demonstrate MDMA causes selective neurotoxic damage to brain 5-HT. Evidence for MDMA related serotonin toxicity comes from studies where results have discovered global depletion of the 5-HT transporter protein (McCann et al. 1998), reduced neuroendocrine functioning (Gerra et al. 2000), and decreased levels of the serotonin metabolite (5HIAA) in the cerebrospinal fluid of MDMA users (McCann et al. 1999). MDMA toxicity has been found in many non-human animal studies (Bolla et al. 1998; Parrott et al. 1998a; Parrott et al. 1998b; Morgan, 1998; Dafters et al. 1999; Klugman et al. 1999; McCann et al. 1999; Morgan. 1999; McCann et al. 1999; Wareing et al. 2000; Fox et al. 2001; Gouzoulis-Mayfrank, 2000; Rodgers, 2000; Waring et al. 2000; Morgan 2000; Verkes et al. 2001; Zakzanis and Young, 2001; Fox et al. 2001). This damage has been demonstrated to be selective in certain neuroanatomaical regions including the amygdala and cortex. Individuals with lowered 5-HT levels have been shown to have deficits in executive functions. Polymorphism of the TPH2 gene results in poor working memory performance and executive functioning dysfunction. Non-human animal studies have demonstrated that MDMA affects the synthesis of TPH, which may consequently lead to cognitive and working memory impairment. As MDMA is selectively neurotoxic to 5-HT in animals it is plausible it is neurotoxic to human 5-HT neurons. Consequently, this MDMA induced neurotoxicity in humans may result in psychological deficits specifically executive functioning. In summary, MDMA may cause damage to serotonin neurons and TPH, which subsequently cause executive dysfunction.

7.1.5 Non-human animal studies and the effects of MDMA on executive functioning

Measuring executive functioning in non-human animals is somewhat limited. These studies rely on rather simple tasks. Numerous animal studies have failed to find a relationship between MDMA use and cognitive decline. Slikker and workers found that although MDMA produced a significant 50% decrease in 5-HT in rats and 80% decrease in 5-HT in monkeys unfortunately no behavioural impairments were observed including executive functioning (Slikker et al. 1989).

In contrast, other studies have found an association between MDMA and executive functioning. Non-human animal research has demonstrated that non-human primates exposed to doses of MDMA similar to those used recreationally by humans resulted in marked loss of 5HT markers including striatal type 2 vesicular monoamine transporters predominantly located in the frontal lobe (Ricaurte et al. 2000). This reduction in the type 2 5-HT transporter resulted in impairments on executive functioning tasks.

Nonetheless, it needs to be pointed out that executive functioning is deemed by many as a higher cognitive function and that humans are more advanced in executive functioning abilities and susceptible to deficits than other non-human primates and non-human animals (Shallice, 1982; Morris et al. 1993; Park et al. 1994; Cockburn, 1995; Nagahama et al. 1996; Stuss et al. 2000; Carlin et al. 2000).

7.1.6   Human studies and the effects of MDMA on executive functioning

There have been numerous studies investigating the effects of MDMA on executive functioning in humans. Initial studies speculating that MDMA maybe linked to cognitive deficiency began by looking at individual case studies; more recently, cohort studies comparing current MDMA users with matched controls including recreational drug users that had never used MDMA have been conducted. Many of these studies have concluded MDMA users perform worse on tasks involving cognitive functioning (Bolla et al. 1998; Parrott et al. 1998; Klugman et al. 1999; McCann et al. 1999; Morgan, 1999; Wareing et al. 2000; Fox et al. 2001; Gouzoulis-Mayfrank, 2000; Rodgers, 2000; Verkes et al. 2001; Murphy et al. 2009). These finding progressed to compare occasional MDMA users with frequent MDMA users. Subsequent results demonstrated frequent MDMA users were associated with increased cognitive impairment (Waring et al. 2000 & Morgan 2000).

McCann et al. (1999) investigated the effects of MDMA on cognitive performance compared 22 MDMA uses and 23 control non-MDMA users. The participants were required to take part in a computerised cognitive performance assessment battery. Cerebrospinal fluid measures of monoamine metabolites were collected from each participant. The findings of the study verified that MDMA users performed significantly worse on tasks requiring complex attention and learning skills. MDMA users exhibited decreases in CSF 5-H1AA. The authors concluded that MDMA was associated with cognitive deficits, related to lower 5-HT brain levels (McCann et al. 1999). This study confirmed non-human animal studies suggesting MDMA was a neurotoxin resulting in a loss of serotonin and subsequently causing cognitive problems. These results have never been replicated due to ethical issues.

Another study investigated 24 MDMA users and 24 non-MDMA controls (Zakzanis & Young, 2001). The participants were tested using the Behavioural Assessment of Dysexecutive Syndrome which is a test battery aimed at predicting everyday problems; including six subtests. The results found significant decline in test scores on specific subtests (time estimation, organization in terms of obeying rules and regulations. There was a significantly linear correlation between the amount of MDMA consumed and the amount of cognitive disruption for these sub domains. The authors concluded that MDMA might cause deficits in executive functioning however, this effect was not global but specific to certain domains of executive functioning: organization, categorisation and time estimation. (Zakzanis & Young, 2001).

Parrott et al. (1998) used a battery of cognitive tests to measure cognitive ability. The study included 10 regular MDMA users, 10 novice MDMA users and 10 control participants that had never used MDMA. The results found that there was no significant difference on the cognitive tasks between the three groups. The authors concluded that MDMA failed to cause cognitive impairment (Parrott et al. 1998). The study failed to control for other recreational drugs and the MDMA group had only used the drug on 10 or more occasions however the authors failed to speculate the mean number of times taken. The study did not investigate the long lasting consequences of MDMA on executive functioning.

Fox et al. (2001) reported a novel study, where they compared three groups of drug users. All participants were young recreational drug users. Participants were selected for one of three groups dependent on whether i) they had used MDMA and had experienced problems associated with using the drug; ii) they had used MDMA but had not experienced any adverse affects associated with the drug; iii) they had never used MDMA. In the experiment, participants were required to give details of the problems that they associated with MDMA. All participants were required to complete i) the uplift, hassles, stressers and cognitive failures questionnaire (Parrott & Kaye, 1999); ii) immediate and delayed prose recall task (Gudjonssons, 1984); iii) a reaction time task; iv) a spatial working memory task; v) Wisconsin card sorting test; vi) a matched verbal recall/recognition task; vii) and finally the Tower of London task. The results from the study firstly confirmed previous studies concluding that MDMA users demonstrate selective cognitive impairment. Secondly, their study confirmed that the results were more persistent for frequent/heavy MDMA users (Fox et al. 2001). Finally, the uniqueness of their study found that MDMA users demonstrated the same cognitive impairment irrespective of whether they complained of MDMA induced problems. The results from their study suggested that individual reports of self-perception of cognitive

ability maybe inaccurate. Furthermore, the study highlighted the need for cognitive ability to be measured rather than relying on self-reports in drug users is an important requirement. This study failed to control for illicit drugs like amphetamine, cocaine and cannabis. Fox et al. (2001) did not investigate the long lasting effects of MDMA, nor did they monitor other psychological functions including sleep, memory, depression and impulsivity.

A multiple regression study investigated the link between executive functioning performance and recreational drugs (Verdejo-Garcia et al. 2005). In this study, they included a small sample of 38 detox polysubstance drug users, to perform numerous cognitive tasks. The study included four regression models (working memory, attention, cognitive flexibility and analogical reasoning) with the predictor scores being cannabis, cocaine, heroin, MDMA and alcohol. The regression analysis concluded MDMA was a significant predictor for working memory and analogical reasoning. Cocaine was a significant predictor for attention and cannabis was a significant predictor for cognitive flexibility. The results from their study confirmed that the behavioural consequences of recreational drugs could still prolong even after a period of abstinence from the drugs (Verdejo-Garcia et al. 2005). The study highlighted the effects of other illicit drugs like cocaine and cannabis on cognitive ability and the importance of controlling for these in MDMA research.

Medina and Shear (2007) investigated the link between executive dysfunction and mood. The sample consisted of 65 men and women, including a diverse range of MDMA and non-MDMA users. The results found that 19-63% demonstrated clinical psychological problems, including anxiety and depression. However, this elevated psychological state was not associated with lifetime use of MDMA but the result of other drug use including alcohol, cannabis and opiates (Medina & Shear, 2007). This study demonstrates the importance to control for other recreational drugs.

However, not all studies have found such cognitive deficits in MDMA users (Morgan, 1998; Dafters et al. 1999). Such studies suggest that other studies lack controllinf for cannabis, alcohol, amphetamine and cocaine use. It is clear that future studies investigating MDMA and executive functioning need to include more stringent control groups.

Montgomery et al. (2010) investigated exposure to MDMA on a virtual reality executive functioning task. The task measured prospective memory and planning based on an office worker's job. The participants included 23 MDMA polydrug users and 26 non-MDMA polydrug users. The results revealed that MDMA disrupted planning only. The authors reported that the task was more ecologically valid and represented a day-to-day activity. The

study failed to control for other recreational drugs and did not investigate the long lasting consequences of MDMA. Finally, the study did not investigate the role of other psychological functions including sleep, depression, memory and impulsivity.

Table 7.3 provides details of some of the studies investigating MDMA and executive functioning. Earlier studies investigating MDMA and its affect on executive functioning tasks have been limited in their sample sizes, and restricted in their control groups. The majority of the studies have failed to control for cannabis, amphetamine, and cocaine. Still in 2011, no single study to date has controlled for these illicit drugs. Studies indicate cannabis, amphetamine, cocaine and alcohol have been shown to affect executive functioning (Croft et al. 2001; Gouzoulis-Mayfrank et al. 2002; Dafters et al. 2004; Daumann et al. 2004; Parrott et al. 2004; Lundqvist et al. 2005; Sala et al. 2005). The tests employed by some of the studies to investigate executive functioning are questionable concerning validity and reliability. Samples from the majority of studies are recruited from drug centres with participants being severe substance users, which complicate their drug history and cognitive functions. This makes it difficult to attribute the results to MDMA and not another substance related problem, health hindrance or social difficulty. Only a handful of studies have investigated the long lasting effects of MDMA with the mean abstinence totalling 12 months. Non-human animal experiments suggest this short time interval of abstinence is not a long enough period to demonstrate behavioural deficits (Parrott et al. 2004 & Daumann et al. 2004).

Currently there is little solid evidence demonstrating the association between MDMA induced 5-HT toxicity and the effects of MDMA on cognitive ability. In summary, there are currently no investigations concerning the effect of MDMA on an aging population and the long lasting effects. They lack adequate sample sizes, and fail to control for other recreation drugs of abuse making it hard to form any valid conclusions from these studies.

Table 7.3   Summary of previous research investigating MDMA and executive functioning

*Provides a summary of some studies investigating the link between MDMA and executive functioning during the period 2000 –
2009. The table provides details of authorship, test employed, the control groups included, whether long lasting effects were
investigated and finally if they found a significant result.*

Author	Test	Groups	Long lasting effects	Result
Fisk et al. 2009	Inhibition/updating process	15 frequent MDMA 39 less frequent MDMA 28 non-drug users	No	Freq users impaired
Medina et al. 2007	Frontal system behavioural scale	MDMA users Cannabis users	No	Non-sig
Quednow et al. 2007	Matching Familiar Figures (MFF) Go-NO-Go task	19 MDMA users 19 cannabis users 19 non-drug controls	No	Elevated MFF scores in comparison to controls
Medina et al. 2005	Battery of psychological tests	48 MDMA users 17 cannabis users	No	MDMA poor scores verbal and memory
Montgomery et al. 2005	Syllogistic reasoning	22 MDMA users 26 non-MDMA drug users	No	MDMA user impaired
Piechatzek et al. 2009	Battery neuropsych tests	MDMA users Cannabis/Alcohol users Control group	No	MDMA resulted in increased error

Author	Test	Groups	Long lasting effects	Result
Verdejo-Garcia et al, 2005	Abstract reasoning Multiple regression analysis Investigating the relationship between MDMA, cocaine, cannabis	38 MDMA/polydrug users	No	MDMA main predictor
Wareing et al, 2004	Working memory	Current MDMA Previous MDMA Non-MDMA users	Yes	MDMA users impaired
Hanson et al, 2004	Battery of executive tests	MDMA users Non-MDMA drug users	No	Non-sig
Wareing et al, 2000	Information processing Executive functioning errors	Current MDMA Previous MDMA Non-MDMA polydrug	Yes	MDMA users less accurate

7.1.7 The association between depression, sleep, memory, impulsivity and executive functioning

To date research has demonstrated a positive association between MDMA use and deficits with depression levels; sleep disturbance, impulsivity, and memory deficits (Wurtman, 1988; Linnoila et al. 1992; Risch et al. 1992). These psychological functions have been associated on numerous occasions to negatively affecting performance on cognition. Even though the research hypothesis was formulated in 2001, to date it remains unanswered and still there is no individual study that has investigated the association between MDMA exposure monitoring behavioural, emotional, psychological well-being (depression, impulsivity, sleep, and memory) and their effects on cognitive functioning. Past experimental research proposes cognitive functioning is dependent on behavioural, emotional and psychological states. More specifically experimental evidence has demonstrated depression and mood can affect cognitive performance (Beck 1988, Elliot et al. 1997). Anxiety and cognitive deficits have been linked (Luu et al. 2009). Research has shown that sleep disturbance can result in cognitive deficiency (Lazarus, 1982). Therefore, it is important to assess the impact of other behaviours (depression, impulsivity, memory, and sleep) on executive functioning rather than a simple causal connection between MDMA and executive functioning only.

7.1.8 The Tower of London

The Tower of London (ToL) is a test that measures executive functioning including problem solving (Shallice, 1982). In order to be able to adequately perform on this ToL test, planning is required. In particular, the ToL test involves the participant having to develop a solution, maintain this solution in their working memory and then to have access to this pathway later to solve the problem. Research has suggested that patients with frontal lobe lesions have a difficultly with handling the planning of non-routine situations as they have to rely on environmental stimuli for clues on how to act in such non-routine situations known as the Supervisory Attention System. The ToL task measures the Supervisory Attention System (Norman & Shallice, 1986).

7.1.9 The Wisconsin card sorting test

The Wisconsin Card Sorting Task (WCST) is considered to be a key tool in the diagnosis of frontal lobe dysfunction (Gant and Berg, 1948; Milner, 1968; Stuss et al. 2000). It measures

the ability to apply cognitive flexibility. It assesses abstract reasoning and the ability to shift cognitive strategies in response to environmental changes. The WCST relies on an intact working memory, visual processing and attention. Imaging studies have concluded that during performance of the test many areas of the brain are activated including the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, and caudate nucleus (Konishi et al. 2001; Monchi et al. 2001). It still remains to be one of the most widely used neuropsychological tests measuring executive functioning being used by neuropsychologists, clinical psychologists, neurologists and psychiatrists (Berman et al. 1995; Nagahama et al. 1996).

The WCST and the ToL were chosen in this study for their simplicity. They are both widely used in research and in the clinical setting. They have been linked with executive dysfunction. The ToL and the WCST have undergone extensive validity and reliability testing. They are used worldwide, and have been translated into different languages (Norman and Shallice, 1986; Berman et al. 1995; Nagahama et al. 1996).

7.1.10 The aims of the study

MDMA continues to be consumed by younger adults (between the ages of 18-24 years old) who believe it to be a 'safe' drug with little long lasting effects despite the constant media attention highlighting its dangers. If MDMA causes longer lasting damage to cognitive functioning current MDMA users may develop a severe cognitive decline, which will affect their everyday lives.

Recent studies have formed speculations concerning a link between performances on executive functioning tasks (ToL and WCST) and other psychological factors (depression, memory, sleep and impulsivity). Particular studies indicate that performances on the executive functioning tasks are disrupted due to abnormal levels of depression, sleep, memory performance and impulsivity. It is important to decipher whether MDMA has a direct effect on executive functioning or whether it has an indirect effect on executive functioning via depression, memory, sleep and impulsivity as this will have an effect on treatment and rehabilitation strategies. Previous studies investigating the long lasting psychological effects of MDMA have investigated executive functioning by the use of a battery of psychological tests. These studies have failed to look at whether any of the psychological areas (depression, memory, depression, and sleep) are effecting performance and causing deficits in executive functioning.

Based on previous research in related areas, the following can be hypothesised. Firstly, that the current MDMA polydrug users will demonstrate poor executive functioning scores in comparison to the non-MDMA polydrug users. Secondly, there will be no difference in executive functioning abilities between past and present MDMA polydrug users. Thirdly, there will be a negative correlation between the level of MDMA consumed and the level of executive functioning ability. Finally, there will be a positive relationship between executive functioning performance and depression/sleep/memory/impulsivity.

7.2   Methodology

7.2.1   Participants

402 participants of the original 1399 participants were involved in this study based a power calculation where N=350 (power=80, α=0.05, 5 groups of 70 – Cohen, 1992; Faul et al. 2007; Faul et al. 2009). Mean overall age was 25.4 years old (52.5% male and 47.5% female). Participants were recruited from a WebPage (34%); local newspaper advertisements (6%); snowballing technique (37%); drug advisory centres (22%) and unspecified (1%). All participants reported good health and had no previous psychiatric history. All participants reported abstaining from using MDMA for at least three weeks prior to participation of the study (mean period of 4 weeks).

Most participants were employed or in education at the time of the study (42% education; 56% employment). Participants were split into 4 control groups and 2 separate MDMA groups (63 non-recreational drug users; 69 alcohol/nicotine users; 72 cannabis/alcohol/nicotine users; 71 polydrug users that had never used ecstasy (but had used other substances such as, heroin, ketamine, amphetamine.); 67 current MDMA polydrug users (used MDMA in the last 6 months); 60 ex-MDMA polydrug users (abstained from MDMA mean 6.5 years (4 – 8.5 years).

7.2.2   Measures

All participants completed the DHQ (refer to chapter 2 for full details, Appendix 2.2) and the ToL and the WCST.

7.2.3   Tower of London (ToL)

The Tower of London test (Shallice, 1982) involves two boards with pegs and several beads of different colour (blue, red, and green). The examiner has one board and the participant has the other board. The examiner is required to place the coloured beads on the board known as the goal position. Initially the participant begins with the beads in a starting position and is required to move their beads to replicate the goal position in as little moves as possible. The participants moved one bead at a time. Verbally participants planned the whole sequence of moves out mentally before attempting to move the beads. Trials consisted of twelve trials in total being two 2-move trials, two 3-move trials, four 4-move trials, and four 5-move trials. All trials were tape recorded so that after the session planning times and solution times could be measured using a stopwatch. Results included preplanning time, average move time, number of trials solved in a minimum period or minimum number of moves, and finally excess moves.

Planning time represented the interval between the last articulation of the examiner and the first move of the apparatus by the participant. Solution time represented the amount of time taken to complete the task. The solution was terminated if 1 minute was exceeded for completion. Average time for planning and solution were recorded across the trials. Mean number of errors made were recorded and total number of categories completed. Finally, the number of moves required for completion was recorded. Administration time is 15 minutes (Shallice, 1982).

7.2.4   Wisconsin card sorting test (WCST)

The WCST is a neuropsychological test measuring flexibility in a situation where the rules are constantly changing (Berman et al. 1995; Nagahama et al. 1996). The tests measures two essential functions: maintaining set and set shifting. The 'maintaining a set' measures the individuals' ability to maintain the current rule and apply it. The 'set shifting' measures the inhibition of previous rules involving planning and replacing. The objective of the test is for the participant to learn a rule. The procedure involves four stimulus cards being provided to the participant. The first card has one red triangle. The second card has two green stars. The third card has three yellow crosses. The fourth has four blue circles. An additional stack of cards are given to the participant and they are asked to place each additional card to one of the

four stimulus cards, to eventually form four separate piles of cards. The participant has to find out the rule and informed whether the card matches this rule once placed on the stimulus card. The rules are colour, shape or number. If the participant correctly stacks 10 of the cards, the rule is changed. The task continues for six trials. The trial was terminated if the rule was not solved in 50 attempts. The whole task takes 20 minutes to complete and generates the following results: number of categories completed measuring the ability to think abstractly, number of trials to first category measuring the ability to be flexible and switch between rules along with learning new rules – set shifting, failure to maintain set measuring the individuals ability to maintain the rules – maintain set, percentage of non-perseverative errors and percentage of perseverative errors measuring the ability to inhibit previously learnt rules (Berman et al. 1995; Nagahama et al. 1996).

7.2.5   Ethical Issues

All participants provided written consent. Participants were able to withdraw at any point throughout the study. All data was anonymous. The study was approved by the local Ethics Committee in 2001, London Metropolitan University, formally known as London Guildhall University. Participants were given a briefing and debriefing (Appendix 2.3).

7.2.6   Statistical Analysis

Data was analysed using SPSS version 16 (Statistical Package for the Social Sciences). Nine one-way ANCOVAs were run; the outcome variable was the subscales of the ToL (planning, solution time, number of trials, and number of errors) and the WCST (% perseverative errors, % non-perseverative errors, categories completed, trials to first category, and failure to maintain set); the predictor variable was the drug group and the covariate was the lifetime use of cannabis, amphetamine, cocaine and ketamine.

The mean overall index scores from the four dimensions of the ToL and the five dimensions of the WCST were analysed separately. Each individual dimension was compared with the four control groups and the two MDMA groups using ANCOVA with drug groups as one of the independent factors (non-recreational drug control group; alcohol/nicotine control group; cannabis/alcohol/nicotine control group; non MDMA polydrug control; current-MDMA polydrug group; ex-MDMA polydrug group) and cognitive dimension as the dependent factor (WCST measuring the following five cognitive dimension: % perseverative errors, % non-

perseverative errors, categories completed, trials to first category; and failure to maintain set; ToL measuring the following four dimensions: planning time, solution time, number of errors and the number of trials completed). Where appropriate the results were further analysed using the Bonferroni test to obtain paired comparisons of individual drug group differences.

The ANOVAs and ANCOVAs were checked for normality using the Kolmogorov-Smirnov and Shapiro-Wilk test. As the tests were significant, the data was transformed to logs and the normality test re-checked. The log transformed data was non-significant, suggesting the data was normally distributed. The kurtosis and skewness were checked for values between -2 and 2. The log transformed data was plotted using the output of a quantile-quantile (Q-Q) plot. As the data did not stray from the predicted line, the data was linear and normally distributed. The covariate in the analysis was checked for its independence from the experimental manipulation; an ANOVA with the covariate as the outcome and the drug group as the predictor was run for all of the covariates (cannabis, amphetamines, cocaine and ketamine).

For the nine ANCOVAs the Levene's test of the homogeneity of variance assumption was checked for non-significance relating to the homogeneity of residuals. The residual plot was checked for assumption of equality of variance. The spread vs. level plot was used to check there was no relationship between the mean and standard deviation. The homogeneity of regression slopes was checked by customising the ANCOVA model in SPSS to look at the independent variable * covariate interaction. The interaction term was tested in addition to the main effects. The log transformed interaction term (independent variable * covariate interaction) was non-significant; the assumption of homogeneity of regression slopes was not broken.

Log transformed self-reported sub-domain scores of the ToL and the WCST were correlated with log transformed self-reported lifetime MDMA exposure using the Pearson correlation coefficient.

Multiple regression analysis was performed on the sub-domains of the ToL and WCST with the log transformed depression, memory, sleep and impulsivity scores (BDI-11, general memory sub-domain of the WMS, PSQI and BIS) as the predictor variables. Using SPSS, the variance inflation factor (VIF) and tolerance statistics were checked. The VIF values were below 10 and the tolerance statistics were all above 0.2. The residual statistics was checked for extreme cases. The standardised residuals were all between -2 and 2. The Cook's distance

was checked and all values were below 1. The DFBeta statistics was checked to make sure no value was greater than 1. Examination of the residual plots demonstrated the data did not stray from the predicted line; the data was linear and normally distributed. The Levene's test was checked; it was non-significant thus homogeneity of variance was assumed. Homoscedasticity and hetroscedasticity were checked visually by plotting the standardised residuals (the errors) by the regression standardised predicted value. The residuals were randomly scattered around the horizontal line (0) (Tabachnick and Fidell, 2001).

Median lifetime exposure to all recreational drugs was compared using the Kruskal Wallis test. If the Kruskal Wallis test was significant, the data was further analysed using the Mann Whitney test.

7.3   Results

The ANOVA was non-significant demonstrating independence between the predictor variables and the covariates. The homogeneity of residuals, normality, equality of variance and the homogeneity of the regression slopes were all checked for the ANCOVA.

For the multiple regression, the data was checked for multicollineraity, curvilineraity, hetroscedasticity and homogeneity of variance, and finally normality.

7.3.1   WCST

There was an overall significant difference between the drug groups and the number of perseverative errors made. The covariate, cannabis, was non-significantly related to the number of perseverative errors for the WCST, $F(1, 396) = 0.187$, $p > 0.05$. The covariate, amphetamine, was non-significantly related to the number of perseverative errors for the WCST, $F(1, 396) = 0.059$, $p > 0.05$. The covariate, cocaine, was non-significantly related to the number of perseverative errors for the WCST, $F(1, 396) = 0.050$, $p > 0.05$. The covariate, ketamine, was non-significantly related to the number of perseverative errors for the WCST, $F(1, 396) = 0.236$, $p > 0.05$. There was an overall significant effect of number of perseverative errors for the WCST on drug group controlling for the effect of cannabis, amphetamine, cocaine and ketamine, $F(5, 396) = 41.19$, $p < 0.01$. Further analysis found that there was a significant difference in the number of perseverative errors between the four non-MDMA groups and the two MDMA groups (Bonferroni Post hoc, $p < 0.01$), with the two MDMA

groups making more perseverative errors than the non-MDMA control groups. There was a non-significant difference in the number of perseverative errors made between the current MDMA polydrug group and the ex-MDMA polydrug group (Bonferroni, p>0.05) with both the current and ex-MDMA users making a similar number of perseverative errors (Table 7.4).

Overall, there was a non-significant difference in the number of non-preservative errors made between the six drug groups indicating that all drug users (MDMA and non-MDMA) made a similar number of non-perservative errors suggesting that drug use did not play a role in the number of non-perseverative errors made (Table 7.4). The covariate, cannabis, was non-significantly related to the number of non-perseverative errors for the WCST, $F(1, 396) = 0.003$, p>0.05. The covariate, amphetamine, was non-significantly related to the number of non-perseverative errors for the WCST, $F(1, 396) = 0.1.48$, p>0.05. The covariate, cocaine, was non-significantly related to the number of non-perseverative errors for the WCST, $F(1, 396) = 1.68$, p>0.05. The covariate, ketamine, was non-significantly related to the number of non-perseverative errors for the WCST, $F(1, 396) = 0.085$, p>0.05. There was an overall non-significant effect of number of non-perseverative errors for the WCST on drug group controlling for the effect of cannabis, amphetamine, cocaine and ketamine, $F(5, 396) = 30.29$, p>0.05.

There was no overall significant difference in number of completed categories between the six drug groups suggesting there was no difference in the number of trials completed between the different drug groups (Table 7.4). The covariate, cannabis, was non-significantly related to the number of categories for the WCST, $F(1, 396) = 0.085$, p>0.05. The covariate, amphetamine, was non-significantly related to the number of categories for the WCST, $F(1, 396) = 0.019$, p>0.05. The covariate, cocaine, was non-significantly related to the number of categories for the WCST, $F(1, 396) = 0.001$, p>0.05. The covariate, ketamine, was non-significantly related to the number of categories for the WCST, $F(1, 396) = 3.46$, p>0.05. There was a non-significant effect of number of categories for the WCST on drug group controlling for the effect of cannabis, amphetamine, cocaine and ketamine, $F(5, 396) = 20.41$, p>0.05.

There was an overall significant difference between the mean number of trials to first category (set shifting) and the different drug groups. The covariate, cannabis, was non-significantly related to the number of trials for the WCST, $F(1, 396) = 0.011$, p>0.05. The covariate, amphetamine, was non-significantly related to the number of trials for the WCST,

F(1, 396) = 1.23, p>0.05. The covariate, cocaine, was non-significantly related to the number of trials for the WCST, F(1, 396) = 1.27, p>0.05. The covariate, ketamine, was non-significantly related to the number of trials for the WCST, F(1, 396) = 0.007, p>0.05. There was an overall significant effect of number of trials for the WCST on drug group controlling for the effect of cannabis, amphetamine, cocaine and ketamine, F(5, 396) = 39.79, p<0.01. Further analysis found that there was a significant difference between the four non-MDMA drug groups and the two MDMA groups (Bonferroni Post hoc, p<0.01), with the two MDMA groups (past and present) needing more trials to achieve the correct first category in comparison to the non-MDMA control groups (Table 7.4).

Finally there was a significant overall difference between failure to maintain the set (maintaining the rule) and the different drug groups. The covariate, cannabis, was non-significantly related to maintaining the set for the WCST, F(1, 396) = 0.005, p>0.05. The covariate, amphetamine, was non-significantly related to maintaining the set for the WCST, F(1, 396) = 0.054, p>0.05. The covariate, cocaine, was non-significantly related to maintaining the set for the WCST, F(1, 396) = 0.020, p>0.05. The covariate, ketamine, was non-significantly related to maintaining the set for the WCST, F(1, 396) = 0.258, p>0.05. There was an overall significant effect of maintaining the set for the WCST on drug group controlling for the effect of cannabis, amphetamine, cocaine and ketamine, F(5, 396) = 23.59, p<0.01. Further analysis found a significant difference in failure to maintain set between the four control groups and the ex-MDMA polydrug group only (Bonferroni Post hoc, p<0.01), demonstrating that ex-MDMA users failed to complete the set and maintain the rule in comparison to the current MDMA group and the non-MDMA control groups (Table 7.4).

Table 7.4: Mean (±SD) test performance on the WCST, N=402.

The table displays the mean (SD) on the five measurements of the WCST for non drug users (non drug), alcohol/nicotine users (alc./nic), alcohol/nicotine/cannabis users (alc/nic/can), non-MDMA polydrug users (non MDMA poly), current MDMA polydrug users (current MDMA), ex-MDMA polydrug users (ex-MDMA).

	Non drug	Alc/Nic	Alc/Nic/Can	Non MDMA Poly	Current MDMA	Ex MDMA
% Perseverative errors	12.6 (7.7)	12.8 (7.5)	11.3 (7.1)	12.7 (7.2)	15.7(10.8)*	16.5(10.1)*
% Non perseverative errors	13.7 (8.4)	15.7 (8.6)	15.8 (9.1)	14.7 (8.5)	14.8(14.6)	17.9(14.4)
Categories Completed	5.5 (1.2)	5.4 (1.5)	5.8 (1.8)	5.9 (1.6)	5.1 (2.4)	3.5 (2.2)
Trials to first Category	14.8 (6.6)	13.7 (6.1)	12.7 (7.3)	14.2 (9.7)	20.5(29.7)*	28.7(31.2)*
Failure to maintain set	0.5 (1.1)	0.6 (1.8)	0.7 (1.5)	0.6 (0.7)	0.8 (1.3)	1.7 (1.1)*

* denotes $p<0.05$ between current MDMA and ex-MDMA groups in comparison to non-MDMA groups (non-drug, alcohol/nicotine, alcohol/nicotine/cannabis, non-MDMA polydrug group)

7.3.2 ToL

There was an overall difference between the mean planning time needed to complete the task and the six drug groups (Table 7.5). The covariate, cannabis, was non-significantly related to the planning time for the ToL, $F(1, 396) = 0.037$, $p>0.05$. The covariate, amphetamine, was non-significantly related to the planning time for the ToL, $F(1, 396) = 0.070$, $p>0.05$. The covariate, cocaine, was non-significantly related to the planning time for the ToL, $F(1, 396) = 0.048$, $p>0.05$. The covariate, ketamine, was non-significantly related to the planning time for the ToL, $F(1, 396) = 0.149$, $p>0.05$. There was an overall significant effect of planning time for the ToL on drug group controlling for the effect of cannabis, amphetamine, cocaine and ketamine, $F(5, 396) = 52.8$, $p<0.01$. Further analysis found that there was a significant difference in mean planning time between the two MDMA groups and non-MDMA polydrug group (Bonferroni Post hoc test, $p<0.05$), where the two MDMA groups needed more planning time in comparison to the non-MDMA groups. There was a non-significant difference in mean planning time between the ex-MDMA polydrug users and the current

polydrug MDMA users (Bonferroni Post hoc test, p>0.05). There was a significant difference in mean planning time between the non-drug group and the alcohol/nicotine/cannabis group (Bonferroni Post hoc test, p<0.01), where the alcohol/nicotine/cannabis group needed more planning time than the non-drug control group. There was a significant difference in mean planning times between the ex-MDMA polydrug group and the non-MDMA polydrug group (Bonferroni Post Hoc test, p<0.05), where the ex-MDMA polydrug group needed more planning time than the non-MDMA polydrug group (Table 7.5).

The covariate, cannabis, was non-significantly related to the solution time for the ToL, $F(1, 396) = 1.23$, p>0.05). The covariate, amphetamine, was non-significantly related to the solution time for the ToL, $F(1, 396) = 0.73$, p>0.05). The covariate, cocaine, was non-significantly related to the solution time for the ToL, $F(1, 396) = 0.33$, p>0.05). The covariate, ketamine, was non-significantly related to the solution time for the ToL, $F(1, 396) = 1.67$, p>0.05). There was an overall significant effect of solution time for the ToL on drug group controlling for the effect of cannabis, amphetamine, cocaine and ketamine, $F(5, 396) = 22.58$, p<0.01). Further analysis revealed a significant difference between the four non-MDMA groups and the two MDMA groups (Bonferroni Post hoc, p<0.01), where the two MDMA groups took longer to complete the task than the non-MDMA groups. There was a non-significant difference in mean solution time between the ex-MDMA polydrug group and the current MDMA polydrug group (Bonferroni, p<0.05) with both the current and ex-MDMA users taking similar times to complete the task (Table 7.5).

There was an overall difference in the mean number of errors between the six drug groups (Table 7.5). The covariate, cannabis, was non-significantly related to the number of errors for the ToL, $F(1, 396) = 0.097$, p>0.05. The covariate, amphetamine, was non-significantly related to the number of errors for the ToL, $F(1, 396) = 0.044$, p>0.05. The covariate, cocaine, was non-significantly related to the number of errors for the ToL, $F(1, 396) = 0.053$, p>0.05. The covariate, ketamine, was non-significantly related to the number of errors for the ToL, $F(1, 396) = 0.174$, p>0.05. There was an overall significant effect of number of errors for the ToL on drug group controlling for the effect of cannabis, amphetamine, cocaine and ketamine, $F(5, 396) = 30.95$, p<0.01. Further analysis revealed a significant difference between the non-drug control and the two MDMA groups (Bonferroni Post hoc, p<0.01) where the two MDMA groups made more errors than the non-MDMA control groups. There was a non-significant difference in mean number of errors made between the ex-MDMA polydrug group and the current MDMA polydrug group (Bonferroni Post hoc, p>0.05) with

both current and ex-MDMA users making a similar number of errors. There was a non-significant difference between alcohol/nicotine group and the alcohol/nicotine/cannabis group in terms of the number of errors made (Bonferroni, $p > 0.05$). There was a significant difference between the alcohol/nicotine/cannabis group and the two MDMA groups (Bonferroni, $p < 0.05$) where the current and ex-MDMA groups made more errors than the alcohol/nicotine/cannabis group (Table 7.5).

Finally, overall there was no difference in the mean number of trials completed between the six drug groups, where all groups MDMA and non-MDMA control groups needed a similar number of trials to complete the task (Table 7.5). The covariate, cannabis, was non-significantly related to the number of trials for the ToL, $F(1, 396) = 1.77$, $p > 0.05$. The covariate, amphetamine, was non-significantly related to the number of trials for the ToL, $F(1, 396) = 3.77$, $p > 0.05$. The covariate, cocaine, was non-significantly related to the number of trials for the ToL, $F(1, 396) = 2.95$, $p > 0.05$. The covariate, ketamine, was non-significantly related to the number of trials for the ToL, $F(1, 396) = 3.79$, $p > 0.05$. There was an overall non-significant effect of number of trials for the ToL on drug group controlling for the effect of cannabis, amphetamine, cocaine and ketamine, $F(5, 396) = 7.37$, $p > 0.05$.

Table 7.5 Mean (±SD) test performance on the ToL

The table provides means (SD) for the four measures of the Tower of London for non drug users (non drug), alcohol/nicotine users (alc/nic), alcohol/nicotine/cannabis users (alc/nic/can), non-MDMA polydrug users (non MDMA poly), current MDMA polydrug users (current MDMA), ex-MDMA polydrug users (ex-MDMA), where N=402.

	Non drug	Alc/Nic	Alc/Nic/Can	Non MDMA Poly	Current MDMA	Ex MDMA
Planning Time	8.7 (2.2)	8.5 (3.7)	10.7 (4.6)	16.4(5.7)*	17.5 (11.2)*	18.2 (10.8)*
Solution Time	6.3 (1.7)	5.9 (1.2)	5.7 (1.4)	5.9(1.4)	7.4 (1.6) *	7.8 (1.8) *
No of errors	3.5 (2.1)	3.3 (2.0)	4.1(3.3) **	4.4(2.2)**	5.7(3.9) **	6.2 (3.7)**
No Trials completed	11.5(0.6)	11.6(0.4)	11.2 (0.5)	11.4(0.4)	10.8 (0.4)	9.3 (0.5)

* denotes p<0.05 between the ex MDMA, current MDMA, non MDMA polydrug groups in comparison to the non-drug, alcohol/nicotine, alcohol/nicotine/cannabis groups

** denotes p<0.05 between the ex MDMA, current MDMA, non MDMA polydrug, alcohol/nicotine/cannabis groups in comparison to the non-drug, alcohol/nicotine groups

For the ToL there was a significant correlation between the overall solution time and self-reported lifetime exposure to MDMA (r=0.31, p<0.05) and cannabis (r=0.21, p<0.05) (Table 7.6). This indicates that the more MDMA and cannabis exposure, the longer time needed to complete the task. For the ToL there was a significant correlation between the planning time and self-reported lifetime exposure to MDMA (r=0.43, p<0.05), cocaine (r=0.45, p<0.05), cannabis (r=0.38, p<0.05). Similarly, this indicates that increased exposure to MDMA, cocaine, and cannabis results in more planning time needed to complete the task. For the ToL there was a significant correlation between total number of errors and self-reported lifetime exposure to MDMA (r=0.32, p<0.05), cocaine (r=0.32, p<0.05), and cannabis (r=0.54, p<0.05). Indicating increased exposure to MDMA, cannabis and cocaine resulted in more errors.

Table 7.6 Displays correlations between MDMA and ToL

*The table displays the correlation scores between self-reported lifetime exposure to MDMA and four measurements of the ToL (planning time, solution time, no of errors, no of trials completed), * p<0.05, where N=127.*

ToL subscale	MDMA	Cocaine	Cannabis	Amphetamine
Planning time	0.43*	0.45*	0.38*	0.26
Solution time	0.31 *	0.16	0.21*	0.16
No of errors	0.32*	0.32*	0.54*	0.17
No of trials completed	0.12	0.13	0.19	0.04

* Denotes a significant positive correlation between MDMA and planning time/solution time/total number of errors

For the WCST there was a significant positive correlation between the trials to first category and self-reported lifetime exposure to MDMA (r=0.42, p<0.05) and cocaine (r=0.23, p<0.05) (Table 7.7), suggesting that increased exposure to MDMA and cocaine resulted in more attempts needed to complete the first category. There was a significant positive correlation between failure to maintain set and lifetime exposure to MDMA (r=0.44, p<0.05). Indicating that increased exposure to MDMA results in an inability to complete the set and maintain the rule.

Table 7.7 Displays the correlation between MDMA and WCST

Displays the correlation scores between self-reported lifetime exposure to MDMA and five measurements of the WCST (% Perseverative errors, % non- perseverative errors, completed categories, trials to first category), * p<0.05, where N=127.

WCST subscale	MDMA	Cocaine	Cannabis	Amphetamine
	(r)	(r)	(r)	(r)
% Perseverative errors	0.24	0.14	0.11	0.00
% non- Perseverative errors	0.21	0.12	0.25*	0.17
Completed categories	0.23	0.17	0.19	0.21
Trials to first category	0.42*	0.23*	0.15	0.16
Failure to maintain set	0.44*	0.15	0.18	0.14

* denotes a significant positive correlation (p<0.05) between MDMA and trials to first category/failure to maintain set

7.3.3   Correlations for the ToL

There is a significant positive correlation between the mean planning time for the ToL self-reported sleep scores as measured by the PSQI (r=0.75, p<0.000) suggesting that the more time needed for planning the more sleep disturbances reported. There was a significant positive correlation between the mean planning time for the ToL and the self-reported depression scores as measured by the BDI-II (r=0.83, p<0.000) indicating that an increase in depression resulted in more time needed in planning. There was a significant positive linear correlation between the planning task of the ToL and the self-reported impulsivity scores as measured by the BIS (r=0.687, p<0.000) proposing that increased impulsivity results in more time needed to plan a task. Finally, there was a negatively significant linear correlation between the planning task of the ToL and the general memory task of the WMS-R (r=-0.775, p<0.000) (Table 7.8) indicating that poor memory results in more time needed to formulate plans.

There was a significant positive linear correlation between the mean solution time for the ToL task and the self-reported sleep scores (r=0.717, p<0.000) indicating that sleep disturbance

results in more time needed to complete the task. There was a significant positive linear correlation between the mean solution time for the ToL task and the self-reported depression scores (r=0.734, p<0.000), suggesting depression results in longer time needed to complete a task. There was a significant positive linear correlation between the mean solution time for the ToL task and the self-reported impulsivity scores (r=0.578, p<0.000), proposing that more time is needed to complete a task if impulsivity scores are elevated. There was a significant negative linear correlation between the mean solution time for the ToL task and the general memory scores (r=-0.616, p<0.000) (Table 7.8), signifying that poor memory results in more time required to complete the task.

Table 7.8 Reports mean correlation scores between psychological functions and ToL

Displays the correlations between the four measurements of the Tower of London and the self-reported depression, sleep, impulsivity and general memory scores (sub-test of the Weschler Memory Test). Where N=127.

	Memory	Sleep	Depression	Impulsivity
Planning Task Tower of London	-0.67 **	0.750 **	0.830 **	0.687 **
Mean Solution Time Tower of London	-0.616 **	0.717 **	0.734 **	0.578 **
Number of Trials Tower of London	-0.843 **	0.631 **	0.822 **	0.753 **
Number of Errors Tower of London	-0.673 **	0.70 **	0.707 **	0.593 **

*** denotes a significant positive correlation (p<0.05)*

There was a significant positive linear correlation between the mean number of trials completed for the ToL task and the self-reported sleep scores (r=0.631, p<0.000) demonstrating that poor sleep results in increased number of attempts needed. There was a

significant positive linear correlation between the mean number of trials completed for the ToL task and the self-reported depression scores (r=0.822, p<0.000) suggesting that increase depression scores resulted in more trials needed. There was a significant positive linear correlation between the mean number of trials completed for the ToL task and the self-reported impulsivity scores (r=0.753, p<0.000), signifying that increase number of trials was associated with increase impulsivity scores. There was a significant negative linear correlation between the mean number of trials completed for the ToL task and the general memory scores (r=-0.843, p<0.000) (Table 7.8) indicating that poor memory scores resulted in an increase in the number of trials needed.

There was a significant negative linear correlation between the mean number of errors made in the ToL task and the self-reported sleep scores (r= 0.7, p<0.000), suggesting the greater errors made were associated with lower sleep scores. There was a significant negative linear correlation between the mean number of errors made in the ToL task and the self-reported depression scores (r= 0.707, p<0.000) indicating more errors were linked to lower depression scores. There was a significant negative linear correlation between the mean number of errors made in the Tower of London task and the self-reported impulsivity scores (r= 0.753, p<0.000) demonstrating higher impulsivity scores were linked with a smaller number of errors. There was a positive linear correlation between the mean number of errors made in the ToL task and the general memory scores (r=-0.673, p<0.000) (Table 7.8) signifying the more errors made the worse the memory score.

7.3.4   Correlations for the WCST

There was a significant positive linear correlation between the number of perseverative errors made in the WCST and the self-reported sleep scores (r= 0.661, p<0.000) demonstrating that increased sleep disturbance results in more perseverative errors. There was a significant positive linear correlation between the percentage of perseverative errors made in the WCST and the self-reported depression scores (r=0.723, p<0.000) indicating increased depression causes more perseverative errors being made. There was a significant positive linear correlation between the percentage of perseverative errors made in the WCST and the self-reported impulsivity scores (r=0.639, p<0.000) signifying more preseverative errors are associated with increased impulsivity. There was a significant negative linear correlation between the percentage of perseverative errors made in the WCST and the general memory

scores (r=-0.696, p<0.000) (Table 7.9); proposing that poor memory results in more perseverative errors.

Table 7.9 Reports the correlations between psychological functions and WCST

Displays the correlations between the percent of perseverative errors made, percentage non-perseverative errors, number of completed categories and number of trials to first category in the WCST and the self-reported depression, sleep, impulsivity and general memory scores (sub-test of the Wechsler Memory Test). N=127.

	Memory	Sleep	Depression	Impulsivity
% Perseverative errors WCST	-0.696*	0.661 *	0.723 **	0.639*
% Non-Perseverative errors WCST	-0.214	0.164	0.216	0.368
Completed Categories WCST	0.333	- 0.351	- 0.321	- 0.298
Trials to First Category WCST	- 0.715 **	0.679 *	0.744 **	0.621 *
Failure to maintain set WCST	- 0.572	0.523	0.712 **	0.721 **

* *denotes a significant positive correlation (p<0.05)*

** *denotes a significant positive correlation (p<0.01)*

There was a significant positive linear correlation between the number of trials to first category in the WCST and the self-reported sleep scores (r= 0.679, p<0.000) demonstrating that increased sleep disturbance was associated with increase number of trials needed to complete the first category. There was a significant positive linear correlation between the number of trials to first category in the WCST and the self-reported depression scores (r= 0.744, p<0.000) suggesting that depression is linked with an increase in the number of trials needed to complete the first category. There was a significant positive linear correlation

between the number of trials to first category made in the WCST and the self-reported impulsivity scores (r= 0.621, p<0.000) signifying that elevated impulsivity scores is associated with more trials required before completing the first category. There was a significant negative linear correlation between the number of trials to first category in the WCST and the general memory scores (r= -0.715, p<0.000) (Table 7.9) indicating that poor memory performance is associated with less trials needed to complete the first category.

There was a significant positive linear correlation between failure to maintain set in the WCST and the self-reported depression scores (r=0.712, p<0.01); suggesting that increased depression was associated with a decreased chance of completing the task. There was a significant positive linear correlation between failure to maintain set in the WCST and the self-reported impulsivity scores (r=0.721, P<0.01) indicating that increased impulsivity resulted in more of a chance of not completing the task.

7.3.5   Regression analysis for the ToL

The regression model for the mean planning time of the ToL found that overall memory, impulsivity, sleep and depression predicted 70% of the mean planning time, F=277.318, df=4, df=122, p<0.000, n=127. However, sleep (t=3.63, sr^2=0.531, p<0.000) and depression (t=9.176, sr^2=0.223, p<0.000) were the significant predictors for the mean planning time in the ToL tasks.

For the total solution time of the ToL the regression model found that overall memory, impulsivity, sleep and depression predicted 66% of the mean solution time, $F_{(4, 122)}$=91.454, df=122, df=474, p<0.000, n=127. Similarly sleep (t=3.68, sr^2=0.391, p<0.000) and depression (t=2.23, sr^2=0.247, p<0.000) were the main predictors of the total solution time in the ToL.

Memory, sleep, depression and impulsivity predicted 73% of the total number of trials completed for the ToL task, $F_{(4, 122)}$=332.7, p<0.000, n=127. The main predictors were depression (t=3.9, sr^2=0.611, p<0.000), impulsivity (t=3.375, sr^2=0.132, p<0.000) and memory (t= -8.328, sr^2=0.075, p<0.000).

73% of the total number of errors was predicted by memory, sleep, depression and impulsivity, $F_{(4, 122)}$=133.439, p<0.000, n=127. The main predictors for the total number of

errors made were sleep (t= -4.867, sr^2=0.47, p<0.000) and depression (t= -4.544, sr^2=0.371, p<0.000, n=127).

7.3.6 Regression analysis for the Wisconsin Card Sorting Test

The regression model for the total percentage of perseverative errors for the WCST found memory, sleep, depression and impulsivity predicted 63% of the total number of errors, $F_{(4, 122)}$=140.3, p<0.000, n=127. Depression was the main predictor for the total number of perseverative errors (t= 4.697, sr^2=0.611, p<0.000).

41% of the non-perseverative errors for the WCST was predicted by memory, sleep, depression and impulsivity, $F_{(4, 122)}$=23.7, df=4, df=122, p<0.000, n=127. The main predictors for the total number of non- perseverative errors were sleep (t= -2.196, sr^2=0.37, p<0.000) and impulsivity (t=8.141, sr^2=0.031, p<0.000).

For the total number of categories completed (WCST) memory, sleep, depression and impulsivity predicted 36% of the total number of errors, F=(4, 122)=17.8, p<0.000, n=127. The main predictor for the total number of errors in the WCST was sleep (t= -2.965, sr^2=0.291, p<0.000).

The main predictors for the number of trials to first category in the WCST were depression (t=5.678, sr^2=0.671, p<0.000) and memory (t= -2.662, sr^2=0.073, p<0.000). The regression model found that overall memory, sleep, depression and impulsivity predicted 76% of the total number of errors, $F_{(4, 122)}$ =157.7 p<0.000, n=127).

Memory, sleep, depression and impulsivity predicted 64% for the failure to maintain set in the WCST, $F_{(4, 122)}$=83.3 p<0.000, n=127. The main predictor for the failure to maintain the set in the WCST were depression (t=3.8, sr^2=0.601, p<0.000) and impulsivity (t= 2.339, sr^2=0.036, p<0.000).

7.3.7 Demographics

The mean age of the total sample was 24 years old (SD=5.9; ranging from 18-46 years). The sample consisted of 47% females and 53% males. The majority, 38% of the sample lived in non-metropolitan city, 27% outer metropolitan city and 35% lived inner metropolitan. The ethnicity was split into 42% white, 10% black, 12% Asian, 36% were other.

The ex-MDMA group reported taking MDMA for the first time at an older age (mean age 26) in comparison to the current-MDMA group (mean age 18) (t=2.71, df=125, p<0.01, Table 7.10). The current-MDMA group reported taking more MDMA (mean tablets of 1.42) during their first experience of MDMA than the ex-MDMA group (mean tablets of 1.15) (t=0.47, df=125, p>0.05, Table 7.10). The current-MDMA group reported using more MDMA during a single occasion (mean tablets on single occasion 2.31) than the ex-MDMA group (mean tablets on single occasion 1.49) (t=0.251, df=125, p>0.05, Table 7.10). Finally, the current MDMA group reported consuming more MDMA tablets in a lifetime (mean lifetime tablets 989) than the ex-MDMA group (mean lifetime tablets 582) (t=11.6, df=125, p<0.01, Table 7.10). Finally, all MDMA participants reported that their usual route of administration of MDMA was via tablet and they normally consumed MDMA with friends.

Table 7.10: Basic demographics for the current and ex-MDMA groups

*The table provides details concerning MDMA use including: mean (SD) age first used MDMA, mean (SD) amount of MDMA first used, mean (SD) amount of MDMA normally consumed and mean (SD) lifetime amount of MDMA consumed; (N=127). Where * p<0.05.*

	Age first tried MDMA	No first Used	No Used Permanently	Total used in lifetime
Current MDMA	18.0* (3.2)	1.42 (0.82)	2.31 (1.25)	989* (778)
EX-MDMA group	26.9* (6.24)	1.15 (0.58)	1.49 (1.18)	582* (688)

There was a slight variation in the exposure to other recreational drugs of abuse (Table 7.11a and 7.11b). Overall a higher percentage of ex-MDMA users reported exposure to nicotine, alcohol, steroids, cocaine, crack cocaine, psiolocybin/psilocin and gases in comparison to the non-drug polydrug users and current MDMA polydrug groups (Table 7.11a – chi

square=69.1, df=60, p>0.05). A higher percentage of current polydrug MDMA users reported exposure to amphetamines, heroin, and GHB (Table 7.11a).

Table 7.11a: Illicit drug use in different drug groups

Percentage of drug users self-reported exposure to recreation drugs of abuse for the three drug groups, which includes non-MDMA polydrug (n=71), current MDMA polydrug (n=67) and ex-MDMA polydrug ((n=60), Chi square =69.1, df=60, p>0.05).

Recreational Drug	Non-MDMA polydrug	current MDMA polydrug	ex-MDMA polydrug
Nicotine	62%	67%	80%
Tranquilisers	11%	22%	17%
Alcohol	95%	93%	97%
Steroids	14%	16%	17%
Cannabis	97%	96%	97%
Cocaine	29%	54%	41%
LSD	17%	39%	36%
Psiolocybin/Psilocin	28%	33%	38%
Alkyl nitrites	14%	38%	40%
Amphetamine	50%	54%	48%

Table 7.11b: Lifetime use of illicit drugs

The table provides details of the total self-reported lifetime exposure to recreational drugs of abuse. Calculated using the formula: number of occasions per week * number of months per year* number of years. Where* Mann Whitney= p<0.05.N=339.

	Nicotine/Alcohol (Mean/SD)	Nicotine/ Alcohol/Cannabis (Mean/SD)
Alcohol	1188 (1172)	759 (754)
Nicotine	46649 (41057)	31631 (26422)

	Polydrug (non-MDMA) (Mean/SD)	Current MDMA (Mean/SD)	Ex-MDMA (Mean/SD)
Alcohol	1293 (1231)	1597 (779)	2144 (985) *
Cannabis	1925 (892)	2668 (934)	3745 (782) *
Nicotine	53710 (22852)	49454 (24175)	81025 (38211) *
Amphetamine	56 (84)	155 (67)	148 (77) *
Tranquillisers	1.92 (5.1)	18.3 (3.5)	17.44 (4.4) *
Steroids	9.61 (17.8)	11.11 (16.26)	18.25 (17.6)
Cocaine	1.18 (2.19)	12.49 (3.1)	15.15 (2.2) *
Crack	33 (21)	44 (56)	55(36)
LSD	35 (12)	38 (34)	95 (180) *
Psilocybin/psilocin	5.1 (2.5)	12.1 (4.1)	13.3 (3.8)
Alkyl nitrites	46.2 (27)	26.6 (38)	45.1 (32.1)
Gases	26.9 (13.6)	15.3 (12.2)	32.9 (27.5)
Heroin	2..5 (2.4)	6.3 (7.3)	6.1 (4.7)
GHB	0.54 (1.8)	9.67 (1.9)	4.51 (1.1)
Ketamine	0.34 (0.24)	11.9 (1.5)	1.5(1.8) *

7.4   Discussion

7.4.1   Overall Findings

In summary, the results from this study confirmed the hypothesis that MDMA polydrug users demonstrated deficits in executive functioning tasks in comparison to non-MDMA users. The results further indicated that past and present MDMA polydrug users exhibit similar executive functioning problems. These findings suggest that psychological deficits caused by MDMA are long lasting. This is the first study to date to investigate past and present MDMA users on executive functioning tasks, monitoring performance on other psychological functions: memory, depression, sleep, impulsivity and depression. These findings are discussed in more detail for the remainder of this chapter.

7.4.1.1   WCST

The findings from this study found that MDMA users past and present had difficulties in specific measures within the WCST, including the number of perseverative errors made and the ability to set shift thus being able to inhibit previously learnt rules (the number of trials to first categories) in comparison to non-MDMA control groups. These results imply that MDMA users have problems with divided working memory, rigid thinking and cognitive inflexibility. The past MDMA users displayed problems maintaining the set, indicating a problem with remembering the current rule in comparison to present MDMA users and non-MDMA groups. It is plausible cognitive problems like attention and abstract thinking may get worse with the aging process per se and not be associated with MDMA exposure. Previous studies have demonstrated an association between poor executive functioning (disinhibition, rigid thinking, inattention and a decline in working memory) and the aging process, where there is a decreased efficiency in the brains dopaminergic levels in the frontal lobe (Backman et al. 2010). Alternatively, attention and abstract thinking may take more time before the behaviour manifests. There could be a critical period between MDMA exposure and onset of symptoms and/or behavioural deficits. These results demonstrate past and present MDMA users suffer from cognitive problems including executive functioning deficits (working memory, rigid thinking and cognitive flexibility) which seem to be long lasting and may even get worse with the aging process, as has been shown in previous research (Allain et al, 2007). The results from this study could be further explained by findings from non-human animal

studies that demonstrate MDMA is a neurotoxin to selective brain 5-HT, which is long lasting and possibly permanent (Bolla et al. 1998; Parrott et al. 1998; Fox et al. 2001; Wareing et al. 2000). The positive correlation found between the self-reported lifetime exposure of MDMA and the number of perseverative errors in this study supports the MDMA induced neurotoxicity theory. Verdejo-Garcia and co-workers found similar regression results where they found that MDMA was the main predictor of abstract reasoning in current polydrug MDMA users, with cannabis and cocaine failing to play a significant role in predicting abstract reasoning deficits (Verdejo-Garcia et al. 2005).

7.4.1.2 TOL

Results from this study for the ToL revealed that present and past MDMA polydrug users spent more time finding a solution than the non-MDMA polydrug users and non-drug controls. This implies that past and present MDMA polydrug users have problems with planning and decision-making (Norman and Shallice, 1986). The positive association between the self-reported life time exposure to MDMA and time spent finding a solution further supported this finding.

In terms of planning time for the ToL, past and present MDMA polydrug users in addition to non-MDMA polydrug users needed more time than cannabis/alcohol/nicotine drug users. This finding suggests that MDMA may not have caused the problems associated with planning time and it maybe a consequence of other substances including amphetamine, cocaine and heroin. It is unlikely to be cannabis, as the cannabis group had similar planning times to the non-drug control group. Verdejo-Garcia and co-workers investigated cognitive memory tasks, inhibition and decision-making in poly drug users. Their findings suggested that cocaine users had more pronounced deficits than other drug users (MDMA, cannabis, amphetamine) in the executive functioning tasks (Verdejo-Garcia et al. 2007). In the present study, the MDMA polydrug group had used both MDMA and cocaine, which may result in more severe consequences. Further research is required investigating the role of amphetamine, cocaine and heroin on executive functioning tasks.

In terms of the number of errors made in the ToL, the past and present MDMA users in addition to the cannabis group had an increased number of errors in comparison to the non-drug control group. This finding suggests that the number of errors were determined by another substance/factor other than MDMA. The likely substance would be cannabis. The role

of cannabis in executive functioning needs to be further investigated as previous research suggests cannabis affects cognitive performance (Croft et al. 2001; Gouzoulis-Mayfrank et al. 2002; Dafters et al. 2004; Daumann et al. 2004; Parrott et al. 2004; Lundqvist et al. 2005; Sala et al. 2005).

In summary, these findings found that past and present MDMA users demonstrated problems with divided working memory, rigid thinking, cognitive inflexibility, and decision-making. These deficits were similar between past and present MDMA users suggesting it is a long lasting consequence of MDMA.

7.4.2 General Discussion

The demographic characteristics between the past and present MDMA polydrug users were similar to those of the control groups including ethnicity and employment. The age of the past MDMA users were greater in comparison to the other groups. This was to be expected as the past MDMA users had to abstain from MDMA for a mean period of 78 months (ranging from 49 – 102 months) so they would be older in age. The similarity in demographic details suggests the results from this study along with the differences found between the past/present MDMA users and the non-MDMA drug users were likely to a be a consequence of MDMA use rather than a result of the demographic differences.

Linking executive functioning to the frontal lobe has recently been under controversy. Shallice has linked deficits on performance of the ToL to left anterior frontal lobe lesions. Evidence for this has come from studies comparing frontal lobe lesion patients with matched control patients on performance of the ToL. The results found that patients with frontal lobe damage performed significantly worse in cognitive tests in comparison to the controls. Critics argue this reduced performance in executive functioning cannot be linked to an exact region of the frontal lobe: left or right anterior frontal lobe. However, this does provide supporting evidence for the role of the frontal lobe in executive functioning tasks (Owen et al. 1990). PET studies have reported activation of specific areas of the brain during performance of the ToL (Owen et al. 1990; Morris et al. 1993; Baker et al. 1996; Morris et al. 1996). These anatomical regions include the frontal cortex, temporal cortex, amygdala, hippocampus and striatum (Owen et al. 1990; Morris et al. 1993; Baker et al. 1996; Morris et al. 1996). This study found that MDMA users demonstrated difficulties with planning and decision-making. As previous research have associated planning and decision making with the frontal lobe, it

seems likely that MDMA users past and present are finding difficulty with such functions, due to a deficiency within the frontal lobe. Neuroanatomically the main source of CNS 5-HT is the raphe nuclei. Axons from the raphe nuclei innervate virtually all areas of the brain, including the cerebellum/spinal cord to the cortex. Non-human animal studies have demonstrated that MDMA is a selective neurotoxin damaging 5-HT nerve terminals within the raphe nuclei (Francken et al. 2000; Hirst et al. 2003). Thus, it may be possible to imply that MDMA causes anatomical damage to 5-HT raphe nuclei, which consequently results in frontal lobe behavioural problems, including executive functioning deficits. Future studies need to investigate each subscale of the ToL, behavioural consequences of MDMA and localise the anatomical region. More evidence is required investigating the role of the frontal lobe in MDMA users, particularly targeting older users in addition to controlling for other illicit drugs. Secondly, future studies need to investigate the consequences of MDMA on the 5-HT receptors found within the frontal lobe and raphe nucleus: 5-HT1A, 5-HT2B, and 5-HT2C.

Verdego-Garcia and co-workers (2005) suggested that exposure to MDMA affected working memory and abstract reasoning. In addition, they demonstrated that cocaine affected inhibition control and cannabis affected cognitive flexibility (Verdejo-Garcia et al. 2005). The MDMA groups in this study were exposed to cocaine, cannabis and MDMA, implying that a cocktail of drugs will complicate findings and may cause substantially more impairment. This study found MDMA polydrug users demonstrated cognitive inflexibility, and rigid thinking. These results could be due to a combination of MDMA, cannabis and cocaine.

These results suggest that certain domains of executive functioning were affected by MDMA whilst other areas remained intact; indicating that MDMA is domain specific, in terms of possible behavioural deficits. Fisk et al. (2009) found similar results, where 14 frequent MDMA users, 39 less frequent users and 28 non-drug users were tested on a battery of executive functioning tasks. The results found that MDMA users were not affected by inhibition on the contrary they were impaired on update processing. The authors concluded that future MDMA research needs to investigate the separate domains of executive functioning tasks as MDMA induced behavioural problems maybe specific to certain executive functions (Fisk et al. 2009).

Recently researchers have proposed MDMA is not a 5-HT neurotoxin causing cognitive related deficiency, and the behavioural deficits found are due to cannabis. As most MDMA

recreational drug users are cannabis users, researchers propose this is the reason why MDMA users have cognitive problems. In this study, the study included a separate cannabis group. The results found that the cannabis group alone failed to exhibit the same severity of executive functioning problems as the past and current MDMA polydrug groups. It is plausible cannabis alone does not cause executive functioning deficiency and it may be a combination of MDMA and cannabis. Most previous studies have not employed a separate MDMA group, which had abstained from cannabis. It is difficult to conclude that the results were due to MDMA alone and not a combination of MDMA and cannabis. On the other hand, this study failed to find a correlation between life time exposure to cannabis and performance on the executive functioning tasks suggesting it is likely to be MDMA. Croft et al. (2001) investigated cannabis and its relationship to MDMA-related cognitive problems. Their study included MDMA only users, MDMA/cannabis users and non-MDMA/cannabis drug users. It measured a battery of neuropsychological tests. The results found that cannabis and MDMA/cannabis users did not differ significantly on test scores (Croft et al. 2001). The authors concluded that cannabis plays an important role in MDMA-related cognitive impairment. Criticism of their study is that other recreational drugs were not controlled: cocaine, amphetamine and alcohol. Other recreational drugs were controlled in this study: alcohol, nicotine, amphetamine and cocaine. This study seems to indicate that the executive functioning deficits were due to MDMA.

Studies have reported that MDMA users, in addition to other drug users and frontal lobe lesion patients, demonstrate elevated impulsivity in addition to impulse control disorder, which could arise due to impaired inhibitory control a core aspect of executive functioning (Lawrence et al. 2009). It is plausible to suggest individuals would initiate action without a coordinated goal and pre-planning. This would result in shorter planning times and less accurate performances than non-MDMA users (Drewe, 1975). On the contrary, the results from this study found that past and present MDMA users demonstrated longer planning times in comparison to the control groups.

In the present study, regression analysis of the mean performance on the ToL and the WCST found that lifetime exposure of MDMA was the main significant predictor. The regression suggests MDMA causes the selective cognitive impairment. In addition, non-MDMA polydrug users demonstrated a cognitive decline in specific subscales of the ToL and WCST; however, this decline was not as severe as the scores of the MDMA users. As the

alcohol/nicotine/cannabis group failed to differ from the non-drug group it suggests alcohol, nicotine or cannabis alone are not the cause of this selective decline in cognitive decline.

The prefrontal cortex, an area associated with executive functioning, is innervated with neurons transmitting dopamine, noradrenaline, acetylcholine and serotonin. Imaging studies and rats studies have proposed that DA is involved in attention and working memory (Chudassma et al. 2004). Further evidence includes studies using selective DA knock out genes (Robins et al. 2007). The role of dopamine and MDMA is still needed to be explored further, particularly as MDMA users will often co-use MDMA with cocaine and amphetamine. Recreational drugs like cocaine and amphetamine affect DA levels particularly areas like the amydala.

7.4.3   Depression, sleep, memory and impulsivity

Results from the correlations and the regression analysis of this study demonstrate that in the planning stages of the ToL, deficits in sleep and depression have an impact on the performance of ToL (Figure 7.12). This suggests that the inability of MDMA users to plan moves, could be due to MDMA affecting sleep and depression, which directly influences cognitive planning. This may explain the discrepancies in previous MDMA research. If an individual does not have deficits in sleep and depression, they will not have problems with executive planning. This suggests that MDMA directly affects sleep and depression, which indirectly disrupts executive functioning. Alternatively, MDMA may directly impinge on executive functioning with the sleep and depression being secondary factors. In addition, it seems other illicit drugs like amphetamine, cocaine and heroin may play a role on performance. This requires further investigation, with sleep and depression controlled for in future MDMA related executive functioning studies.

Figure 7.12   MDMA and planning time for ToL

The figure suggests the possible links between performance on the Tower of London (planning time) with lifetime use of MDMA, lifetime use of other illicit drugs, self-reported sleep and self-reported depression.
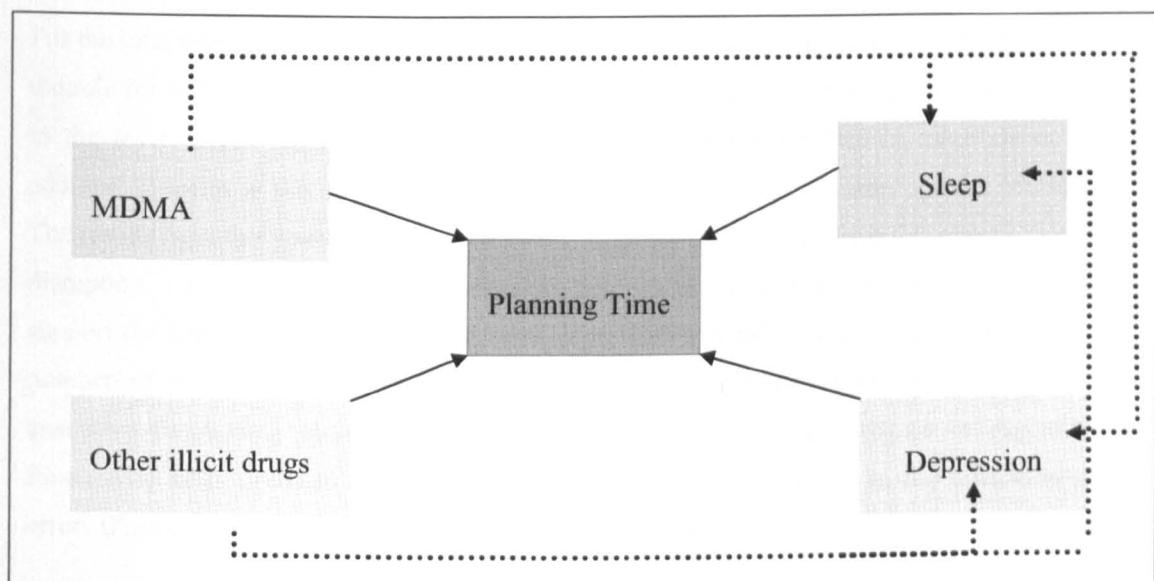
Note   ·········   *MDMA/other illicit drugs indirectly via sleep and depression*
           ——————→   *MDMA /other illicit drugs directly*
           ——————→   *Depression/Sleep directly*

For the total number of trials completed in the ToL task the regression and correlation results supported the role of depression, impulsivity and memory in disrupting the number of trials completed.   Increased self-reported depression and impulsivity scores resulted in a fewer number of trials being completed and an increase in memory ability resulted in more trials being completed. These results predict that depression and increased impulsivity may result in a decline in the ability to complete trials in the ToL task. In addition, an increase in memory may act as an advantage and increase the number of trials completed. These findings support the hypothesis that MDMA is a neurotoxin to selective 5-HT neurons, which subsequently directly causes depression and impulsivity, which indirectly disrupts the ability to complete trials.

Depression and sleep interrupt the time needed to complete the ToL task. Increased self-reported depression and sleep disturbances resulted in more time being required to complete the task. The findings from this study indicate that MDMA induces depression and sleep deficits, which indirectly effects the time needed to complete the task. On the other hand, MDMA may directly disrupt the time needed. Future research investigating executive functioning with regard to amount of time needed to solve a problem needs to control for the effects of depression and sleep disturbances.

For the total number of errors in the ToL task the regression and correlation results supported the role for depression and sleep having an effect on the number of errors made. An increase in the level of self-reported depression and sleep disturbance resulted in more errors. In addition, it seems in this study the primary illicit drug involved is cannabis and not MDMA. The results from this study are supported by other studies that indicate cannabis plays a role in disrupting executive functioning (Fernandez-Serrano et al. 2010). The present findings support the hypothesis that cannabis disrupts depression and sleep, which directly affects the number of errors made. Alternatively, cannabis directly affects the number of errors in executive functioning tasks. The role of depression and sleep disturbance in executive functioning tasks needs to be addressed further in particular their role in the formation of errors (Pace-Schott and Hobson, 2002; Alexopoulos, 2004).

For the WCST correlations and regression results found the total number of perseverative errors made was affected by the level of self-reported depression. Increased depression seems to result in more errors. These findings suggest that MDMA subsequently causes depression, which indirectly increases the number of errors. This needs to be investigated further with future research concentrating on excluding the effects of depression on the number of perseverative errors made in the ToL.

For the number of trials to first category in the WCST were effected by the level of self-reported depression and memory ability (Figure 7.13). From this study, it can be proposed that MDMA disrupts memory and depression, which indirectly has an effect on the ability to complete trials. Alternatively, MDMA directly interrupts performance on trials to first category. Research in the future needs to investigate the long lasting role of MDMA on executive functioning controlling for depression and memory.

Figure 7.13   MDMA and the trials to first category for the WCST

The figure suggests the possible links between the performance on the Wisconsin card sorting test (Trials to first categories) with lifetime use of MDMA, memory and self-reported depression.
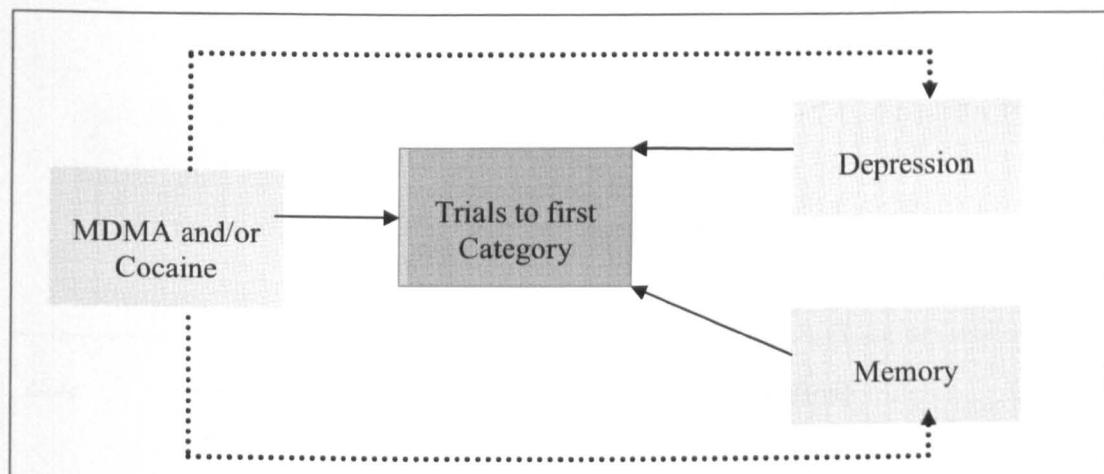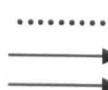
Note   ·········   *MDMA indirectly via depression/memory*
            ⟶   *MDMA directly*
            ⟶   *Depression/memory directly*

Finally, in the WCST the correlation and regression analysis found that the failure to maintain set was dependent on self-reported depression and impulsivity (Figure 7.14). However, this was only found for those MDMA users that abstained from MDMA. Findings from this study suggest that MDMA disrupts memory and depression, which indirectly affects the ability to maintain the set. Alternatively, MDMA directly affects the ability to maintain the set, however the consequences of being exposed to MDMA may take some time to develop. Future research investigating executive functioning needs to control for depression and impulsivity.

Figure 7.14   MDMA and the failure to maintain set for the WCST

The figure suggests the possible links between the performance on the Wisconsin card sorting test (failure to maintain set) with previous lifetime use of MDMA, self-reported impulsivity and self-reported depression.
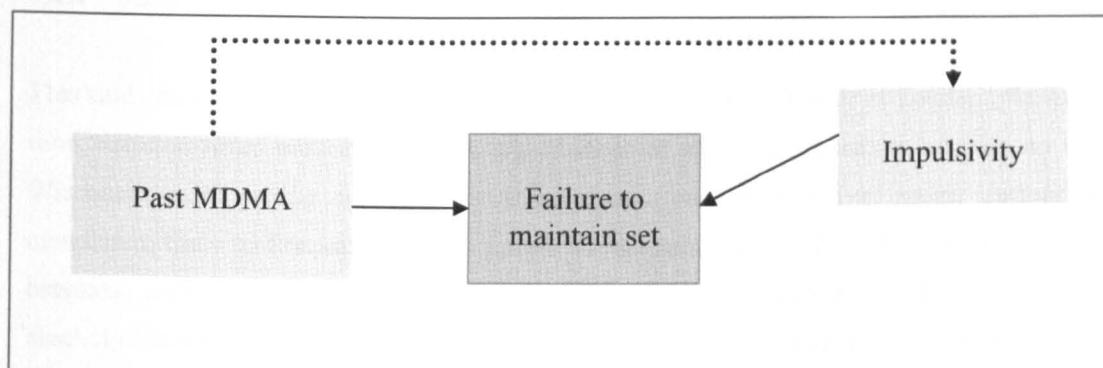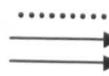
Note .... *Past MDMA users only indirectly via impulsivity*
——→ *Past MDMA users only directly*
——→ *Impulsivity directly*

Clinical studies have shown that later life lesions or other brain abnormalities of the frontostriatal pathway (frontal cortex and caudate nucleus regions of the brain) results in depression, along with disturbances in problem solving, sequencing, planning, organising and abstracting (Alexopoulos, 2004). This has led to the DED (depression-executive dysfunction) syndrome. Current theorists have indicated that these individuals are pre-disposed to depression with the lesion/brain abnormality in later life contributing to later life depression and the DED syndrome. Interestingly, the DED syndrome does not respond to atypical antidepressants. Future MDMA studies need to look into the DED syndrome to see if it will provide further information on MDMA related toxicity.

Studies investigating sleeping habits of non-clinical adults suggest that a high proportion (39%) sleep less than seven hours per night during the work week, and more than two-thirds (68%) sleep less than eight hours per night (NSF, 2002). Research indicates that this lack of sleep affects their cognitive performance (Anderson and Horne, 2003; Gosselin et al. 2005). It

is hypothesised that the loss of sleep can result in changes within brain functioning: prefrontal cortex, anterior cingulated cortex, and dorsomedial thalamus). As the loss of sleep in healthy individuals can drastically influence frontal lobe and executive functions (creative thinking, cognitive flexibility, rule attainment, response initiation, and response inhibition), the loss in clinical populations would be even more drastic (Anderson and Horne, 2003). Future MDMA and drug-related studies need to investigate the complex interaction between basic cognitive functions (attention, sleep, and depression) and the more complex functions like cognition.

7.4.4 Limitations

This study measured performance on the different domains of the Tower of London (planning time, solution time, number of errors and number of trails completed) in addition to the Wisconsin card sorting test (perseverative errors, non-perseverative errors, categories completed, trials to first category and failure to maintain set). ANCOVAs were performed between each of the domains and the different groups (non-drug, alcohol/nicotine, alcohol/nicotine/cannabis, non-MDMA polydrug, current MDMA polydrug and past MDMA polydrug). If there was a significant difference in mean scores between MDMA users and control groups (non-drug, alcohol/nicotine, alcohol/nicotine/cannabis, non-MDMA polydrug) the domain was considered to be disrupted by the exposure of MDMA. Correlations were performed between lifetime use of MDMA, cannabis, cocaine and amphetamine. If the correlation was greater than r=0.7, we then reported that the lifetime exposure of that particular illicit drug played a role in predicting scores of the specific domain of the ToL and/or WCST. Finally, correlations were performed between the psychological functions (sleep, memory, depression, and impulsivity). If the correlations was greater than r=0.7 it was proposed that the psychological state (depression, memory, impulsivity, and sleep) disrupted domains of the ToL and/or WCST directly or indirectly via MDMA and/or another illicit drug. These predictions were further confirmed using multiple regressions. This statistical analysis can be heavily criticised and there are shortcomings in forming conclusions from such analysis. It is acknowledged the shortcomings in employing this methodology; the next step would be to measure executive functioning in drug users whilst controlling for all illicit drugs in addition to depression, memory, sleep and impulsivity. On the other hand, the regression predictions and the correlations provide some indication MDMA induced neurotoxicity is more complicated in terms of psychological behavioural consequences and needs further exploration in the future research.

A limitation of this study is the use of the executive functioning tests: WCST and ToL test. There is ample debate concerning the WCST/ToL tasks and their ability to measure executive functions (Shallice, 1982; Berman et al. 1995; Nagahama et al. 1996). Some research feel tasks like the WCST and ToL maybe too complex and fail to isolate individual executive functioning components (Odhuba et al. 2005). These critics argue that there is too much overlap between the different executive components measured in the ToL and WCST. Executive functions are difficult to assess directly since they incorporate other cognitive skills. Damage to memory, language, visuospatial skills and other cognitive functions can influence how a person performs on tests of executive functioning. Secondly, executive skills are grounded within real world experiences. Any methodology employed to assess executive behavior require mental agility, foresight, planning and freedom from distraction. On the other hand, these ToL and WCST tests have undergone reliability and validity testing (Shallice, 1982; Berman et al. 1995; Nagahama et al. 1996). Future studies need to look at each individual components of executive functioning and test each one individually to form a clearer picture of the long term effects of MDMA on executive cognition functioning. These tests include the Stroop task, Keep track task – a working memory task; random letter generation task, Word Fluency Task, Trailmaking Test and Porteus Mazes. The results from tests need to be supported and correlated with other more advance techniques; including brain imaging and scans. In addition future studies need to investigate performance on real life, every day tasks: ability to drive, ability to react to hazard, the ability to foresee hazards, and the ability to work complex machinery.

A major problem with executive dysfunction is the role of memory. Short-term memory has been associated with executive functioning performance (Baddeley, 1986). The primary role of short-term memory is to support long-term learning, which is done via working memory (Baddeley & Hick, 1974). It is difficult to determine the exact cause of the executive dysfunction from the present results. MDMA may have caused the executive dysfunction; alternatively MDMA may have affected short-term memory, which consequently affected executive functioning. Future studies need to investigate the consequences of MDMA on short-term memory and/or executive functioning.

Illicit substances have long been associated with executive dysfunction including alcohol, cocaine, heroin, and amphetamine (Fernandez-Serrano et al. 2010). It is difficult to establish a correlation between different drugs and executive functioning as most drug users are polysubstance users. Where many drugs like alcohol, amphetamine and cannabis will be

common confounding factors. However, regression analysis has predicted that alcohol, cannabis, cocaine, and heroin all have deleterious effects on executive functioning (Fernandez-Serrano et al. 2010). Secondly, neuroimaging studies have revealed neurocognitive alterations within the brain (frontal and temporal cortex; amygdala, hippocampus, striatum) for substance users (cocaine, opiates, MDMA and cannabis); where these changes are more pronounced in cocaine users. As MDMA users are polysubstance users they will be co-using substances, future studies need to combine neuropsychological findings and imaging studies to look at adaptations which would be relevant for future rehabilitation of drug users.

Deficiencies in executive functioning have been previously associated to psychiatric disorders: ADHD, Tourette's syndrome, OCD, traumatic brain injury, learning disabilities and autism spectrum disorders (Tan, 2009; Foley et al. 2010, Senathi Raja et al. 2010; Brown et al. 2010). These results could indicate that MDMA users are more prone to these psychiatric disorders, and will need diagnostic screening. Alternatively, it maybe postulated that MDMA users were predisposed to these psychiatric disorders consequently; they sought MDMA as a form of self-medication. These psychiatric disorders have been associated with frontal lobe dysfunction and 5-HT deficiencies.

Finally, research has linked executive dysfunction, attention and working memory to DA abnormalities (Chudasama and Robins, 2004). Cohen and Durstewitz proposed a model suggesting that DA plays a role in stabilising representations within the prefrontal cortex. The model suggests that DA also gates relevant and irrelevant information (Cohen and Durstewitz, 2000). Interestingly, in this study the results found that the MDMA polydrug users failed to have a problem with set shifting, which the 'Cohen and Durstewitz' model argues attention and DA are required. This would then imply, as previous studies have, that MDMA does not affect DA levels (McGregor et al. 2003; Milani et al. 2004; Thompson et al. 2004).

7.4.5 Summary

The main results from this study found that past and present MDMA polydrug users demonstrated impairment on executive functioning tasks (ToL and WCST) in comparison to non-drug users and other non-MDMA recreational drug users. This study confirmed previous research demonstrating that the behavioural deficiency was not global but specific to certain domains of the ToL and WCST. To the authors knowledge no previous study has controlled

so robustly for other recreational drugs: cocaine, amphetamines, and ketamine. Additionally, this is the first study to investigate past recreational drug users that have withdrawn from the drug MDMA for more than 5 years on executive functioning. These findings are supported by non-human animal studies, which indicate that MDMA is a selective 5-HT neurotoxin that targets selective domains of executive functioning. These findings suggest these specific disruptions are long lasting. Previous studies have investigated executive functioning on MDMA users however, they have failed to take into account the role of memory, depression, sleep, and impulsivity on overall executive functioning (Bolla et al. 1998; Parrot et al. 1998; Fox et al. 2001; Wareing et al. 2000). With respect to the ToL, the level of self-reported depression plays a role in the ability to plan moves, total number of trials competed and total number of errors made. Sleep plays a role in the total number of moves planned. Impulsivity and memory play a role in the total number of trials completed. For the WCST, memory and depression play a role in the total number of perseverative errors made, and the total number of trials to first category. Additionally, MDMA may directly affect solution time and cognitive speed. Performance on non- perseverative errors and total number of categories completed on the WCST were not dependent on level of depression, sleep, impulsivity and memory ability. This suggests that MDMA may directly increase cognitive errors, disrupt planning and decision-making. Finally, future MDMA studies need to investigate the consequences of MDMA on the interaction between higher level functioning (cognition) and lower level functioning (sleep, depression, impulsivity); as well as controlling for co-use of all illicit and licit substances.

General Discussion

8.1   Summary of main overall findings

To date this is the largest single study investigating the long lasting psychological consequences and their sub-domains of MDMA, comparing past and present polydrug users. Even though this hypothesis was formulated in 2001, there is still no previous published study to date which has focused on such a large and diverse population of both past and present MDMA polydrug users. This study is a good representation of the general population of MDMA polydrug users rather than targeting just 'club drug users'. Consequently, this study is an updated representation of past and present MDMA polydrug users, their opinions of MDMA and the long lasting psychological consequences of MDMA. Secondly, no previous study has focussed on the separate domains of the psychological functions (depression, memory, impulsivity, and sleep) comparing past and present polydrug users. Finally, this is the first study to investigate the long lasting consequences of MDMA in polydrug users on executive functioning tasks taking into account deficits in memory, impulsivity, depression, and sleep. Previous studies investigating the consequences of MDMA have many flaws raising doubts on the significance of reported findings, including the lack of data on previous illicit drug exposure, limited time allowed between last MDMA use and experimental procedure, and the lack of pre-morbid psychiatric history. The present study has controlled for psychiatric history, other illicit and/or licit drug use, and included a minimum 3 week period between last MDMA use and participation in the study, making this study the largest most robust study on the acute and long lasting effects of MDMA to date.

Findings from this study suggest that the majority of present and past MDMA polydrug users in the South East of England were of mixed ethnicity and in their late-20s during the period 2001-2007. They were employed, single and living in the inner metropolitan areas. MDMA users past and present use more illicit drugs in term of overall frequency than non-MDMA polydrug users. Present MDMA polydrug users are more likely to co-use MDMA with other illicit drugs (cannabis, amphetamine, alcohol and cocaine) than past MDMA users. This study found that past and present MDMA polydrug users self reported increased lifetime exposure to cocaine, and LSD on comparison to non-MDMA polydrug users. Present MDMA polydrug users seem to be exposed to MDMA for the first time at a younger age than past MDMA polydrug users and they will use larger doses of MDMA in comparison to past MDMA users. This increased dosage of MDMA, frequency and co-use of drugs in present MDMA polydrug

drug users suggest that they may be increasing the risk of possible long lasting damage to psychological functions (Curran, 2000; Parrot, 2001).

The main findings from this study suggested that the use of MDMA resulted in the overall disruption of psychological functioning: depression, impulsivity, memory, and sleep (Figure 8.1). Both past and present MDMA polydrug users self-reported elevated depression scores (cognitive-affective subscale), heightened impulsivity scores (motor impulsiveness subscale and attentional impulsiveness subscale), memory deficits (verbal memory, visual memory, and delayed memory) and overall sleep disturbance in comparison to non-MDMA polydrug users. Therefore this study suggests that MDMA causes acute and long lasting consequences in depression, memory, impulsivity and sleep, confirming previous studies (Curran, 2000; Parrot, 2001). This study confirmed results from previous published studies demonstrating that 'psychological and cognitive task' dysfunction was dose related. The 'frequent MDMA polydrug users' had more pronounced difficulties often being classified as 'clinical' than the 'milder less frequent MDMA polydrug users' in depression, impulsivity and sleep whose levels fell within the normal range.

In the present study, the past MDMA polydrug users had abstained from MDMA for a mean of 5 years and they self-reported similar elevated depression scores (cognitive-affective subscale), sleep disturbances, enhanced personality impulsivity scores (motor impulsiveness subscale and attentional impulsiveness subscale) and memory dysfunction (visual, verbal and delayed), as the present MDMA polydrug users. This finding indicates that MDMA induces long lasting and possibly permanent selected psychological damage to functions like depression, sleep, memory and impulsivity. This is further supported by non-human animal including primate studies, which demonstrate that MDMA causes structural damage to 5-HT neurons that not only affects the terminal but also the neuronal axon. This renders the neuron structurally and neurologically dysfunctional. This results in a lack of activity in the cell body which has limited if no effect on 5-HT release (Franfurt et al. 1984; Frith et al. 1987; Ricaurte et al. 1988; Frederick et al. 1997; Scheffel et al. 1998; Shankaran et al. 1998; Ricaurte et al. 2000a, 2000b, 2000c; Ricaurte et al. 2001; Gurtman et al. 2002; Blessing et al. 2003; Bogan et al. 2003; Bowyer et al. 2003; Buchert et al. 2004; Wang et al. 2004; Garcia Osta et al. 2004; Fornai et al. 2004; Conductier et al. 2005; Escobedo et al. 2005; Galineau et al. 2005; Jones et al. 2005). A debated question is whether there is an adaptive compensatory change in the regulation and activity of 5-HT neurons following a period of abstinence from MDMA and whether recovery occurs (O'Hearn et al. 1984). The results from this study suggest that

there is little difference in overall performance on psychological functions (sleep, memory, impulsivity, depression and executive functioning) between past and present MDMA polydrug users, suggesting that either the MDMA damages the 5-HT neurons fully or compensatory change occurs however this affects performance on specific psychological tasks (sleep, memory, impulsivity, and depression).

One major discussion involves the similarities between the acute effects of MDMA in humans and non-human animals. Both non-human animal and humans studies have demonstrated that MDMA is a 5-HT agonist. Acutely MDMA causes a range of desired and undesired physical and psychological effects (De La Torre et al. 2000; Kalant, 2001). Both the acute and long lasting effects of MDMA in non-human animals can be attributed to the action of 5-HT within the brain including the well-documented 'serotonin-syndrome', which can be observed in both humans and non-human animals (Parrott, 2000; Ricaurte et al. 2000a, 2000b, 2000c). It could therefore be argued that if the short-term acute effects of MDMA are similar between non-human animals (rats, mice, monkeys) and humans, it is plausible to suggest that there will be similarities with the long-lasting effects of MDMA between non-human animals and humans. There is considerable debate concerning the practicality of predicting MDMA induced neurotoxicity in humans based on results from non-human animal studies. The majority of the research on the long lasting effects of MDMA comes from non-human animal studies: rats (Battaglia et al. 1987a, 1987b; Battaglia, 1988), mice (Logan et al. 1988), dogs (Ricaute et al. 1988), and primates (Ricaute et al. 1988). To date there is questionable debate concerning its relevance to human users, since neuronal toxicity research indicates that the level of damage can vary from one species to another (Green et al. 1995; Ricaurte et al. 2000a, 2000b, 2000c). Presently the strongest evidence indicating that humans are affected in the same way as non-human animals comes from comparing humans and non-human primates including monkeys via the 'interspecies scale' (Ricaurte et al. 2000a, 2000b). Most non-human animal studies of MDMA neurotoxicity involve systematic administration of MDMA twice daily for 4 consecutive days. In comparison, humans typically use MDMA orally, and although they may use up to 10 doses of MDMA per night, however MDMA polydrug users will seldom abuse MDMA on 4 consecutive days. Encouragingly further evidence comes from a study using non-human primates that was administered a single 5mg dose of MDMA, which has resulted in significant 5-HT neurotoxicity. The dose administered is comparable to doses typically abused by a frequent MDMA polydrug user, if not considerably less than that used by humans (Ricaurte et al. 1988; Ricaurte et al. 2000a, 2000b). Recently, the amount of MDMA generally found in a tablet of ecstasy is between 80-150mg (Schifano, 1991; Parrott,

2000) with some reports suggesting tablets can contain up to 350mg of MDMA (www.dancesafe.org/labtesting). Amongst scientists today, there is an accepted theory that smaller species require higher doses of a toxic drug to achieve equivalent drug effects, being predicted by the interspecies scaling. This method utilises known relations between body mass/surface area and accounts for differences in drug clearance (Green et al. 2003). Using such a technique it is possible to predict doses of MDMA, which would be neurotoxic to humans based on doses that are neurotoxic to either rats or monkeys. Applying the known neurotoxic dose of 5 mg/kg in a 1-kg squirrel monkey, the equivalent dose in humans is predicted at 1.28 mg/kg or approximately 96mg in a 75 kg human (Ricaurte et al. 2000a, 2000b). Human MDMA users typically use a single dose of 75-125 mg of MDMA, which falls into the neurotoxic range predicted by the interspecies scaling method (O'Shea et al. 1998; Ricaurte et al. 2000a, 2000b). This formula suggests that the doses administered in non-human primate studies are comparable to those abused by recreational MDMA polydrug users. In addition, studies have demonstrated that the larger animals are more susceptible to the neurotoxic effects of an administered dosage of a drug than a smaller animal. These studies have demonstrated that primates are more susceptible to MDMA neurotoxicity than rats, which in turn is more susceptible than mice (Green et al. 1995). Primate studies have concluded that non-human primates are more sensitive to the neurotoxic effects of MDMA, and may not recover from MDMA induced 5-HT neuronal injury, especially after several lesions (Hatzidimitriou et al. 1999). If these interspecies scale findings suggested are correct, it is predicted that MDMA will be substantially more neurotoxic to humans than non-human primates. It is also proposed that even if the damaged human central 5-HT neurones could undergo 'regenerative sprouting' following MDMA exposure, as demonstrated in non-human primates, it is still unknown whether they would regenerate back with normal functioning or consequently result in psychological impairment (Fisher et al. 1995). It is furthermore a well established fact that humans are more susceptible to neurotoxic substances in general than other species including rats or primates. An example would include MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), which is mildly toxic in rats however, extremely toxic in humans (Burns et al. 1983). Suggestions from the interspecies scale and evidence from MPTP indicates that comparable doses of MDMA would be far more neurotoxic to humans in comparison to non-human primates. The debate whether evidence from non-human animal studies can be a predictor of the risk of developing long lasting damage in humans is controversial. Evidence for this argument would include as the acute affects between non-human animals and humans seem to correlate, it is plausible to predict that the long lasting effects of MDMA in non-human animals may be comparable to those occurring in humans.

The results from this study suggest that both past and present MDMA users demonstrate psychological deficits which seem to be long lasting. These results compliment the non-human animal studies that suggest MDMA is a long-lasting selective irreversible neurotoxin to 5-HT.

The present study examined the essential relationship between: MDMA, sleep, impulsivity memory, and depression. The findings found a strong correlation between depression and sleep in addition to a positive association between impulsivity and sleep. Furthermore, the results failed to find a strong correlation between depression and impulsivity. These findings suggest that sleep plays an important role in maintaining baseline levels of depression and impulsivity. These psychological states (sleep, depression and impulsivity) seemed to play an important role in executive functioning and need to be investigated further and monitored in future MDMA studies as they could affect treatment outcome and rehabilitation.

In the current study the findings concerning executive functioning and MDMA were far more complicated (Figures 8.1 and 8.2). These results concluded that MDMA directly effected performance on these three domains of the ToL (planning, solution time and number of errors). The number of trails completed in the ToL was not affected by the direct exposure to MDMA; however correlation and regression analysis suggested depression, memory and impulsivity influenced these scores. This suggested that MDMA directly effects depression, memory and impulsivity, which consequently effects performance on the ToL task being the number of trials. These results were further complicated by exposure to other illicit drugs including cocaine and cannabis. For the total number of errors in the ToL, exposure to cannabis emerged as the main predictor. Cocaine and cannabis affected the performance for the total planning time for the ToL.

For the WCST only the number of trials to 1st category appeared to be effected directly by past and present MDMA exposure (Figure 8.2) as well as other recreational drug including cocaine. The failure to maintain set domain of the WCST was only affected in past MDMA users and seemed to be influenced more by impulsivity and depression scores. This finding could be explained by the normal aging process or alternatively it could suggested that MDMA requires further time before it disrupts the psychological functions. For the other domains of the WCST (% perservative errors, % non-perservative errors, categories completed) the scores were not affected by past nor present MDMA exposure.

The findings from the executive functioning tasks (ToL and WCST) suggests that MDMA induced deficits to executive functioning tasks are more complicated than suggested in previous publicised studies. This may explain the diverse and often differing results obtained from similar cohort studies. Previous studies have failed to measure and control for the many diverse psychological functions (sleep, memory, impulsivity, depression and executive functioning) which could consequently mask the results, producing incorrect conclusions (Figures 8.1 and 8.2). The present study suggests that MDMA seems to influence scores on specific aspects of cognitive functioning. Nonetheless additional factors need to be considered, including the exposure to cannabis, and cocaine in addiction to the influence of the normal aging process.

Additional psychological factors including any deficits in impulsivity, depression, memory and sleep functioning need to be monitored as they appear to play a role in executive functioning performance overall and these results suggest MDMA directly disrupt these functions. Future studies need to target whether MDMA affects memory, impulsivity, depression and sleep which indirectly effects executive abilities. Alternatively MDMA may directly affect performance on executive functions. These two theories need to be further investigated in future research.

This unique study presented investigates the relationship between the various psychological functions and their interactions (Figures 8.1 and 8.2). The results from this novel study indicated that performance on executive functioning tasks (planning and decision making) emerged as dependent on memory ability, depression scores, sleep disturbance and impulsivity scores. From the present findings it could be hypothesised that if MDMA polydrug users failed to demonstrate decreased performance in memory, depression, sleep, and impulsivity they would consequently have little problems with planning and decision making. Comparisons now need to be made between MDMA polydrug users with and without depression, with and without memory disruptions, with and without increased impulsivity and with and without sleep disturbances, whilst measuring their interactions on executive functioning abilities. If this hypothesis is correct then MDMA polydrug users demonstrating lowered depression, increased impulsivity, sleep disturbances and memory scores will report similar deficits with executive functioning tasks. On the other hand MDMA users that fail to demonstrate memory, sleep disturbances, enhanced impulsivity scores, and depression dysfunction will demonstrate no disruptions in executive functioning tasks. This is the

direction that future MDMA induced research needs to take and such studies now need to be completed including non-human animal and human studies.

In summary the findings from the present study indicates that MDMA polydrug users are abusing MDMA at a greater frequency and co-abusing it with other recreational drugs, this exposure of illicit drug(s) may heighten the possible long lasting effects of MDMA. Secondly, MDMA directly affects certain sub-domains of depression, impulsivity, memory, and sleep causing acute and long lasting deficits in past and present MDMA polydrug users. This study found that MDMA caused acute and long lasting disruptions to executive functioning as measured by the ToL and WCST (trials completed, planning, solution, number of errors and on the ToL and trials to first category on the WCST). Finally, this study suggests that MDMA induced psychological consequences are more far complicated than previous publicised studies have indicated. In terms of performance on executive functioning tasks future research needs to investigate the different sub-domains of executive functioning taking into account other illicit drugs (cannabis and cocaine), other psychological functions (heightened depression, enhanced impulsivity, sleep disturbances and memory dysfunction) and finally the normal aging process.

Figure 8.1: Summary of the acute and long lasting consequences of MDMA on psychological functions

A diagram to demonstrate the hypothesised acute and long lasting effects of MDMA on depression, sleep, impulsivity, memory and indirectly effecting the trials completed on the ToL and WCST task. The diagram suggests that MDMA effects cognitive subscale of depression (cognitve-affective subscale), sleep, motor and attention aspects of impulsivity, and memory (subscales being verbal, visual, and delayed) which subsequently indirectly effect perseverative errors (WCST), trials to first category (WCST), failure to maintain set (WCST), number of errors (ToL), planning time (ToL) and solution time (ToL). .
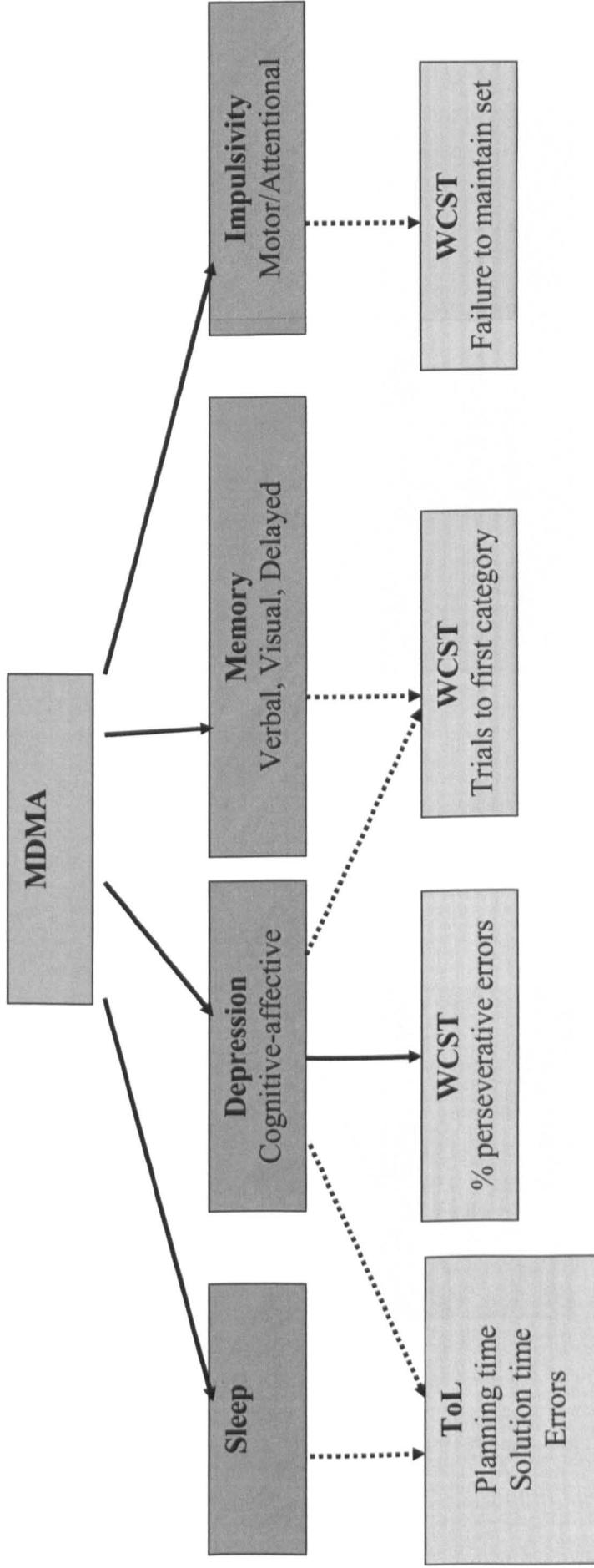
Figure 8.2: Summary of the direct acute and long lasting effects of MDMA on the sub-domains of Tower of London (ToL) and Wisconsin Card Sorting test (WCST).

The diagram demonstrates the acute and long lasting effects of MDMA, on the sub-domains of the ToL (planning, solution time and errors) and WCST (trials to 1st category and maintaining set).

MDMA

WCST

Trials to first category
Failure to maintain set (past users)

ToL

Planning time
Solution time
Errors
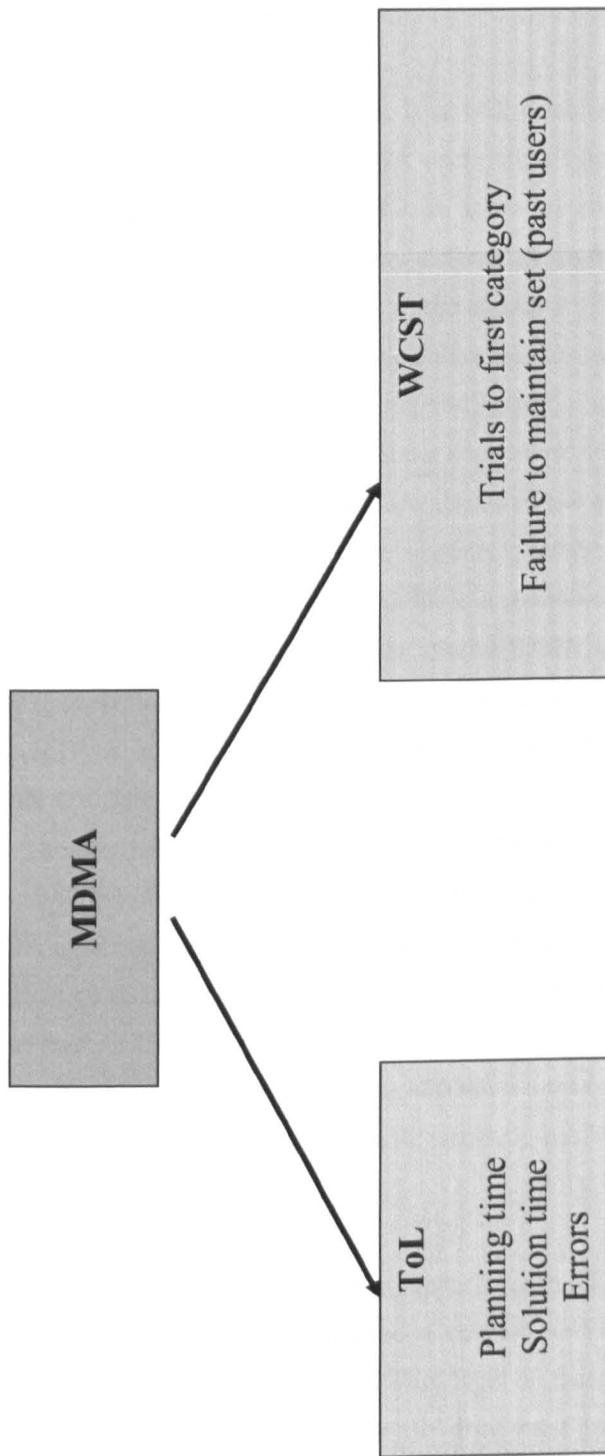
8.2   Limitations

All research has limitations and this study is no exception. It is well established that one major flaw with this type of cohort research is that MDMA users are all polydrug users (Jansen, 1996; Morgan, 1998a; 1999; Schifano et al. 1998). In terms of control groups, previous publicised research has failed to control for the many different types of recreational drugs, making the findings hard to conclude and relate purely to the exposure of MDMA. The results from the present study summarised that the psychological disturbances found were not a results of nicotine, alcohol, cannabis, amphetamine, cocaine, and ketamine exposure. The results can not exclude the possibility that the disturbances found: depression, sleep, memory, impulsivity and executive functioning, were due to MDMA use alone and not a combination of MDMA with other recreational drugs including cannabis, cocaine, ketamine, heroin, and amphetamine. As with previous studies the present study confirms a pseudo-dose response function between MDMA and psychological functioning (the more MDMA consumed the higher the deficit to the psychological function). However, whether this level of psychological functioning can be related to MDMA use alone is arguable (Curran, 2000; Parrott, 2001). It has been well documented that DA may enhance the neurotoxicity of MDMA (McGregor et al. 2003; Milani et al. 2004; Thompson et al. 2004). The majority of polydrug MDMA users in this present study have reported the co-use of MDMA with cannabis, cocaine and amphetamine these are all DA agonists. Secondly, tablet analysis has reported that MDMA tablets show traces of amphetamine (Dancesafe, 2004). Non-human animal studies would be advantageous to compare the level of brain 5-HT neurotoxicity between MDMA alone and MDMA with a DA agonist. Finally, future research addressing MDMA neurotoxicity needs to bare this in mind and possibly compare MDMA users with those whom co-use MDMA with a dopamine agonist.

A further criticism for this type of research is whether the participant was exposed to MDMA, and the exact amount of lifetime exposure. It is an imprecise method having to rely on participants self-reported accounts of their drug history. This type of data collection is required, since it is unethical for researchers to administer the drug itself to participants. MDMA for recreational use is produced in 'backstreet' laboratories with no constraints on the substances used to make the MDMA tablet. Consequently, the user may not be aware of the exact content of the tablet and the possibility of taking a so-called ecstasy/MDMA tablet, which is a mixture of several psychoactive substances. Amphetamine, MDA and MDEA drug mixtures have been reported mixed with non-amphetamine substances like caffeine, ephedrine, and/or ketamine (Parrott, 2004). However, toxicology reports between the period late 1990s and early 2000s suggest the majority of MDMA tablets contain between 90-100%

MDMA (Parrott, 2004). A possible way of alleviating this problem would be to do longitudinal studies; where the participant is monitored over a long period of time being routinely examined and monitored. Regrettably such a study would be time consuming, financially costly and could be warranted unethical, since MDMA is an illegal drug of abuse. Post-mortem analysis would be beneficial in establishing the percentage of degeneration of 5-HT in past and present MDMA users. However, often such techniques are often complicated by factors such as the cause of death and suicide, the length of time between death and post-mortem analysis which can affect the results.

This study relied on self-reported measures including sleep, impulsivity and depression scores. It should be kept in mind that all self-report inventories are subject to response bias. Consequently, some individuals may report increased symptoms resulting in inaccurately higher scores. Participants may try to deny symptoms resulting in lowered scores. One particular reason for this may be due to the current media attention on MDMA and its affects on mood. Results would be accurate if a measure of depression could be obtained that does not rely on participants self-reports. A study by Fox, 2001 investigated the subjective accounts of cognitive decline associated with MDMA use. They asked three groups of participants: those that felt lower cognitive functioning was due to MDMA use, those that experienced no cognitive problems but used MDMA and non-MDMA control group. The results found that both the MDMA groups exhibited similar cognitive deterioration in comparison to non-MDMA control group. The author concluded that most MDMA users were not aware of the cognitive damage that MDMA was causing (Fox et al. 2001). The present study found that the majority of MDMA users were unaware of the reduced psychological and biological effects in particular depression, and sleep disturbances. Future studies need to use alternative methods for measuring psychological performance other than self-reported measures. Self-reported measures can be considered to be very unreliable as the participant is required to rely on their memory. Future studies need to rely on measured psychological and cognitive tests. However, it should be noted that all self-reported questionnaires employed in this study had undergone extensive validity and reliability testing and are constantly used in both the clinical and for research purposes.

The issue of interpretation of causality is a major problem within the field of recreational drug research. It is very difficult to prove in human studies whether the cause of the deficiency in psychological functioning was due to exposure to a recreational drug, or whether the deficit already existed beforehand with the individual deciding to use the recreational drug as a form of self-medication (McCann & Ricaurte, 1991; McGuire et al. 1994; Morgan, 2000). MDMA is a 'class A' scheduled illegal drug; consequently it is very difficult to assess both its acute

and long-term effects using the more traditional methodologies of double-blind techniques; randomly allocating participants to either a placebo/active drug condition. There have, however, been a limited number of studies which have administered low doses of MDMA (Vollenweider et al. 1998; Curran, 2000). Unfortunately, the problem persists that it is unethical to repeatedly administer larger doses of MDMA, a possible neurotoxin, to allow the investigation of possible neurodegeneration of nerves in human participants. As a result the only possible solution is to compare MDMA polydrug users with matched control groups; whom have never abused MDMA, the methodology employed in this study. There are a number of growing case reports in which chronic psychosis and mood disturbance have persisted following MDMA intoxication. Such results suggest a role for MDMA in the onset of psychiatric disorders (McGuire et al, 1994; de Win et al, 2004). Irrespectively of whether the recreational drugs cause cognitive and psychological decline, or, whether poor psychological and cognitive decline attracts recreational drug use, has little bearing on the fact that this study provides evidence that recreational MDMA polysubstance drug users suffer from both psychological and cognitive impairment, which is predicted to get worse with the aging process and will require some form of treatment in the future.

8.3   Future studies

Presently there is a lack of research investigating the psychobiological consequences following abstinence from the drug MDMA. The majority of previously publicised research investigating the psychological consequences of MDMA has investigated the immediate effects of MDMA (Morgan, 2000; Curran, 2000; Parrot, 2001). There are few studies that have begun to investigate MDMA polydrug users that have abstained from MDMA usually ranging from 12 moths to 18 months, however to date no single study has compared present MDMA users with past MDMA users that have abstained for more than 5 years (Morton, 2005). Additionally, non-human animal studies have demonstrated that selective brain damage caused by MDMA is non-repairable even after 7 years (Fisher et al. 1995). These non-human primate findings raise the question whether similar patterns of neurotoxicity are occurring in past MDMA polydrug users. The present study is novel in the fact it makes a comparison between present and past polydrug MDMA users. Evidence from human imaging studies is slowly emerging demonstrating that there is a neurotoxic effect of MDMA upon 5-HT. The link between reduced SERT and previous MDMA users was reported using PET (McCann et al. 1998; Cowan, 2007), SPECT (Reneman et al, 2001; Cowan, 2007) and finally levels of 5-HIAA in CSF (Bolla et al. 1998). These studies now need to be replicated and continued using similar techniques (PET and SPECT) controlling for levels of depression,

memory, impulsivity and sleep disturbances when investigating executive dysfunction between non-MDMA users, present and past MDMA users.

One further question that has not been answered by the present study and warrants further investigation, is the issue of whether it can be concluded that MDMA ingestion causes direct psychological and cognitive impairments or whether MDMA polydrug users suffer from these psychological impairments beforehand, thus seeking MDMA as a means of self-medication (Curran, 2000; Parrot, 2001). Does the psychological problems (memory, depression, impulsivity, executive functioning, and sleep) cause individuals to take MDMA in order to eliminate the already established decline in psychological functioning? Alternatively do individuals with normal baseline psychological functioning levels take MDMA, which consequently results in a lowered level of psychological ability due to neurotoxicity? Research investigating drug use has been split into two separate areas. One of these suggests that people that use drugs of abuse have neuropsychological alterations prior to drug use which makes them vulnerable to drugs and can also act as a causal factor for consuming the illicit drugs (Verheul, 2001). On the other hand there has been ample research investigating the long lasting effects of using recreational drugs as already discussed in depth in previous chapters (Curran, 2000; Parrot, 2001). These studies have proposed that drugs like alcohol, cannabis, cocaine, amphetamines, methamphetamines and opioids all have detrimental effects on numerous psychological and cognitive processes (refer to chapter 1). One fundamental question that needs answering would be whether the decline in biological and psychological functioning occurs before drug onset or as a consequence of drug use. As yet no single study has provided enough evidence to find a satisfactory conclusion. Previous discussions regarding research investigating acute and long lasting effects of MDMA have been unable to establish the argument of 'cause or effect'. Overall psychological functioning can be difficult to establish. One plausible method to try to over come this 'cause or effect' argument would be to interview close friends and relatives. Secondly, another methodology would involve measuring psychological functioning from first-degree relatives to see if there are any similarities between family members and the MDMA polydrug user. If the decline in psychological functioning is due to genetics then it would be hypothesised that a similar pattern would be observable across the immediate family (Silberg et al. 1990; Eley et al. 1999).

Experimental studies have demonstrated that when rats are administered MDMA in crowded conditions and have a lack of water they are more susceptible to neuronal damage than rats administered MDMA alone with ample water. Such studies suggest that crowded conditions, loud noise and lack of water can extenuate the 5-HT damage caused by MDMA (Cornish et

al. 2003). All MDMA participants from the present study reported consuming MDMA in company including night-clubs. Non-human animal data suggests individual's exposing themselves to MDMA at night-clubs and raves are more likely to suffer psychological damage in comparison to an individual that has consumed it in a quiet spacious environment. Future studies need to investigate the different environmental settings in MDMA drug users and the level of MDMA induced psychological dysfunction.

Additional issues which need to be addressed in future research includes investigating the total amount of MDMA consumed on a single occasion and the age of initial exposure of MDMA with the level of psychological problems (depression, sleep, memory, impulsivity and executive functioning) (Green et al. 2004). Non-human animal studies propose the amount of psychological damage is associated with the age of initial exposure and frequency of drug use (De Win et al. 2004). There is currently no published research investigating the age of onset of MDMA exposure and the level of psychological disruption. Studies have found that brain maturation normally occurs around mid-twenties particularly the frontal lobe (Parrott, 2000) and research has also suggested that before this time of maturation of the brain, the brain can be more vulnerable to toxins. If young drug adolescences are abusing possible 'neurotoxic' drugs like MDMA before this brain maturation period occurs it is hypothesised that such individual's are increasing the chance of brain damage and psychological disturbance (memory, depression, sleep, impulsivity and executive functioning). Future studies including non-human animal studies should address this matter further. As yet there is currently limited data investigating the initial age of exposure to MDMA and the level of long lasting psychological damage. Future studies need to investigate the age of initial use of MDMA and dosage, brain maturation and finally the level of long lasting psychological damage.

Future research needs to investigate whether MDMA can affect embryos in terms of a pregnant mother being exposed to MDMA. Broening et al, 2001 investigated the effects of MDMA on the developing brain of a rat. Neonatal rats were administered MDMA on either days 1-10 or 11-20. These time intervals correspond with early and late human trimester brain development. MDMA affected body weight gain during treatment. MDMA for the 11-20 day group of rats resulted in impairments in learning and memory, in comparison to these rats given MDMA at 1-10 days. Further investigation is needed investigating exposure of MDMA to embryos during late and early trimester brain development and any level of neurotoxicity including any possible psychological deficits (Broening et al. 2001).

Due to the recent media coverage of MDMA there has been an influx of health information available suggesting the safety precautions required when taking MDMA. If future research

can find ways to avoid this possible 'neurotoxicity' and probable long lasting psychological damage safety precautions can be published, so MDMA users can protect themselves. Non-human animal studies have employed drug discrimination techniques where rats are able to detect MDMA from other substances (Virden & Baker, 1999). In one study the rats were given either MDMA plus saline or MDMA plus fluoxetine, a SSRI. Post mortem results found that rats given MDMA plus saline had significantly reduced 5-HT levels in the prefrontal cortex in comparison to the MDMA plus fluoxetine rats (Virden & Baker, 1999). This study highlights the possibility of drugs like SSRIs providing a protection from possible MDMA induced damage. The co-administration of fluoxetine with MDMA given to rats resulted in brain 5-HT levels remaining the same as the control rats (Curran, 2000). To date these results have not been replicated in humans. These drugs need to be further investigated as the possibility that co-using MDMA with a SSRI may decrease the extent of psychological damage caused by MDMA use could be beneficial. If MDMA causes long lasting depression, memory, impulsivity, sleep and cognitive disturbances as the present study implies it is possible that in 20-30 years time past MDMA polydrug users will be suffering from psychological deficits requiring treatment and therapy. It has been debated that MDMA may have therapeutic benefits in particular as a possible treatment option for psychiatric disorders. It may be that if MDMA can be administered safely with no adverse brain neurotoxicity and long lasting psychological deficits it may subsequently be used medically/therapeutically.

An important issue raised following the outcome of this study surrounds the age of the past MDMA users. The past MDMA users in this study ranged between the ages 30-40 years old. They would not be deemed as an elderly sample. Nonetheless, with the normal aging process it could be argued that to exposure to MDMA may result in premature aging in terms of depression, cognitive dysfunctions, memory deficits, and sleep disturbances. These psychological problems are often heightened in the elderly. MDMA may cause acceleration to the normal aging process and dementia. In addition past and present MDMA polydrug users may become more susceptible to neurodegenerative disorders resulting in early onset. These would include early onset of Parkinson's disease and Alzheimer's disease (Frey et al. 1996; Huges et al. 2004; Kish et al. 2010; Kuniyoshi et al. 2003; Parrott et al. 2003). Particularly, as these neurological disorders have frequently been associated with memory, sleep, impulsivity and mood disturbances. Thus further research is required addressing this issue, with particular attention paid to those with family history of neurodegenerative disorders.

Non-human animal studies have demonstrated that Parkinson's disease symptoms will only manifest if more than 80% of neuronal damage has occurred (Frey et al. 1996; Huges et al. 2004; Kish et al. 2010; Kuniyoshi et al. 2003; Parrott et al. 2003). It could be argued that a

similar pattern of neuronal damage is required with MDMA polydrug users. This would mean that in order for MDMA polydrug users to show psychological disruption a certain degree of degeneration of 5-HT neurons would be required. Previous non-human animal research has found that rats exposed to MDMA fail to demonstrate behavioural deficits; however brain 5-HT neurotoxicity was evident (Parrott et al. 2000). Hence, this could be the reason that there are currently inconsistencies, in terms of results in previous MDMA research. It could be suggested that those MDMA polydrug users in previous studies demonstrating little psychological deficits still have neuronal damage. In addition it could be argued that a proportion of individuals might be more prone to degeneration and neurodegenerative disorders than others thus making them more susceptible to MDMA induced damage. Non-human animal studies would be particularly advantageous in providing accurate answers in terms of investigating possible genetic links.

One area that may need further exploration is the role of cortisol in memory, executive functioning, sleep, depression and impulsivity (Parrot, 2009). It has been clearly demonstrated that cortisol via the HPA (hypothalamo-pituitary-adrenal) axis plays an important role in regulating core psychobiological functions (Lovallo, 1997). Human laboratory studies have demonstrated that MDMA causes significant acute increases in cortisol levels (De la Torre et al. 2000; Dumont & Verkes, 2006; Parrot et al. 2009). Furthermore additional studies have demonstrated that chronically, prolonged use of MDMA can result in a reduced cortical HPA axis response (Gerra et al. 2003). The authors concluded that this HPA basal hyper activation and reduced responsiveness to stress may represent a complex neuroendocrine dysfunction associated with MDMA use. It could be proposed that cortisol and other neurohormones including: prolactin, luteinizing hormone, oestradiol, follicle-stimulating hormone, progesterone and growth hormone; need to be investigated in future research for their role as possible modulatory factor(s) for MDMA.

The field of behavioural genetics has received a substantial amount of attention over the last decade (Eley & Stevenson, 1999). A discipline with numerous unanswered questions is the role of genetics within the area of drug addiction (Soar et al. 2001). Do people take drugs because it is in their genes? Do they lack and/or have certain characteristics that have been passed to them via genes through different generations; for example due to a mutation, or the process of natural selection? Future MDMA related neurotoxicity research needs to start addressing the involvement of genetics, finding answers to these unrequited questions. Approximately, 10% of the population are deficient in the enzyme that is involved in the demethyylation of MDMA, known as debrisoquine hydroxylase, coded by the gene CYP2D6 (Tucker et al. 1994). This enzyme slows down the metabolism of MDMA. It is therefore

proposed that individuals low deficient in this enzyme maybe at greater risk for the acute and long lasting consequences of MDMA (Tucker et al. 1994; Parrot, 2001).

Although this thesis is dominantly focussed on 5-HT, it is recognised that 5-HT is ubiquitous in its distribution within the CNS. It is involved in all functional systems and their regulation/control. 5-HT neurons innervate virtually every part of the CNS and play a dominating role in modulating all other neurotransmitters, it is reasonable to conclude that if MDMA is a selective 5-HT neurotoxin (Curran, 2000; Parrot, 2001), all cognitive and psychological functions other than those specifically associated with 5-HT, will be affected by MDMA exposure. Future non-human animal studies need to include a combination of *in vitro* and *in vivo* studies the role of MDMA on additional neurotransmitters other than 5-HT. Secondly, future studies need to investigate the effects of MDMA on other psychological functions other than those linked to 5-HT.

8.4   Summary of thesis

To date, the study presented is the single largest and most robust research investigating the 'long lasting neurotoxic effects of MDMA' on psychological performance and functioning. This study demonstrates that during the period 2001-2007 MDMA was a recreational drug abused by a diverse population. Present MDMA polydrug users are likely to be increasing the risk of MDMA induced neurotoxicity due to the increased frequency and pattern of use including co-using with other illicit drugs. In addition the results found that frequently using MDMA resulted in long lasting damage to the psychological functioning including overall sleep disturbances, memory deficits (visual, verbal and delayed), depression (cognitive-affective sub-domain) and heightened impulsivity trait (motor and attention sub-domains). MDMA may directly effect executive functioning as measured by planning on ToL, solution time on ToL, number of errors on ToL and trials to 1st category, failure to maintain set on the WCST. Alternatively, MDMA may indirectly effect executive functioning by affecting sub-domains of depression, memory, impulsivity and sleep, which consequently effect trials completed, planning time, solution time and errors on the ToL and trials to first category, failure to maintain set on WCST. This study found that these psychological problems were similar between past and present MDMA polydrug users, suggest MDMA causes acute and long lasting psychological deficits. It is predicted that this MDMA induced psychological deficits combined with the normal aging process will cause problems in later life affecting all areas of daily living including social, family and employment. Both past and present MDMA users, as well as, health professionals need to be educated and warned about the possible long lasting dangers of using MDMA and the help available for those that may need it.

Reference List

Aldridge J, Parker H and Measham F. (1998). Illegal Leisure: The Normalisation of Adolescent Recreational Drug Use. London: Routledge.

Aldridge J. (2008). Decline but no fall? New millennium trends in young people's use of illegal and illicit drugs in Britain. Health education; 108 (3); 189-206

Alciati A, Scaramelli B, Fusi A, Butteri E, Cattaneo ML, Mellado C. (1999). Three cases of delirium after "ecstasy" ingestion. J Psychoactive Drugs; 31(2):167-70.

Alexopoulos GS. (2004). Role of executive function in late-life depression. J Clin Psychiatry; 64 Suppl 14:18-23. Review.

Ali SF, Jairaj K, Newport GD, Lipe GW, Slikker W Jr (1990). Thallium intoxication produces neurochemical alterations in rat brain. Neurotoxicology; 11(2):381-90.

Allain H, Bentué-Ferrer D, Akwa Y. (2007). Treatment of the mild cognitive impairment (MCI). Hum Psychopharmacol; 22(4):189-97. Review.

Allen RP, McCann UD, Ricaurte GA (1993). Persistent effects of (+/-)3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") on human sleep. Sleep; 16(6):560-4.

Alvarenga TA, Andersen ML, Ribeiro DA, Araujo P, Hirotsu C, Costa JL, Battisti MC, Tufik S (2010). Single exposure to cocaine or ecstasy induces DNA damage in brain and other organs of mice. Addict Biol; 15(1):96-9.

American Psychiatric Association, 2000 at <http://www.psych.org>

Anderson C, Horne JA. (2003). Electroencephalographic activities during wakefulness and sleep in the frontal cortex of healthy older people: links with "thinking". Sleep; 26(8):968-72.

Back-Madruga, C, Boone, K.B, Chang, L, Grob, C.S, Lee, A, Nations, H. & Poland, R.E. (2003). Neuropsychological effects of 3,4-methylenedioxymethamphetamine (MDMA or ecstasy) in recreational users. Clinical Neuropsychology; 17(4), 446-59.

Baca-García E, Salgado BR, Segal HD, Lorenzo CV, Acosta MN, Romero MA, Hernández MD, Saiz-Ruiz J, Fernandez Piqueras J, de Leon J. (2005). A pilot genetic study of the continuum between compulsivity and impulsivity in females: the serotonin transporter promoter polymorphism. Prog Neuropsychopharmacol Biol Psychiatry; 29(5):713-7.

Bäckman L, Lindenberger U, Li SC, Nyberg L. (2010). Linking cognitive aging to alterations in dopamine neurotransmitter functioning: recent data and future avenues. Neurosci Biobehav Rev; 34(5):670-7.

Baddeley A. (1986). Modularity, mass-action and memory. Q J Exp Psychol A; 38(4):527-33.

Baddeley, A.D., & Hitch, G. (1974). Working memory. In G.H. Bower (Ed.), The psychology of learning and motivation: Advances in research and theory (Vol. 8, pp. 47–89). New York: Academic Press.

Balster et al. (1988) Pharmacological effects of cocaine relevant to its abuse. NIDA Res Monogr; 88:1-13. Review.

Balogh, B, Molnar, E, Jakus, R, Quate, L, Olverman, H.J, Kelly, P.A, Kantor, S, Bagdy, G. (2004). Effects of a single dose of 3,4-methylenedioxymethamphetamine on circadian patterns, motor, activity and sleep in drug-naïve and rats previously exposed to MDMA. Psychopharmacology; 173(3-4), 296-309.

Baker HF, Ridley RM, Harder JA. (1996). Neurochemical modulation of the hippocampus in learning, remembering and forgetting in primates. Neurodegeneration; 5(4):467-71. Review.

Bankson MG, Yamamoto BK. (2004) Serotonin-GABA interactions modulate MDMA-induced mesolimbic dopamine release. J Neurochem; 91(4):852-9.

Battaglia G, Yeh SY, O'Hearn E, Molliver ME, Kuhar MJ, De Souza EB. (1987). 3,4-Methylenedioxymethamphetamine and 3,4-methylenedioxyamphetamine destroy serotonin terminals in rat brain: quantification of neurodegeneration by measurement of [3H]paroxetine-labeled serotonin uptake sites. J Pharmacol Exp Ther; 242(3):911-6.

Battaglia G, Yeh SY, De Souza EB. (1987). MDMA-induced neurotoxicity: parameters of degeneration and recovery of brain serotonin neurons. Pharmacol Biochem Behav; 29(2):269-74.

Battaglia G, Brooks BP, Kulsakdinun C, De Souza EB. (1988). Pharmacologic profile of MDMA (3,4-methylenedioxymethamphetamine) at various brain recognition sites. Eur J Pharmacol; 149(1-2):159-63.

Barratt E.S, Patton JH. (1983). Factor structure of the Barratt impulsiveness scale. J Clin Psych; 51 (6): 768-74.

Barratt E. S. (1985). Impulsiveness subtraits: Arousal and information processing. In J. T. Spence and C. E. Izard (Eds.), Motivation, Emotion and Personality (pp. 137-146). Elsevier Science, North Holland.

Beck A.T., Ward C., Mendelson M. (1961). Beck Depression Inventory (BDI). Arch Gen Psychiatry; 4: 561-571.

Beck AT, Kovacs M, Weissman A. (1975). Hopelessness and suicidal behavior. An overview. JAMA; 234(11):1146-9.

Beck A.T. (1988). Beck Hopelessness Scale. The Psychological Corporation.

Beck, A. T., R. A. Steer, and G. M. Garbin. (1988) "Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation." Clinical Psychology Review; 8: 77-100.

Beck AT and Weishaar ME (1990). Suicide risk assessment and prediction. Crisis; 11(2):22-30.

Bedi G, Redman J. (2008). Ecstasy use and higher-level cognitive functions: weak effects of ecstasy after control for potential confounds. Psychol Med; 38(9):1319-30.

Bedi G, Redman J. (2009). Metamemory in recreational ecstasy polydrug users: what do self-reports of memory failures mean? J Psychopharmacol; 22(8):872-81.

Berman KF, Ostrem JL, Randolph C, Gold J, Goldberg TE, Coppola R, Carson RE, Herscovitch P, Weinberger DR. (1995). Physiological activation of a cortical network during performance of the Wisconsin Card Sorting Test: a positron emission tomography study. Neuropsychologia; 33(8):1027-46.

Beyth IJ, Baratta A. (1996). Nutrition and behavior. N J Med; 93(4):45-7.

Bhattachary, S & Powell, J.H. (2001). Recreational use of 3,4- Methylenedioxymethamphetamine (MDMA) or 'ecstasy': evidence for cognitive impairment. Psychological Medicine, 31, 647-658.

Björklund AJ, Emson PC, Gilbert RF, Skagerberg G. (1979). Further evidence for the possible coexistence of 5-hydroxytryptamine and substance P in medullary raphe neurones of rat brain. Br J Pharmacol; 66(1):112P-113P.

Bjork JM, Moeller FG, Dougherty DM, Swann AC, Machado MA, Hanis CL. (2002). Serotonin 2a receptor T102C polymorphism and impaired impulse control. Am J Med Genet; 114(3):336-9.

Blagrove M, Seddon J, George S, Parrott AC, Stickgold R, Walker MP, Jones KA, Morgan MJ (2010). Procedural and Declarative Memory Task Performance, and the Memory Consolidation Function of Sleep, in Recent and Abstinent Ecstasy/Mdma Users. J Psychopharmacol. 8.

Blanchard MM, Mendelsohn D, Stamp JA. (2009). The HR/LR model: Further evidence as an animal model of sensation seeking. Neurosci Biobehav Rev; 33(7):1145-54.

Blessing WW, Seaman B. (2003). 5-hydroxytryptamine(2A) receptors regulate sympathetic nerves constricting the cutaneous vascular bed in rabbits and rats. Neuroscience; 117, 939-948.

Bliss TV, Collingridge GL. (1993). A synaptic model of memory: long-term potentiation in the hippocampus. Nature; 361(6407):31-9. Review.

Biello SM, Dafters RI. (2001). MDMA and fenfluramine alter the response of the circadian clock to a serotonin agonist in vitro. Brain Res; 920(1-2):202-9.

Biezonski DK, Meyer JS. (2010). Effects of 3,4-methylenedioxymethamphetamine (MDMA) on serotonin transporter and vesicular monoamine transporter 2 protein and gene expression in rats: implications for MDMA neurotoxicity. J Neurochem; 112(4):951-62.

Bogen IL, Haug KH, Myhre O, Fonnum F. (2003). Short- and long-term effects of MDMA ("ecstasy") on synaptosomal and vesicular uptake of neurotransmitters in vitro and ex vivo. Neurochem Int; 43(4-5), 393-400.

Bolla KI, McCann UD, Ricaurte GA. (1998). Memory impairment in abstinent MDMA ("Ecstasy") users. Neurology; 51(6):1532-7.

Borbély AA, Trachsel L, Tobler I. (1988). Effect of ritanserin on sleep stages and sleep EEG in the rat. Eur J Pharmacol; 156(2):275-8.

Brown GG, Thompson WK. (2010). Functional brain imaging in schizophrenia: selected results and methods. Curr Top Behav Neurosci; 4:181-214. Review.

Brower, KJ. (2003). Insomnia, alcoholism and relapse. Sleep Med Rev; 7(6):523-39. Review.

Boot, B.P, McGregor, I.S. & Hall, W. (2000). MDMA (Ecsasty) neurotoxicity: assessing and communicating the risks. Lancet, 355, 1818-21

Boys, A, Marsden, J. & Strang, J. (2001). Understanding reasons for drug use amongst young people: a functional perspective. *Health Education Research*, 16(4), 457-469.

Bowyer, J.F, Young, J.F, Slikker, W, Itzak, Y, Mayorga, A.J, Newport, G.D, Ali, S.F, Frederick, D.L. & Paule, M.G. (2003). Plasma Levels of Parent Compound and Metabolites after Doses of Either d-Fenfluramine or d-3,4-Methylenedioxymethamphetamine (MDMA) that Produce Long-Term Serotonergic Alterations. Neurotoxicology; 24, 379-390.

Braida D, Iosuè S, Pegorini S, Sala M. (2005). 3,4 Methylenedioxymethamphetamine-induced conditioned place preference (CPP) is mediated by endocannabinoid system. Pharmacol Res; 51(2):177-82.

Brecht ML. (2002). Differences between Ecstasy-using and nonusing methamphetamine users. J Psychoactive Drugs; 34(2):215-23.

Bremner JD, Randall P, Scott TM, Capelli S, Delaney R, McCarthy G, Charney DS. (1995). Deficits in short-term memory in adult survivors of childhood abuse. Psychiatry Res; 59(1-2):97-107.

Broening HW, Morford LL, Inman-Wood SL, Fukumura M, Vorhees CV. (2001). 3,4-methylenedioxymethamphetamine (ecstasy)-induced learning and memory impairments depend on the age of exposure during early development. J Neurosci; 21(9):3228-35.

Brown J, McKone E, Ward J (2010). Deficits of long-term memory in ecstasy users are related to cognitive complexity of the task. Psychopharmacology (Berl); 209(1):51-67.

Buchert, R, Thomasius, R, Wilke, F, Petersen, K, Nebeling, B, Obrocki, J, Schulze, O, Schmidt, U. & Clausen, M. (2004). A voxel-based PET investigation of the long-term effects of Ecstasy consumption on brain serotonin transporters. American Journal of Psychiatry; (161) 1181-1189.

Buckholtz JW, Treadway MT, Cowan RL, Woodward ND, Li R, Ansari MS, Baldwin RM, Schwartzman AN, Shelby ES, Smith CE, Kessler RM, Zald DH. (2010). Dopaminergic network differences in human impulsivity. Science; 329(5991):532.

Bubeníková V, Votava M, Horácek J, Pálenícek T. (2005). Relation of sex and estrous phase to deficits in prepulse inhibition of the startle response induced by ecstasy (MDMA). Behav Pharmacol; 16(2):127-30.

Butters N, Granholm E. (1988). Associative encoding and retrieval in Alzheimer's and Huntington's disease. Brain Cogn; 7(3):335-47.

Butler GK, Montgomery AM. (2003). Impulsivity, risk taking and recreational 'ecstasy' (MDMA) use. Drug Alcohol Depend; 76(1):55-62.

Butler GK, Montgomery AM (2004). Impulsivity, risk taking and recreational 'ecstasy' (MDMA) use. Drug Alcohol Depend: 76(1):55-62.

Buss and Plomin, 1975 cited in Rowe DC, Plomin R. (1977). Temperament in early childhood. J Pers Assess; 41(2):150-6.

Burns RS, Chiueh CC, Markey SP, Ebert MH, Jacobowitz DM, Kopin IJ. (1983). A primate model of parkinsonism: selective destruction of dopaminergic neurons in the pars compacta of the substantia nigra by N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Proc Natl Acad Sci U S A.; 80(14):4546-50.

Buysee B, Michiels E, Bouillon R, Bobbaers H, Demedts M. (1998). Relief of sleep apnoea after treatment of acromegaly: report of three cases and review of the literature. Eur Respir J; 10(6):1401-4.

Cadet, J.L & Brannock, C. (1998). Free radicals and the pathobiology of brain dopamine systems. Neurochemistry International; 32, 117-131.

Camarero, J, Sanchez, V, O'Shea, E, Green, A.R & Colado, M.I. (2002). Studies, using in vivo microdialysis, on the effect of the dopamine uptake inhibitor GBR 12909 on 3,4-Methylenedioxymethamphetamine ('Ecstasy')-induced dopamine release and free radical formation in the mouse striatum. Journal of Neurochemistry; 81, 961-972.

Camarasa J, Marimón JM, Rodrigo T, Escubedo E, Pubill D. (2008). Memantine prevents the cognitive impairment induced by 3,4-methylenedioxymethamphetamine in rats. Eur J Pharmacol; 589(1-3):132-9.

Cardinal RN, Pennicott DR, Sugathapala CL, Robbins TW, Everitt BJ. (2001). Impulsive choice induced in rats by lesions of the nucleus accumbens core. Science; 292(5526):2499-501.

Carli M, Baviera M, Invernizzi RW, Balducci C. (2006). Dissociable contribution of 5-HT1A and 5-HT2A receptors in the medial prefrontal cortex to different aspects of executive control such as impulsivity and compulsive perseveration in rats. Neuropsychopharmacology; 31(4):757-67.

Carlin, D, Bonerba, J, Phipps, M, Alexander, G, Shapiro, M. & Grafman, J. (2000). Planning impairments in frontal lobe dementia and frontal lobe lesion patients. Neuropsychologia, 38(5), 655-65.

Carlson NR. (2001). Physiology of behaviour. Pearson publishers. 7th Edition.

Carhart-Harris RL, Nutt DJ, Munafò M, Wilson SJ (2009). Current and former ecstasy users report different sleep to matched controls: a web-based questionnaire study. J Psychopharmacol; 23(3):249-57.

Cassidy G, Bannister C, Mohan RN. (1994a). Prevalence, symptom profile, and aetiology of depression in dementia sufferers. J Affect Disord; 29(1):1-6.

Cassidy T, Ballard CG (1994b). Fluctuations in attention: PD dementia vs DLB with parkinsonism. Neurology; 59(11):1714-20.

Chafee MV, Goldman-Rakic PS. (1998). Matching patterns of activity in primate prefrontal area 8a and parietal area 7ip neurons during a spatial working memory task. J Neurophysiol; 79(6):2919-40.

Chapin EM, Andrade R. (2001). A 5-HT(7) receptor-mediated depolarization in the anterodorsal thalamus. II. Involvement of the hyperpolarization-activated current I(h). J Pharmacol Exp Ther; 297(1):403-9.

Chase JE, Gidal BE. (1997). Melatonin: therapeutic use in sleep disorders. Ann Pharmacother.:31(10):1218-26.

Christianson SA, Engelberg E. (1997). Complex memory function for mental trauma. Memory and forgetting are necessary for the emotional adaptation process. Lakartidningen; 94(18):1721-4. Review.

Clarke HF, Walker SC, Dalley JW, Robbins TW, Roberts AC. (2006). Cognitive inflexibility after prefrontal serotonin depletion is behaviorally and neurochemically specific. Cereb Cortex; 17(1):18-27.

Clark L, Roiser JP, Robbins TW, Sahakian BJ. (2009). Disrupted 'reflection' impulsivity in cannabis users but not current or former ecstasy users. J Psychopharmacol; 23(1):14-22.

Climko, R.P, Roehrich, H, Sweeney, D.R, & Al-Razi, J. (1986-1987). Ecstacy: A review of MDMA and MDA. International Journal of Psychiatry in Medicine; 16(4), 359-372.

Chait LD, Fischman MW, Schuster CR. (1985). 'Hangover' effects the morning after marijuana smoking. Drug Alcohol Depend; 15(3):229-38.

Chandler JD, Gerndt J. (1988). Cognitive screening tests for organic mental disorders in psychiatric inpatients. A hopeless task? J Nerv Ment Dis; 176(11):675-81

Chen YT, Chen CY, Chen WJ. (2011). Comparative epidemiology of betel nut use versus ecstasy use among Taiwanese adolescents: findings from a national survey. Drug Alcohol Depend; 113(2-3):177-83.

Chou FH, Lee MB, Lung F, Lin GG, Teng CY, Chung YT, Wang YC, Sun FC. (2011). The relationships between quality of life, psychiatric illness, and suicidal ideation in geriatric veterans living in a veterans' home: a structural equation modeling approach. Am J Geriatr Psychiatry; 19(6):597-601.

Chudasama Y, Robbins TW. (2004). Dopaminergic modulation of visual attention and working memory in the rodent prefrontal cortex. Neuropsychopharmacology; 29(9):1628-36.

Cockburn J. (1995). Performance on the Tower of London test after severe head injury. J Int Neuropsychol Soc; 1(6):537-44.

Cohen J. (1992). A power primer. Psychol Bull; 112(1):155-9.

Cohen RB. (1995). Obstructive sleep apnea: a mandibular positioning device for treatment and diagnosis of an obstruction site. Compend Contin Educ Dent; 16(6): 622-8. Review.

Cohen, Durstewitz D, Seamans JK, Sejnowski TJ. (2000). Dopamine-mediated stabilization of delay-period activity in a network model of prefrontal cortex. J Neurophysiol; 83(3):1733-50.

Cohen, R.S & Cocores, J. (1997). Neuropsychiatric Manifestations Following the Use of 3,4-Methylenedioxymethamphetamine (MDMA: "Ecstasy"). Prog Neuro-Psychopharmacol & Biol Psychiat, 21, 727-734.

Cohen GD. (1998). Aging. To sleep, perchance to dream. Am J Geriatr Psychiatry; 6(2):93-6.

Cornish, J.L., Shahnawaz, Z., Thompson, M.R., Wong, S., Morley, K.C., Hunt, G.E. & McGregor, I.S. (2003). Heat increases 3,4-methylenedioxymethamphetamine self-administration and social effects in rats. European Journal of pharmacology, 482(1-3), 339-41.

Colbron S, Jones M, Biello SM. (2002). MDMA alters the response of the circadian clock to a photic and non-photic stimulus. Brain Res; 956(1):45-52.

Cole, J.C, Sumnall, H.R. & Wagstaff, G.F. (2002). What is a dose of ecstasy? Journal of Psychopharmacology, 16(2), 189-191.

Commins DL, Vosmer G, Virus RM, Woolverton WL, Schuster CR, Seiden LS. (1987). Biochemical and histological evidence that methylenedioxymethylamphetamine (MDMA) is toxic to neurons in the rat brain. J Pharmacol Exp Ther; 241(1):338-45.

Cornish JL, Shahnawaz Z, Thompson MR, Wong S, Morley KC, Hunt GE, McGregor IS. (2003). Heat increases 3,4-methylenedioxymethamphetamine self-administration and social effects in rats. Eur J Pharmacol; 482(1-3):339-41.

Conductier, G. Crosson, C, Hen, R, Bockaert, J. & Compan, V. (2005). 3,4-N-Methlenedioxymethphetamine-Induced Hypophagia is Maintained in 5-HT Receptor Knockout Mice, but Suppressed by the 5-HT Receptor Antagonist RS102221. Neuropsychopharmacology, 30, 1056-1063.

Cowan RL. (2007). Neuroimaging research in human MDMA users: a review. Psychopharmacology (Berl); 189: 539-556.

Cowen T, Woodhoo A, Sullivan CD, Jolly R, Crutcher KA, Wyatt S, Michael GJ, Orike N, Gatzinsky K, Thrasivoulou C. (2003). Reduced age-related plasticity of neurotrophin receptor expression in selected sympathetic neurons of the rat. Aging Cell; 2(1):59-69.

Cowan RL, Joers JM, Dietrich MS. (2009). N-acetylaspartate (NAA) correlates inversely with cannabis use in a frontal language processing region of neocortex in MDMA (Ecstasy) polydrug users: a 3 T magnetic resonance spectroscopy study. Pharmacol Biochem Behav; 92(1):105-10.

Cox DE. (1993). 'Rave' to the grave. Forensic Sci Int; 60(1-2):5-6.

Creighton FJ, Black DL, Hyde CE. (1991). 'Ecstasy' psychosis and flashbacks. Br J Psychiatry; 159:713-5.

Crockett MJ, Clark L, Hauser MD, Robbins TW. (2010). Serotonin selectively influences moral judgment and behavior through effects on harm aversion. Proc Natl Acad Sci U S A; 107(40):17433-8.

Croft, R.J, Mackay, A.J, Mills, A.T.D & Gruzelier, J.G.H. (2001). The relative contributions of ecstasy and cannabis to cognitive impairment. Psychopharmacology; 153, 373-379.

Crossen JR, Wiens AN. Johnstone B, Callahan CD, Kapila CJ, Bouman DE. (1988). The comparability of the WRAT-R reading test and NAART as estimates of premorbid intelligence in neurologically impaired patients. Arch Clin Neuropsychol; 11(6):513-9.

Curran HV, Travill RA. (1997). Mood and cognitive effects of +/-3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'): week-end 'high' followed by mid-week low. Addiction; 92(7):821-31.

Curran, H.V. (2000). Is MDMA ('Ecstasy') Neurotoxic in Humans? An Overview of Evidence and of Methodological Problems in Research. Neuropsychobiology; 42, 34-41

Curran, H.V. & Verheyden, S.L. (2003). Altered response to tryptophan supplementation after long-term abstention from MDMA (ecstasy) is highly correlated with human memory function. Psychopharmacology; 169(1), 91-103.

Curzon G, Hutson PH, Kantamaneni BD, Sahakian BJ, Sarna GS. (1985). 3,4-Dihydroxyphenylethylamine and 5-hydroxytryptamine metabolism in the rat: acidic metabolites in cisternal cerebrospinal fluid before and after giving probenecid. J Neurochem; 45(2):508-13.

Curzon G, Kennett GA. (1990). M-CPP: a tool for studying behavioural responses associated with 5-HT1c receptors. Trends Pharmacol Sci; (5):181-2. Review.

Dafters RI, Duffy F, O'Donnell PJ, Bouquet C. (1999). Level of use of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) in humans correlates with EEG power and coherence. Psychopharmacology (Berl); 145(1):82-90.

Dafters RI. (2001). Impulsivity, inhibition and negative priming in ecstasy users. Addict Behav; 31(8):1436-41.

Dafters RI, Hoshi R, Talbot AC. (2004a). Contribution of cannabis and MDMA ("ecstasy") to cognitive changes in long-term polydrug users. Psychopharmacology (Berl); 173(3-4):405-10.

Dafters RI, Duffy F, O'Donnell PJ, Bouquet C. (2004b). Level of use of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) in humans correlates with EEG power and coherence. Psychopharmacology (Berl); 145(1):82-90.

Daumann J, Schnitker R, Weidemann J, Schnell K, Thron A, Gouzoulis-Mayfrank E. (2003). Neural correlates of working memory in pure and polyvalent ecstasy (MDMA) users. Neuroreport; 14(15):1983-7.

Daumann J Jr, Fischermann T, Heekeren K, Thron A, Gouzoulis-Mayfrank E. (2004). Neural mechanisms of working memory in ecstasy (MDMA) users who continue or discontinue ecstasy and amphetamine use: evidence from an 18-month longitudinal functional magnetic resonance imaging study. Biol Psychiatry; 56(5):349-55.

Daumann J, Fischermann T, Heekeren K, Henke K, Thron A, Gouzoulis-Mayfrank E. (2005). Memory-related hippocampal dysfunction in poly-drug ecstasy (3,4-methylenedioxymethamphetamine) users. Psychopharmacology (Berl). 2005 Aug;180(4):607-11.

Daniulaityte R, Falck R, Wang J, Carlson RG, Leukefeld CG, Booth BM. (2010). Predictors of depressive symptomatology among rural stimulant users. J Psychoactive Drugs; 42(4):435-45.

Diamantopoulou S, Rydell AM, Thorell LB, Bohlin G. (2007). Impact of executive functioning and symptoms of attention deficit hyperactivity disorder on children's peer relations and school performance. Dev Neuropsychol; 32(1):521-42

Darvesh, A.S, Yamamoto, B.K. & Gudelsky, G.A. (2005). Evidence for the involvement of nitric oxide in 3,4-methylenedioxymethamphetamine-induced serotonin depletion in the rat brain. Journal of pharmacology and experimental therapeutics; 312(2), 694-701.

Daza-Losada M, Rodríguez-Arias M, Aguilar MA, Miñarro J. (2009). Acquisition and reinstatement of MDMA-induced conditioned place preference in mice pre-treated with MDMA or cocaine during adolescence. Addict Biol; 14(4):447-56.

Daza-Losada M, Rodríguez-Arias M, Maldonado C, Aguilar MA, Guerri C, Miñarro J. (2009). Acute behavioural and neurotoxic effects of MDMA plus cocaine in adolescent mice. Neurotoxicol Teratol; 31(1):49-59.

De la Torre R, Farré M, Roset PN, Lopez CH, Mas M, Ortuño J, Menoyo E, Pizarro N, Segura J, Camí J. (2000). Pharmacology of MDMA in humans. Ann N Y Acad Sci; 914:225-37.

De la Torre, R, Farre, M, Roset, P.N, Pizarro, N, Abanades, S, Segura, M, Segura, J. & Cami, J. (2004). Human pharmacology of MDMA: Pharmacokinetics, metabolism and disposition. Therapeutic Drug Monitoring; 26(2), 137-144.

De Sola S, Tarancón T, Peña-Casanova J, Espadaler JM, Langohr K, Poudevida S, Farré M, Verdejo-García A, de la Torre R. (2008a). Auditory event-related potentials (P3) and cognitive performance in recreational ecstasy polydrug users: evidence from a 12-month longitudinal study. Psychopharmacology (Berl); 200(3):425-37.

De Sola Llopis S, Miguelez-Pan M, Peña-Casanova J, Poudevida S, Farré M, Pacifici R, Böhm P, Abanades S, Verdejo García A, Langohr K, Zuccaro P, de la Torre R. (2008b). Cognitive performance in recreational ecstasy polydrug users: a two-year follow-up study. J Psychopharmacol; 22(5):498-510.

De Win MM, Reneman L, Reitsma JB, den Heeten GJ, Booij J, van den Brink W. (2004). Mood disorders and serotonin transporter density in ecstasy users--the influence of long-term abstention, dose, and gender. Psychopharmacology (Berl); 173(3-4):376-82.

De Win MM, Schilt T, Reneman L, Vervaeke H, Jager G, Dijkink S, Booij J, van den Brink W. (2006). Ecstasy use and self-reported depression, impulsivity, and sensation seeking: a prospective cohort study. J Psychopharmacol; 20(2):226-35

De Win MM, Jager G, Booij J, Reneman L, Schilt T, Lavini C, Olabarriaga SD, den Heeten GJ, van den Brink W. (2008). Sustained effects of ecstasy on the human brain: a prospective neuroimaging study in novel users. Brain; 131(Pt 11):2936-45.

De Wit J, Sylwestrak E, O'Sullivan ML, Otto S, Tiglio K, Savas JN, Yates JR 3rd, Comoletti D, Taylor P, Ghosh A. (2009). LRRTM2 interacts with Neurexin1 and regulates excitatory synapse formation. Neuron; 64(6):799-806

Delis DC, Freeland J, Kramer JH, Kaplan E. (1988). Integrating clinical assessment with cognitive neuroscience: construct validation of the California Verbal Learning Test. J Consult Clin Psychol; 56(1):123-30.

Di Ciano, P, Coury, A, Depoortere, R.Y, Egilmez, Y, Lane, J.D, Emmett-Oglesby, M.W, Lepiane, F.G, Phillips, A.G & Blaha, C.D. (1995). Comparison of changes in extracellular dopamine concentrations in the nucleus accumbens during intravenous self-aministration of cocaine or d-amphetamine. Behavioural Pharmacology; 6, 311-322.

Di Forti M, Morrison PD, Butt A, Murray RM. (2007). Cannabis use and psychiatric and cogitive disorders: the chicken or the egg? Curr Opin Psychiatry; 20(3):228-34. Review.

Diagnostic and Statistical Manual of Mental Disorders (DSM). (1994). Fourth edition. American Psychiatric Association.

Dixon CE, Kochanek PM, Yan HQ, Schiding JK, Griffith RG, Baum E, Marion DW, DeKosky ST (1999). One-year study of spatial memory performance, brain morphology, and cholinergic markers after moderate controlled cortical impact in rats. J Neurotrauma; 16(2):109-22.

Dowling GP, McDonough ET 3rd, Bost RO. (1990). 'Eve' and 'Ecstasy'. A report of five deaths associated with the use of MDEA and MDMA. JAMA; 257(12):1615-7.

Drewe EA. (1975). Go - no go learning after frontal lobe lesions in humans. Cortex; 11(1):8-16.

Dughiero G, Schifano F, Forza G. (2001). Personality dimensions and psychopathological profiles of Ecstasy users. Hum Psychopharmacol; 16(8):635-639.

Dumont GJ, Verkes RJ. (2006). A review of acute effects of 3,4-methylenedioxymethamphetamine in healthy volunteers. J Psychopharmacol; 20(2):176-87.

Dupuy JM, Ostacher MJ, Huffman J, Perlis RH, Nierenberg AA. (2011). A critical review of pharmacotherapy for major depressive disorder. Int J Neuropsychopharmacol; 14(10):1417-31.

Durdle H, Lundahl LH, Johanson CE, Tancer M. (2008). Major depression: the relative contribution of gender, MDMA, and cannabis use. Depress Anxiety; 25(3):241-7.

Dworkin, S.I & Smith, J.E. (1988). Neurobehavioral Pharmacology of Cocaine. NIDA Res Monogr; 88, 185-195.

Ebmeier KP, Donaghey C, Steele JD. (2006). Recent developments and current controversies in depression. Lancet; 367(9505):153-67. Review.

Eichenbaum H. (2001). The hippocampus and declarative memory: cognitive mechanisms and neural codes. Behav Brain Res; 127(1-2):199-207. Review.

Eley TC, Stevenson J. (1999). Exploring the covariation between anxiety and depression symptoms: a genetic analysis of the effects of age and sex. J Child Psychol Psychiatry; 40(8):1273-82.

Eley TC. (1999). Behavioral genetics as a tool for developmental psychology: anxiety and depression in children and adolescents. Clin Child Fam Psychol Rev; 2(1):21-36. Review.

Elliott, J.M. & Beveridge, J.R. (2005). Psychostimulants and monoamine transporters: upsetting the balance. Current Opinion in Pharmacology; 5, 94-100.

Elliot R. (1997). Genetic therapy, person-regarding reasons and the determination of identity. Bioethics; 11(2):151-60.

Erikson GC, Hager LB, Houseworth C, Dungan J, Petros T, Beckwith BE. (1985). The effects of caffeine on memory for word lists. Physiol Behav; 35(1):47-51.

Escobedo, I, O'shea, E, Orio, L, Sanchez, V, Segura, M, De la Torre, R, Farre, M, Green, A.R. & Colado, M.I. (2005). A comparative study on the acute and long-term effects of MDMA and 3,4-dihydroxymethphetamine (HHMA) on brain monoamine levels after i.p or striatal administration in mice, British Journal of Pharmacology; 144, 231-241.

Esteban B, O'Shea E, Camarero J, Sanchez V, Green AR, Colado MI. (2001). 3,4-Methylenedioxymethamphetamine induces monoamine release, but not toxicity, when administered centrally at a concentration occurring following a peripherally injected neurotoxic dose. Psychopharmacology (Berl); 154(3):251-60.

European Monitoring Centre for Drugs and Drug Addiction, (2008). Report can be found at: www.emcdda.europa.eu

Evans WJ, Cayten CG, Green PA. (1981). Determining the generalizability of rating scales in clinical settings. Med Care; 19(12):1211-20.

Everitt BJ, Robbins TW. (2005). Neural systems of reinforcement for drug addiction: from actions to habits to compulsion. Nat Neurosci; 8(11):1481-9. Review.

Evers S. (2005). Cognitive processing in cluster headache. Curr Pain Headache Rep; 9(2):109-12. Review.

Everston CA. (2003). Sustained sleep deprivation impairs host defense. Am J Physiol; 265(5 Pt 2):R1148-54.

Everton WJ, Mastrangelo PM, Jolton JA. (2005). Personality correlates of employees' personal use of work computers. Cyberpsychol Behav; 8(2):143-53.

Evenden JL. (1999). Varieties of impulsivity. Psychopharmacology (Berl); 146(4):348-61. Review.

Eysenck HJ. (1985). Behaviourism and clinical psychiatry. Int J Soc Psychiatry; 31(3):163-9.

Falck RS, Wang J, Carlson RG. (2008). Depressive symptomatology in young adults with a history of MDMA use: a longitudinal analysis. J Psychopharmacol; 22(1):47-54.

Fantegrossi, W.E, Godlewski, T, Karabenick, R.L, Stephens, J.M, Ullrich, T, Rice, K.C. & Woods, J.H. (2003). Pharmacological characterization of the effects of 3,4-methylenedioxymethamphetamine ("ecstasy") and its enantiomers on lethality, core temperature, and locomotor activity in singly housed and crowded mice. Psychopharmacology; 166(3), 202-11.

Faul, F, Erdfelder E, Lang AG, Buchner A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods, 39,* 175-191.

Faul F, Erdfelder E, Lang AG, Buchner A. (2009). Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. Behavior Research Methods, 41, 1149-1160.

Feduccia AA, Kongovi N, Duvauchelle CL. (2010). Heat increases MDMA-enhanced NAcc 5-HT and body temperature, but not MDMA self-administration. Eur Neuropsychopharmacol; 20(12):884-94.

Fernández-Serrano MJ, Pérez-García M, Schmidt Río-Valle J, Verdejo-García A. (2010). Neuropsychological consequences of alcohol and drug abuse on different components of executive functions.J Psychopharmacol; 24(9):1317-32.

Fisher, C, Hatzidimitriou, G, Wlos, J, Katz, J. & Ricaurte, G. (1995). Reorganization of Ascending 5-HT Axon Projections in Animals Previously exposed to the Recreational Drug 3,4-Methylenedioxymethamphetamine (MDMA, Ecstacy). The Journal of Neuroscience; 15(8), 5476-5485.

Filakovszky J, Kantor S, Halasz P, Bagdy G. (2001). 8-OH-DPAT and MK-801 affect epileptic activity independently of vigilance. Neurochem Int; 38(7):551-6.

Fletcher PJ, Robinson SR, Slippoy DL. (2001). Pre-exposure to (+/-)3,4-methylenedioxy-methamphetamine (MDMA) facilitates acquisition of intravenous cocaine self-administration in rats. Neuropsychopharmacology; 25(2):195-203.

Frankfurt, M. & Azmitia, E. (1984). Regeneration of Serotonergic Fibers in the Rat Hypothalamus following Unilateral 5,7-Dihydroxytryptamine Injection. Brain Research; 298, 273-282.

Fisk JE, Warr P. (1996). Age and working memory: the role of perceptual speed, the central executive, and the phonological loop. Psychol Aging; 11(2):316-23.

Fisk JE, Montgomery C. (2009a). Sleep impairment in ecstasy/polydrug and cannabis-only users. Am J Addict; 18(5):430-7.

Fisk JE, Montgomery C, Murphy PN. (2009b). The association between the negative effects attributed to ecstasy use and measures of cognition and mood among users. Exp Clin Psychopharmacol; 17(5):326-36.

Fisk JE, Montgomery C. (2009c). Evidence for selective executive function deficits in ecstasy/polydrug users. J Psychopharmacol; 23(1):40-50.

Fisher S, Kent TA, Bryant SG. (1995). Postmarketing surveillance by patient self-monitoring: preliminary data for sertraline versus fluoxetine. J Clin Psychiatry; 56(7):288-96.

Francken BJ, Josson K, Lijnen P, Jurzak M, Luyten WH, Leysen JE. (2000). Human 5-hydroxytryptamine(5A) receptors activate coexpressed G(i) and G(o) proteins in Spodoptera frugiperda 9 cells. Mol Pharmacol; 57(5):1034-44.

Frey KA, Koeppe RA, Kilbourn MR, Vander Borght TM, Albin RL, Gilman S, Kuhl DE. (1996). Presynaptic monoaminergic vesicles in Parkinson's disease and normal aging. Ann Neurol; 40(6):873-84.

Frisk V, Milner B. (1990). The role of the left hippocampal region in the acquisition and retention of story content. Neuropsychologia; 28(4):349-59.

Frith, C.H, Chang, L.W, Lattin, D.L, Walls, R.C, Hamm, J. & Doblin, R. (1987). Toxicity of methylenedioxymethamphetamine (MDMA) in the dog and the rat. Fundam Appl Toxicol; 9(1), 110-9.

Frederick, D.L. & Paule, M.G. (1997). Effects of MDMA on Complex Brain Function in Laboratory Animals. Neuroscience and Behavioral Reviews; 21(1), 67-78.

Fritschy JM, Grzanna R. (1992a). Restoration of ascending noradrenergic projections by residual locus coeruleus neurons: compensatory response to neurotoxin-induced cell death in the adult rat brain. J Comp Neurol; 321(3):421-41.

Fritschy JM, Grzanna R. (1992b). Degeneration of rat locus coeruleus neurons is not accompanied by an irreversible loss of ascending projections. Evidence for reestablishment of forebrain innervation by surviving neurons. Ann N Y Acad Sci; 648:275-8. No abstract available.

Foley JA, Cantagallo A, Della Sala S, Logie RH. (2010). Dual task performance and post traumatic brain injury. Brain Inj; 24(6):851-8.

Fornai F, Gesi M, Lenzi P, Ferrucci M, Lazzeri G, Pizzanelli C, Pellegrini A, Battaglia G, Ruggieri S, Paparelli A. (2004). Effects of repeated low doses of MDMA on EEG activity and fluoro-jade B histochemistry. Ann N Y Acad Sci; 1025:181-8.

Fornai, F, Lenzi, P, Ferrucci, M, Lazzeri, G, di Poggio, A.B, Natale, G, Busceti, C.L, Biagioni, F, Giusuani, M, Ruggieri, S. & Paprelli, A. (2005). Occurrence of neuronalinclusions combined with increased nigral expression of α-synuclein within dopaminergic neurons following treatment with amphetamine derivatives in mice. Brain Research Bulletin; 65, 405-413.

Fox HC, Parrott AC, Turner JJ. (2001). Ecstasy use: cognitive deficits related to dosage rather than self-reported problematic use of the drug. J Psychopharmacol; 15(4):273-81.

Fuster JM, Alexander GE. (1971). Neuron activity related to short-term memory. Science; 173(997):652-4.

Gamma A, Buck A, Berthold T, Vollenweider FX. (2001). No difference in brain activation during cognitive performance between ecstasy (3,4-methylenedioxymethamphetamine) users and control subjects: a [H2(15)O]-positron emission tomography study. J Clin Psychopharmacol; 21(1):66-71.

Gamma A, Jerome L, Liechti ME, Sumnall HR. (2005). Is ecstasy perceived to be safe? A critical survey. Drug Alcohol Depend; 77(2):185-93.

Grant and Berg, D.A. Grant and E.A. Berg, (1948). A behavioural analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card sorting problem, Journal of Experimental Psychology; 38: 404-411.

Galineau, L, Belzung, C, Kodas, E, Bodard, S, Guilloteau, D. & Chalon, S. (2005). Prenatal 3,4-methylenedioxymethamphetamine (ecstasy) exposure induces long-term alterations in the dopaminergic and serotonergic functions in the rat. Developmental Brain Research; 154, 165-176.

Gardani M, Blance RN, Biello SM. (2005). MDMA alters the response of the mammalian circadian clock in hamsters: effects on re-entrainment and triazolam-induced phase shifts. Brain Res; 1046(1-2):105-15.

Garcia-Osta, A, Del Rio, J. & Frechilla, D. (2004). Increased CRE-binding activity and trytophan hydroxylase mRNA expression induced by 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") in the rat frontal cortex but not in the hippocampus. Molecular brain research; 126, 181-187.

Gerra G, Zaimovic A, Ferri M, Zambelli U, Timpano M, Neri E, Marzocchi GF, Delsignore R, Brambilla F. (2000). Long-lasting effects of (+/-)3,4-methylenedioxymethamphetamine (ecstasy) on serotonin system function in humans. Biol Psychiatry; 47(2):127-36.

Gerra G, Bassignana S, Zaimovic A, Moi G, Bussandri M, Caccavari R, Brambilla F, Molina E. (2003). Hypothalamic-pituitary-adrenal axis responses to stress in subjects with 3,4-methylenedioxy-methamphetamine ('ecstasy') use history: correlation with dopamine receptor sensitivity. Psychiatry Res; 120(2):115-24.

Gillham B. (2002). Developing a questionnaire. Continuum International Publishing Group Ltd. 1ª edition.

Gold JM, Randolph C, Carpenter CJ, Goldberg TE, Weinberger DR. (1992). Forms of memory failure in schizophrenia. J Abnorm Psychol; 101(3):487-94.

Golding JF, Groome DH, Rycroft N, Denton Z. (2007). Cognitive performance in light current users and ex-users of ecstasy (MDMA) and controls. Am J Drug Alcohol Abuse; 33(2):301-7.

Goldstein RZ, Alia-Klein N, Leskovjan AC, Fowler JS, Wang GJ, Gur RC, Hitzemann R, Volkow ND. (2005). Anger and depression in cocaine addiction: association with the orbitofrontal cortex. Psychiatry Res; 138(1):13-22.

Gosselin A, De Koninck J, Campbell KB. (2005). Total sleep deprivation and novelty processing: implications for frontal lobe functioning. Clin Neurophysiol; 116(1):211-22.

Gouzoulis E, Steiger A, Ensslin M, Kovar A, Hermle L. (1992). Sleep EEG effects of 3,4-methylenedioxyethamphetamine (MDE; "eve") in healthy volunteers. Biol Psychiatry; 32(12):1108-17.

Gouzoulis E, Steiger A, Ensslin M, Kovar A, Hermle L. (1993). Sleep EEG effects of 3,4-methylenedioxyethamphetamine (MDE; "eve") in healthy volunteers. Biol Psychiatry; 32(12):1108-17.

Gouzoulis-Mayfrank, E, Daumann, J, Tuchenhagen, F, Pelz, S, Becker, S, Kunert, H, Fimm, B & Sass, H. (2000) Impaired cognitive performance in drug free users of recreational ecstacy (MDMA). Journal of Neurology, Neurosurgery & Psychiatry; 68:719-725.

Gouzoulis-Mayfrank E, Becker S, Pelz S, Tuchtenhagen F, Daumann J. (2002). Neuroendocrine abnormalities in recreational ecstasy (MDMA) users: is it ecstasy or cannabis? Biol Psychiatry; 51(9):766-9.

Gouzoulis-Mayfrank, E, Thimm, B, Rezk, M, Hensen, G. & Daumann, J. (2003). Memory impairment suggests hippocampal dysfunction in abstinent ecstasy users. Progress in Neuro-Psychopharmacology & Biological Psychiatry, 27(5), 819-827.

Gouzoulis-Mayfrank E. (2004). Dual diagnosis of psychosis and addiction. From principles to practice]. Nervenarzt; 75(7):642-50. Review. Translated.

Gouzoulis-Mayfrank E, Fischermann T, Rezk M, Thimm B, Hensen G, Daumann J. (2005). Memory performance in polyvalent MDMA (ecstasy) users who continue or discontinue MDMA use. Drug Alcohol Depend; 78(3):317-23.

Grafman J. (1995). Similarities and distinctions among current models of prefrontal cortical functions. Ann N Y Acad Sci; 769:337-68. Review.

Granado N, Ares-Santos S, Oliva I, O Shea E, Martin ED, Colado MI, Moratalla R. (2011). Dopamine D2-receptor knockout mice are protected against dopaminergic neurotoxicity induced by methamphetamine or MDMA. Neurobiol Dis; 42(3):391-403.

Green, A.R, Cross, A.J. & Goodwin, G.M. (1995). Review of the pharmacology and clinical pharmacology of 3,4-Methylenedioxymethamphetamine (MDMA or "Ecstasy"). Psychopharmacology; 119, 247-260.

Green, A.R, Mechan, A.O, Elliott, J.M, O'Shea, E. & Colado, M.I. (2003). The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy). Pharmacological Review; 55(3), 463-508.

Green, A.R, O'Shea, E. & Colado, M.I. (2004a). A review of the mechanisms involved in the acute MDMA (ecstasy)-induced hyperthermic response. European Journal of Pharmacology; 500, 3-13.

Green, A.R, Sanchez, V, O'Shea, E, Saadat, K.S, Elliott, J.M. & Colado, M.I. (2004b). Effect of ambient temperature and a prior neurotoxic dose of 3,4-methylenedioxymethamphetamine (MDMA) on the hyperthermic response of rats to a single or repeated (binge ingestion) low dose of MDMA. Psychopharmacology; 173(3-4), 264-9.

Greer G, Tolbert R. (1998). Subjective reports of the effects of MDMA in a clinical setting. J Psychoactive Drugs; 18(4):319-27.

Green AR, O'shea E, Colado MI. (2004). A review of the mechanisms involved in the acute MDMA (ecstasy)-induced hyperthermic response. Eur J Pharmacol; 500(1-3):3-13. Review.

Green AR, Mechan AO, Elliott JM, O'Shea E, Colado MI. (2003). The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). Pharmacol Rev; 55(3):463-508. Review.

Green AR, Cross AJ, Goodwin GM. (1995). Review of the pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA or "Ecstasy"). Psychopharmacology (Berl); 119(3):247-60. Review.

Griffiths P, Mravcik V, Lopez D, Klempova D. (2008). Quite a lot of smoke but very limited fire--the use of methamphetamine in Europe. Drug Alcohol Rev; 27(3):236-42. Review.

Groth-Marnat G, Howchar H, Marsh A. (2007). Memory performance in abstinent 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") users. Percept Mot Skills; 104(1):43-55.

Gudelsky GA, Yamamoto BK. (2003). Neuropharmacology and neurotoxicity of 3,4-methylenedioxymethamphetamine. Methods Mol Med; 79:55-73. Review

Gudjonsson GH. (1984). Interrogative suggestibility and perceptual motor performance. Percept Mot Skills; 58(2):671-2.

Guillot CR, Berman ME. (2006). MDMA (Ecstasy) use and psychiatric problems. Psychopharmacology (Berl); 189(4):575-6.

Gurtman, C.G., Morley, K.C., Li, K.M, Hunt, G.E, & McGregor, I.S. (2002). Increased anxiety in rats after 3,4-methelenedioxymethamphetamine: association with serotonin depletion. European Journal of Pharmacology, 446, 89-96.

Gustafson EL, Moore RY. (1987). Noradrenaline neuron plasticity in developing rat brain: effects of neonatal 6-hydroxydopamine demonstrated by dopamine-beta-hydroxylase immunocytochemistry. Brain Res; 465(1-2):143-55.

Hale AS. (1997). ABC of mental health. Depression. BMJ; 315(7099):43-6. Review.

Haddad PM, Strickland P, Anderson I, Deakin JF, Dursun SM. (2002). Effects of MDMA (ecstasy) use and abstention on serotonin neurons. Lancet; 359(9317):1616-7.

Hamida SB, Tracqui A, de Vasconcelos AP, Szwarc E, Lazarus C, Kelche C, Jones BC, Cassel JC. (2009). Ethanol increases the distribution of MDMA to the rat brain: possible implications in the ethanol-induced potentiation of the psychostimulant effects of MDMA. Int J Neuropsychopharmacol; 12(6):749-59.

Hammersley R. (1999). The alcohol industry and other 'friends'. Addiction; 88(1):19-20.

Hanson KL, Cummins K, Tapert SF, Brown SA. (2010). Changes in neuropsychological functioning over 10 years following adolescent substance abuse treatment. Psychol Addict Behav; 25(1):127-42.

Hanson KL, Luciana M. (2004). Neurocognitive function in users of MDMA: the importance of clinically significant patterns of use. Psychol Med; 34(2):229-46.

Hasler F, Studerus E, Lindner K, Ludewig S, Vollenweider FX. (2008). Investigation of serotonin-1A receptor function in the human psychopharmacology of MDMA. J Psychopharmacol; 23(8):923-35.

Hatzidimitriou G, McCann UD, Ricaurte GA. (1999). Altered serotonin innervation patterns in the forebrain of monkeys treated with (+/-)3,4-methylenedioxymethamphetamine seven years previously: factors influencing abnormal recovery. J Neurosci; 19(12):5096-107.

Hayaki J, Stein MD, Lassor JA, Herman DS, Anderson BJ. (2005). Adversity among drug users: relationship to impulsivity. Drug Alcohol Depend; 78(1):65-71.

Heal DJ, Philpot J, Molyneux SG, Metz A. (1985). Intracerebroventricular administration of 5,7-dihydroxytryptamine to mice increases both head-twitch response and the number of cortical 5-HT2 receptors. Neuropharmacology; 24(12):1201-5.

Heishman SJ, Arasteh K, Stitzer ML. (1997). Comparative effects of alcohol and marijuana on mood, memory, and performance. Pharmacol Biochem Behav; 58(1):93-101.

Hernandez-Rabaza V, Navarro-Mora G, Velazquez-Sanchez C, Ferragud A, Marin MP, Garcia-Verdugo JM, Renau-Piqueras J, Canales JJ. (2010). Neurotoxicity and persistent cognitive deficits induced by combined MDMA and alcohol exposure in adolescent rats. Addict Biol; 15(4):413-23.

Hirst WD, Abrahamsen B, Blaney FE, Calver AR, Aloj L, Price GW, Medhurst AD. (2003). Differences in the central nervous system distribution and pharmacology of the mouse 5-hydroxytryptamine-6 receptor compared with rat and human receptors investigated by radioligand binding, site-directed mutagenesis, and molecular modeling. Mol Pharmacol; 64(6):1295-308.

Hollander E, Rosen J. (2000). Impulsivity. J Psychopharmacol; 14(2 Suppl 1):S39-44.

Hollander E, Evers M. (2001). New developments in impulsivity. Lancet; 358(9286):949-50.

Houston RJ, Stanford MS. (2003). Mid-latency evoked potentials in self-reported impulsive aggression. Int J Psychophysiol; 40(1):1-15.

Horan B, Gardner EL, Ashby CR Jr. (2000). Enhancement of conditioned place preference response to cocaine in rats following subchronic administration of 3, 4-methylenedioxymethamphetamine (MDMA). Synapse; 35(2):160-2.

Horesh N. (2001). Self-report vs. computerized measures of impulsivity as a correlate of suicidal behavior. Crisis; 22(1):27-31.

Hoshi R, Mullins K, Boundy C, Brignell C, Piccini P, Curran HV. (2007). Neurocognitive function in current and ex-users of ecstasy in comparison to both matched polydrug-using controls and drug-naïve controls. Psychopharmacology (Berl); 194(3):371-9

Hughes TA, Ross HF, Mindham RH, Spokes EG. (2004). Mortality in Parkinson's disease and its association with dementia and depression. Acta Neurol Sc; 110(2):118-23.

Indlekofer F, Piechatzek M, Daamen M, Glasmacher C, Lieb R, Pfister H, Tucha O, Lange KW, Wittchen HU, Schütz CG. (2009). Reduced memory and attention performance in a population-based sample of young adults with a moderate lifetime use of cannabis, ecstasy and alcohol. J Psychopharmacol; 23(5):495-509.

Insel TR, Battaglia G, Johannessen JN, Marra S, De Souza EB. (1989). 3,4-Methylenedioxymethamphetamine ("ecstasy") selectively destroys brain serotonin terminals in rhesus monkeys. J Pharmacol Exp Ther; 249(3):713-20.

Iravani, M.M, Asari, D, Patel, J, Wieczorek, W.J. & Krug, Z.L. (2000). Direct effects of 3,4-Methylenedioxymethamphetamine (MDMA) on serotonin or dopamine release and uptake in the caudate putamen, nucleus accumbens, substantia nigra pars reticulata and the dorsal raphe nucleus slices. Synapse; 36, 275-285.

Isaac M, Slassi M, Xin T, Arora J, O'Brien A, Edwards L, MacLean N, Wilson J, Demschyshyn L, Labrie P, Naismith A, Maddaford S, Papac D, Harrison S, Wang H, Draper S, Tehim A. (2004). Design, synthesis and biological activity of novel dimethyl-[2-[6-substituted-indol-1-yl]-ethyl]-amine as potent, selective, and orally-bioavailable 5-HT(1D) agonists. Bioorg Med Chem Lett; 13(24):4409-13.

Jacobsen CF & Fulton JF. (1935). Fonctions des lobes frontaux; etude comparee chez l'homme et les singes chimpanzes. In Proceedings of the International Neurological Congress, London, p. 552. Translated.

Jacobsen LK, Mencl WE, Pugh KR, Skudlarski P, Krystal JH. (2004). Preliminary evidence of hippocampal dysfunction in adolescent MDMA ("ecstasy") users: possible relationship to neurotoxic effects. Psychopharmacology (Berl); 173(3-4):383-90.

Jaehne EJ, Majumder I, Salem A, Irvine RJ. (2011). Increased effects of 3,4-methylenedioxymethamphetamine (ecstasy) in a rat model of depression. Addict Biol; 16(1):7-19

Jansen MA. (1996). Prevention research for alcohol and other drugs: a look ahead to what is needed. Subst Use Misuse; 31(9):1217-22.

Janowsky JS, Shimamura AP, Kritchevsky M, Squire LR. (1989). Cognitive impairment following frontal lobe damage and its relevance to human amnesia. Behav Neurosci; 103(3):548-60.

Jenkins TA, Amin E, Pearce JM, Brown MW, Aggleton JP. (2004). Novel spatial arrangements of familiar visual stimuli promote activity in the rat hippocampal formation but not the parahippocampal cortices: a c-fos expression study. Neuroscience; 124(1):43-52.

Jimerson DC, Lesem MD, Kaye WH, Hegg AP, Brewerton TD. (1990). Eating disorders and depression: is there a serotonin connection? Biol Psychiatry; 28(5):443-54. Review.

Jones, D.C, Duvauchelle, C, Ikegami, A, Olsen, C.M, Lau, S.S, de la Torre, R. & Monks, T.J. (2005). Serotonin neurotoxic metabolites of ecstasy identified in rat brain. Journal of pharmacology and experimental therapeutics, 313 (1), 422-431.

Johnson DG. (2000) Population, food, and knowledge. Am Econ Rev; 90(1):1-14

Jonsson G, Nwanze E. (1982). Selective (+)-amphetamine neurotoxicity on striatal dopamine nerve terminals in the mouse. Br J Pharmacol; 77(2):335-45.

Kalant H. (2001). The pharmacology and toxicology of "ecstasy" (MDMA) and related drugs. CMAJ; 165(7):917-28.

Kantor S, Anheuer ZE, Bagdy G. (2000) High social anxiety and low aggression in Fawn-Hooded rats. Physiol Behav; 71(5):551-7.

Kantor S, Graf M, Anheuer ZE, Bagdy G. (2001). Rapid desensitization of 5-HT(1A) receptors in Fawn-Hooded rats after chronic fluoxetine treatment. Eur Neuropsychopharmacol; 11(1):15-24.

Kesner RP, Giles R. (1998). Neural circuit analysis of spatial working memory: role of pre- and parasubiculum, medial and lateral entorhinal cortex. Hippocampus; 8(4):416-23.

Klaus P, Donaghey Claire, and Steele J D. (2006). Recent developments and current controversies in depression. Lancet, 367(9505):153-67

Kinner SA, Degenhardt L. (2008). Crystal methamphetamine smoking among regular ecstasy users in Australia: increases in use and associations with harm. Drug Alcohol Rev; 27(3):292-300.

King M, Davidson O. (1995). Problem solving treatment for major depression in primary care. Problem solving treatment is time consuming; 310(6989):1266.

Kish SJ, Lerch J, Furukawa Y, Tong J, McCluskey T, Wilkins D, Houle S, Meyer J, Mundo E, Wilson AA, Rusjan PM, Saint-Cyr JA, Guttman M, Collins DL, Shapiro C, Warsh JJ, Boileau I. (2010). Decreased cerebral cortical serotonin transporter binding in ecstasy users: a positron emission tomography/[(11)C]DASB and structural brain imaging study. Brain; 133(Pt 6):1779-97.

Kirilly E. (2010). Long-term neuronal damage and recovery after a single dose of MDMA: expression and distribution of serotonin transporter in the rat brain. Neuropsychopharmacol Hung; 12(3):413-23.

Klaassen T, Riedel WJ, Schmitt JA. (2002). Tryptophan, mood, and cognitive function. Brain Behav Immun; 16(5):581-9. Review.

Klugman A, Hardy S, Baldeweg T, Gruzelier J. (1999). Toxic effect of MDMA on brain serotonin neurons. Lancet; 353(9160):1269-70; author reply 1270-1.

Knyazev GG. (2006). Motivation, emotion, and their inhibitory control mirrored in brain oscillations. Neurosci Biobehav Rev; 31(3):377-95.

Kubota K, Niki H. (1971). Prefrontal cortical unit activity and delayed alternation performance in monkeys. J Neurophysiol; 34(3):337-47.

Kuniyoshi SM, Jankovic J. (2003). MDMA and Parkinsonism. N Engl J Med; 349(1):96-7.

Koprich JB, Campbell NG, Lipton JW. (2003). Neonatal 3,4-methylenedioxymethamphetamine (ecstasy) alters dopamine and serotonin neurochemistry and increases brain-derived neurotrophic factor in the forebrain and brainstem of the rat. Brain Res Dev Brain Res; 147(1-2):177-82.

Konishi S, Donaldson DI, Buckner RL. (2001). Transient activation during block transition. Neuroimage; 13(2):364-74.

Kreth K, Kovar K, Schwab M, Zanger UM. (2000). Identification of the human cytochromes P450 involved in the oxidative metabolism of "Ecstasy"-related designer drugs. Biochem Pharmacol; 59(12):1563-71.

Krystal AD, Weiner RD, Coffey CE, Smith P, Arias R, Moffett E. (1992). EEG evidence of more "intense" seizure activity with bilateral ECT. Biol Psychiatry; 31(6):617-21.

Kuypers KP, Wingen M, Ramaekers JG (2009). Memory and mood during the night and in the morning after repeated evening doses of MDMA. J Psychopharmacol; 22(8):895-903.

Kulynych JJ, Vladar K, Jones DW, Weinberger DR. (1994). Gender differences in the normal lateralization of the supratemporal cortex: MRI surface-rendering morphometry of Heschl's gyrus and the planum temporale. Cereb Cortex; 4(2):107-18.

LaBar KS, Cabeza R. (2006). Cognitive neuroscience of emotional memory. Nat Rev Neurosci; 7(1):54-64. Review.

Lamers CT, Bechara A, Rizzo M, Ramaekers JG. (2006). Cognitive function and mood in MDMA/THC users, THC users and non-drug using controls. J Psychopharmacol; 20(2):302-11.

Landry, M.J. (2002). MDMA: a review of epidemiologic data. Journal of Psychoactive Drugs; 34(2), 163-9.

Lara C, Brezo J, Rouleau G, Lesage A, Dumont M, Alda M, Benkelfat C, Turecki G. (2007). Effect of tryptophan hydroxylase-2 gene variants on suicide risk in major depression. Biol Psychiatry; 62(1):72-80.

Lawrence AJ, Luty J, Bogdan NA, Sahakian BJ, Clark L. (2009). Impulsivity and response inhibition in alcohol dependence and problem gambling. Psychopharmacology (Berl); 207(1):163-72.

Laurent A, Biloa-Tang M, Bougerol T, Duly D, Anchisi AM, Bosson JL, Pellat J, d'Amato T, Dalery J. (2000). Executive/attentional performance and measures of schizotypy in patients with schizophrenia and in their nonpsychotic first-degree relatives. Schizophr Res; 46(2-3):269-83.

Lazarus LW, Weinberg J. (1982). Psychosocial intervention with the age. Psychiatr Clin North Am; (1):215-27.

Lee I, Kesner RP. (2004). Encoding versus retrieval of spatial memory: double dissociation between the dentate gyrus and the perforant path inputs into CA3 in the dorsal hippocampus. Hippocampus; 14(1):66-76.

Lee-Chiong T Jr. Harrington JJ. (2007). Sleep and older patients. Clin Chest Med; 28(4):673-84, Review.

Levitt P, Moore R. (1980). Organization of brainstem noradrenaline hyperinnervation following neonatal 6-hydroxydopamine treatment in the rat. Anat Embryol 158:133-150.

Liechti ME, Vollenweider FX. (2001). Which neuroreceptors mediate the subjective effects of MDMA in humans? A summary of mechanistic studies. Hum Psychopharmacol; 16(8): 589-598.

Li, Teng, S.-F., Wu, S.-C., Liu, CJ.-H., & Chien, C.-S. (2006a). Characteristics and trends of 3,4-methylenedioxymethamphetamine (MDMA) tablets found in Taiwan from 2002 to February 2005. Forensic Science International; 161(2-3), 202-208.

Li CS, Milivojevic V, Kemp K, Hong K, Sinha R. (2006b). Performance monitoring and stop signal inhibition in abstinent patients with cocaine dependence. Drug Alcohol Depend; 85(3):205-12.

Li IH, Huang WS, Shiue CY, Huang YY, Liu RS, Chyueh SC, Hu SH, Liao MH, Shen LH, Liu JC, Ma KH. (2010). Study on the neuroprotective effect of fluoxetine against MDMA-induced neurotoxicity on the serotonin transporter in rat brain using micro-PET. Neuroimage; 49(2):1259-70.

Lin DL, Liu HC, Yin RM, Chen DT, Soong SJ, Liu RH. (2004). Effectiveness of multiple internal standards: deuterated analogues of methylenedioxymethamphetamine, methylenedioxyamphetamine, methamphetamine, and amphetamine. J Anal Toxicol; 28(8):650-4

Linnoila M, Virkkunen M, Scheinin M, Nuutila A, Rimon R, Goodwin FK. (1983) Low cerebrospinal fluid 5-hydroxyindoleacetic acid concentration differentiates impulsive from nonimpulsive violent behavior. Life Sci; 33(26):2609-14.

Linnoila M. (1992). Psychotropic medications and traffic safety. J Clin Psychopharmacol; 12(6):384-5.

Lundqvist T. (2005). Cognitive consequences of cannabis use: comparison with abuse of stimulants and heroin with regard to attention, memory and executive functions. Pharmacol Biochem Behav; 81(2):319-30. Review.

Logan BJ, Laverty R, Sanderson WD, Yee YB. (1988). Differences between rats and mice in MDMA (methylenedioxymethylamphetamine) neurotoxicity. Eur J Pharmacol; 152(3):227-34.

Lovallo WR, Al'Absi M, Blick K, Whitsett TL, Wilson MF. (1996). Stress-like adrenocorticotropin responses to caffeine in young healthy men. Pharmacol Biochem Behav; 55(3):365-9.

Loxton NJ, Wan VL, Ho AM, Cheung BK, Tam N, Leung FY, Stadlin A. (2008). Impulsivity in Hong Kong-Chinese club-drug users. Drug Alcohol Depend; 95(1-2):81-9.

Luu P, Poulsen C, Crane SM, Quiring J, Tucker DM. (2009). Frontolimbic activity and cognitive bias in major depression. J Abnorm Psychol; 118(3):494-506.

Lydiard RB, Brawman-Mintzer O. (1998). Anxious depression. J Clin Psychiatry; 59 Suppl 18:10-7. Review.

Malberg, J.E. & Seiden, L.S. (1998). Small Changes in Ambient Temperature Cause Large Changes in 3,4-Methylenedioxymethamphetamine (MDMA)- Induced Serotonin Neurotoxicity and Core Body Temperature in the Rat. Journal of Neuroscience; 18(13), 5086-5094.

Matthews AJ, Bruno R. (2010). An investigation of factors associated with depressive symptoms among a sample of regular ecstasy consumers. Neuropsychobiology; 61(4):215-22.

Matthies H, Schroeder H, Smalla KH, Krug M. (2000). Enhancement of glutamate release by L-fucose changes effects of glutamate receptor antagonists on long-term potentiation in the rat hippocampus.Learn Mem; 7(4):227-34.

Masi G, Mucci M, Floriani C. (2002). Acute catatonia after a single dose of ecstasy. J Am Acad Child Adolesc Psychiatry; 41(8):892.

Markowitsch HJ. (1994). The memory storehouse. Trends Neurosci; 17(12):513-4.

Martins SS, Tavares H, da Silva Lobo DS, Galetti AM, Gentil V. (2004). Pathological gambling, gender, and risk-taking behaviors. Addict Behav; 29(6):1231-5.

Marston HM, Reid ME, Lawrence JA, Olverman HJ, Butcher SP. (1999). Behavioural analysis of the acute and chronic effects of MDMA treatment in the rat. Psychopharmacology (Berl); 144(1):67-76.

McAllister-Williams RH, Man MS, Young AH. (2002). Corticosterone modulation of somatodendritic 5-HT1A receptor function in mice. J Psychopharmacol; 16(3):245-52.

McCann UD, Ricaurte GA. (1991). Lasting neuropsychiatric sequelae of (+-)methylenedioxymethamphetamine ('ecstasy') in recreational users. J Clin Psychopharmacol; 11(5):302-5.

McCann UD, Ricaurte GA. (1992). MDMA ("ecstasy") and panic disorder: induction by a single dose. Biol Psychiatry; 32(10):950-3.

McCann, U.D, Eligulashvili, V, Mertl, M, Murphy, D.L. & Ricaurte, G.A. (1997). Altered neuroendocrine and behavioral responses to m-chlorophenylpiperazine in 3,4-methylenedioxymethamphetamine (MDMA) users. Psychocharmacology; 147, 56-65.

McCann UD, Szabo Z, Scheffel U, Dannals RF, Ricaurte GA. (1998). Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurons in human beings. Lancet; 31;352(9138):1433-7.

McCann UD, Mertl M, Eligulashvili V, Ricaurte GA. (1999). Cognitive performance in (+/-) 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") users: a controlled study. Psychopharmacology (Berl); 143(4):417-25.

McCann, U.D, Eligulashvili, V, Ricaurte, G.A. (2000). 3,4-Methylenedioxymethamphetamine (Ecstacy)-Induced Serotonin Neurotoxicity: Clinical Studies. Neuropsychobiology; 42(1), 11-16.

McCann UD, Ricaurte GA. (2004). Major metabolites of (+/-)3,4-methylenedioxyamphetamine (MDA) do not mediate its toxic effects on brain serotonin neurons. Brain Res; ;545(1-2):279-82.

McCann UD, Szabo Z, Seckin E, Rosenblatt P, Mathews WB, Ravert HT, Dannals RF, Ricaurte GA. (2005). Quantitative PET studies of the serotonin transporter in MDMA users and controls using [11C]McN5652 and [11C]DASB. Neuropsychopharmacology; 30(9):1741-50.

McCann UD, Peterson SC, Ricaurte GA. (2007). The effect of catecholamine depletion by alpha-methyl-para-tyrosine on measures of cognitive performance and sleep in abstinent MDMA users. Neuropsychopharmacology; 32(8):1695-706.

McCann UD, Wilson MJ, Sgambati FP, Ricaurte GA (2009). Sleep deprivation differentially impairs cognitive performance in abstinent methylenedioxymethamphetamine ("Ecstasy") users. J Neurosci; 29(44):14050-6.

McCardle K, Luebbers S, Carter JD, Croft RJ, Stough C. (2004). Chronic MDMA (ecstasy) use, cognition and mood. Psychopharmacology (Berl); 173(3-4):434-9.

McGregor IS, Gurtman CG, Morley KC, Clemens KJ, Blokland A, Li KM, Cornish JL, Hunt GE. (2003). Increased anxiety and "depressive" symptoms months after MDMA ("ecstasy") in rats: drug-induced hyperthermia does not predict long-term outcomes. Psychopharmacology (Berl); 168(4):465-74.

McGuffin P, Katz R, Rutherford J. (1991). Nature, nurture and depression: a twin study. Psychol Med; 21(2):329-35.

McGuire and Fahy, (1991). Chronic paranoid psychosis after misuse of MDMA ("ecstasy"). BMJ; 302(6778):697.

McGuire PK, Cope H, Fahy TA. (1994). Diversity of psychopathology associated with use of 3,4-methylenedioxymethamphetamine ('Ecstasy'). Br J Psychiatry; 165(3):391-5.

MacInnes N, Handley SL, Harding GF. (2001). Former chronic methylenedioxymethamphetamine (MDMA or ecstasy) users report mild depressive symptoms. J Psychopharmacol; 15(3):181-6.

Mechan AO, O'Shea E, Elliott JM, Colado MI, Green AR. (2001). A neurotoxic dose of 3,4-methylenedioxymethamphetamine (MDMA; ecstasy) to rats results in a long-term defect in thermoregulation. Psychopharmacology (Berl); 155(4):413-8.

Medina KL, Shear PK. (2007). Anxiety, depression, and behavioral symptoms of executive dysfunction in ecstasy users: contributions of polydrug use. Drug Alcohol Depend; 87(2-3):303-11.

Medina KL, Shear PK, Corcoran K. (2005). Ecstasy (MDMA) exposure and neuropsychological functioning: a polydrug perspective. J Int Neuropsychol Soc; 11(6):753-65.

Meyer JS, Piper BJ, Vancollie VE. (2008). Development and characterization of a novel animal model of intermittent MDMA ("Ecstasy") exposure during adolescence. Ann N Y Acad Sci; 1139:151-63.

Meyer MR, Peters FT, Maurer HH. (2008). The role of human hepatic cytochrome P450 isozymes in the metabolism of racemic 3,4-methylenedioxy-methamphetamine and its enantiomers. Drug Metab Dispos; 36(11):2345-54.

Meyer-Bernstein EL, Blanchard JH, Morin LP. (1997). The serotonergic projection from the median raphe nucleus to the suprachiasmatic nucleus modulates activity phase onset, but not other circadian rhythm parameters. Brain Res; 755(1):112-20.

Milner, B. (1968). Disorders of memory after brain lesions in man. Neuropsychologia; 6:175--179.

Milani RM, Parrott AC, Turner JJ, Fox HC. (2004). Gender differences in self-reported anxiety, depression, and somatization among ecstasy/MDMA polydrug users, alcohol/tobacco users, and nondrug users. Addict Behav; 29(5):965-71.

Miller PG, Johnston J, McElwee PR, Noble R. (2007). A pilot study using the internet to study patterns of party drug use: processes, findings and limitations. Drug Alcohol Rev; 26(2):169-74.

Mirjana C, Baviera M, Invernizzi RW, Balducci C. (2004). The serotonin 5-HT2A receptors antagonist M100907 prevents impairment in attentional performance by NMDA receptor blockade in the rat prefrontal cortex. Neuropsychopharmacology; 29(9):1637-47.

Mobini S, Chiang TJ, Ho MY, Bradshaw CM, Szabadi E. (2000). Effects of central 5-hydroxytryptamine depletion on sensitivity to delayed and probabilistic reinforcement. Psychopharmacology (Berl); 152(4):390-7.

Morley KC, Gallate JE, Hunt GE, Mallet PE, McGregor IS. (2001). Increased anxiety and impaired memory in rats 3 months after administration of 3,4-methylenedioxymethamphetamine ("ecstasy"). Eur J Pharmacol; 433(1):91-9.

Morris PL, Mayberg HS, Bolla K, Wong DF, Dannals RF, Starkstein SE, Robinson RG. (1993). A preliminary study of cortical S2 serotonin receptors and cognitive performance following stroke. J Neuropsychiatry Clin Neurosci; 5(4):395-400.

Morris E, Semple WE, Goyer PF, McCormick R, Compton-Toth B, Donovan B, Muswick G, Nelson D, Garnett ML, Sharkoff J, Leisure G, Miraldi F, Schulz SC. (1996). Attention and regional cerebral blood flow in posttraumatic stress disorder patients with substance abuse histories. Psychiatry Res; 67(1):17-28.

Morris K. (2003). Research reawakens ecstasy neurotoxicity debate. Lancet Neurol; 2(11):650.

Monckton JE, McCormick DA. (2003). Neuromodulatory role of serotonin in the ferret thalamus. J Neurophysiol; 87(4):2124-36.

Monchi O, Petrides M, Petre V, Worsley K, Dagher A (2001). Wisconsin Card Sorting revisited: distinct neural circuits participating in different stages of the task identified by event-related functional magnetic resonance imaging. J Neurosci; 21(19):7733-41.

Monk TH, Buysse DJ, Rose LR, Hall JA, Kupfer DJ. (2000). The sleep of healthy people--a diary study. Chronobiol Int; 17(1):49-60.

Monk TH, Petrie SR, Hayes AJ, Kupfer DJ. (1994). Regularity of daily life in relation to personality, age, gender, sleep quality and circadian rhythms. J Sleep Res; 3(4):196-205.

Monks TJ, Bai F, Miller RT, Lau SS. (2001). Serotonergic neurotoxicity of methylenedioxyamphetamine and methylenedioxymetamphetamine. Adv Exp Med Biol; 500:397-406. Review.

Monti JM, Jantos H. (1992). Dose-dependent effects of the 5-HT1A receptor agonist 8-OH-DPAT on sleep and wakefulness in the rat. J Sleep Res; 1(3):169-175.

Montoya AG, Sorrentino R, Lukas SE, Price BH. (2002). Long-term neuropsychiatric consequences of "ecstasy" (MDMA): a review. Harv Rev Psychiatry; 10(4):212-20.

Montgomery AM. Butler GK, (2007a). Subjective self-control and behavioural impulsivity coexist in anorexia nervosa. Eat Behav; 6(3):221-7.

Montgomery C, Fisk JE. (2007b). Everyday memory deficits in ecstasy-polydrug users. J Psychopharmacol; 21(7):709-17.

Montgomery C, Fisk JE, Wareing M, Murphy P. (2007c). Self reported sleep quality and cognitive performance in ecstasy users. Hum Psychopharmacol; 22(8):537-48.

Montgomery C, Fisk JE, Newcombe R, Wareing M, Murphy PN. (2005). Syllogistic reasoning performance in MDMA (Ecstasy) users. Exp Clin Psychopharmacol; 13(2):137-45.

Montgomery C, Hatton NP, Fisk JE, Ogden RS, Jansari A. (2010). Assessing the functional significance of ecstasy-related memory deficits using a virtual paradigm. Hum Psychopharmacol; 25(4):318-25.

Morgan MJ. (1998). Recreational use of "ecstasy" (MDMA) is associated with elevated impulsivity. Neuropsychopharmacology; 19(4):252-64.

Morgan JF. (1999). Ecstasy use and neuropathology. Br J Psychiatry; 175:589.

Morgan, M.J. (2000). Ecstasy (MDMA): A Review of its Possible Persistent Psychological Effects. Psychopharmacology; 152, 230-248.

Morgan MJ, Impallomeni LC, Pirona A, Rogers RD. (2006). Elevated impulsivity and impaired decision-making in abstinent Ecstasy (MDMA) users compared to polydrug and drug-naïve controls. Neuropsychopharmacology; 31(7):1562-73.

Morini R, Mlinar B, Baccini G, Corradetti R. (2011). Enhanced hippocampal long-term potentiation following repeated MDMA treatment in Dark-Agouti rats. Eur Neuropsychopharmacol; 21(1):80-91.

Merland J. (2000). Toxicity of drug abuse--amphetamine designer drugs (ecstasy): mental effects and consequences of single dose use. Toxicol Lett; 112-113:147-52.

Morris K. (2003). Research reawakens ecstasy neurotoxicity debate. Lancet Neurol; 2(11):650.

Morris RG, Ahmed S, Syed GM, Toone BK. (1993). Neural correlates of planning ability: frontal lobe activation during the Tower of London test. Neuropsychologia; 31(12):1367-78.

Morton J. (2005). Ecstasy: pharmacology and neurotoxicity. Curr Opin Pharmacol; 5(1):79-86.

Morón JA, Green TA. (2005) Exploring the molecular basis of addiction: drug-induced neuroadaptations. Neuropsychopharmacology; 35(1):337-8.

Moruzzi G, Magoun HW. (1949). Brain stem reticular formation and activation of the EEG. Electroencephalogr Clin Neurophysiol; 1(4):455-73.

Mokler DJ, Robinson SE, Rosecrans JA. (1987). (+/-)3,4-Methylenedioxymethamphetamine (MDMA) produces long-term reductions in brain 5-hydroxytryptamine in rats. Eur J Pharmacol; 138(2):265-8.

Möller HJ. (2001). Past, present and future of biological psychiatry. World J Biol Psychiatry; 2(3):156-8.

Mueller M, Yuan J, Felim A, Neudörffer A, Peters FT, Maurer HH, McCann UD, Largeron M, Ricaurte GA. (2009a). Further studies on the role of metabolites in (+/-)-3,4-methylenedioxymethamphetamine-induced serotonergic neurotoxicity. Drug Metab Dispos; 37(10):2079-86. Epub 2009 Jul 23.

Mueller M, Kolbrich EA, Peters FT, Maurer HH, McCann UD, Huestis MA, Ricaurte GA. (2009b). Direct comparison of (+/-) 3,4-methylenedioxymethamphetamine ("ecstasy") disposition and metabolism in squirrel monkeys and humans. Ther Drug Monit; 31(3):367-73.

Mueller M, Goodwin AK, Ator NA, McCann UD, Ricaurte GA. (2011). Metabolism and Disposition of 3,4-Methylenedioxymethamphetamine (MDMA, "Ecstasy") in Baboons After Oral Administration: Comparison to Humans Reveals Marked Differences. J Pharmacol Exp Ther; 338(1):310-7.

Murphy PN, Wareing M, Fisk JE, Mongomery C. (2009). Executive working memory deficits in abstinent ecstasy/MDMA users: a critical review. Neuropsychobiology; 60: 159-175.

Nagahama Y, Fukuyama H, Yamauchi H, Matsuzaki S, Konishi J, Shibasaki H, Kimura J. (1996). Cerebral activation during performance of a card sorting test. Brain; 119 (Pt 5):1667-75

Nifosì F, Martinuzzi A, Toffanin T, Costanzo R, Vestri A, Battaglia M, Bertagnoni GE, Lupi A, Amistà P, Carollo C, Perini G. (2009). Hippocampal remodelling after MDMA neurotoxicity: a single case study. World J Biol Psychiatry; 10 (4 Pt 3):961-8.

Norman, D., & Shallice, T. (1986). Attention to action: Willed and automatic control of behavior. In R. Davidson, R. G. Schwartz, & D. Shapiro (Eds.), Consciousness and self-regulation: Advances in research and theory (pp. 1–18). New York: Plenum Press.

Nutt D. (2009). Government vs science over drug and alcohol policy. Lancet; 374(9703):1731-3.

Nutt DJ, King LA, Phillips LD; Independent Scientific Committee on Drugs (2010). Drug harms in the UK: a multicriteria decision analysis. Lancet; 376(9752):1558-65.

Odhuba RA, van den Broek MD, Johns LC. (2005). Ecological validity of measures of executive functioning. Br J Clin Psychol; 44(Pt 2):269-78.

Offending crime and Justice Survey. (2003). www.homeoffice.gov.uk/drugs.

Office on drugs and crime. (2003). Report can be found at: www.unodc.org/unodc/en/data-and-analysis/WDR.html

O'Hearn E, Molliver ME. (1984). Organization of raphe-cortical projections in rat: a quantitative retrograde study. Brain Res Bull; 13(6):709-26.

O'Leary G, Nargiso J, Weiss RD. (2001). 3,4-methylenedioxymethamphetamine (MDMA): a review. Curr Psychiatry Rep; 3(6):477-83.

Olton DS, Papas BC. (1979). Spatial memory and hippocampal function. Neuropsychologia; 17(6):669-82.

O'Shea E, Granados R, Esteban B, Colado MI, Green AR. (1998). The relationship between the degree of neurodegeneration of rat brain 5-HT nerve terminals and the dose and frequency of administration of MDMA ('ecstasy'). Neuropharmacology; 37(7):919-26.

Osinsky R, Schmitz A, Alexander N, Kuepper Y, Kozyra E, Hennig J. (2009). TPH2 gene variation and conflict processing in a cognitive and an emotional Stroop task. Behav Brain Res; 198(2):404-10

Owen AM. (1990). The functional organization of working memory processes within human lateral frontal cortex: the contribution of functional neuroimaging. Eur J Neurosci; 9(7):1329-39. Review.

Paaver M, Nordquist N, Parik J, Harro M, Oreland L, Harro J. (2007). Platelet MAO activity and the 5-HTT gene promoter polymorphism are associated with impulsivity and cognitive style in visual information processing. Psychopharmacology (Berl); 194(4):545-54.

Pace-Schott EF, Hobson JA. (2002). The neurobiology of sleep: genetics, cellular physiology and subcortical networks. Nat Rev Neurosci; 3(8):591-605. Review.

Pallanti S, Mazzi D. (1992). MDMA (Ecstasy) precipitation of panic disorder. Biol Psychiatry; 32(1):91-5.

Patton JH, Stanford MS, Barratt ES. (1995). Factor structure of the Barratt impulsiveness scale. J Clin Psychol; 51(6):768-74

Park J, Kanwisher N. (1994). Negative priming for spatial locations: identity mismatching, not distractor inhibition. J Exp Psychol Hum Percept Perform; 20(3):613-23.

Park SB, Coull JT, McShane RH, Young AH, Sahakian BJ, Robbins TW, Cowen PJ. (1994). Tryptophan depletion in normal volunteers produces selective impairments in learning and memory. Neuropharmacology; 33(3-4):575-88.

Parrott AC. (1997). The psychobiology of MDMA or 'ecstasy': symposium arranged by the Psychobiology Section, at the Annual Conference of the British Psychological Society, Heriot-Watt University, Edinburgh, April 1997. J Psychopharmacol; 12(1):97-102.

Parrott, A.C. & Lasky, J. (1998a). Ecstasy (MDMA) effects upon mood and cognition: before and after a Saturday night dance. Psychopharmacology; 139(3), 261-8.

Parrott, A.C, Lees, A, Garnham, N.J, Jones, M. & Wesnes, K. (1998b). Cognitive performance in recreational users of MDMA or ecstasy: evidence for memory deficits. Journal of Psychopharmacology; 12(1), 79-83.

Parrott, A.C. (1998c). The psychobiology of MDMA or ecstasy: symposium arranged by the Psychobiology section, at the Annual conference of the british psychological society, Heriot-Watt university, edinburgh, April 1997. Journal of psychopharmacology; 12(1), 97-102.

Parrott AC, Kaye FJ. (1999). Daily uplifts, hassles, stresses and cognitive failures: in cigarette smokers, abstaining smokers, and non-smokers. Behav Pharmacol; 10(6-7):639-46.

Parrott, A.C, Sisk, E. & Turner, J.J.D. (2000a). Psychobiological problems in heavy 'ecstacy' (MDMA) polydrug users. Drug and Alcohol Dependence; 60, 105-110.

Parrott, A.C. (2000b). Human Research on MDMA (3,4-Methylenedioxymethamphetamine) Neurotoxicity: Cognitive and Behavioural Indices of Change. Neuropsychobiology; 42(1), 17-24.

Parrott AC. (2001). Human psychopharmacology of Ecstasy (MDMA): a review of 15 years of empirical research. Hum Psychopharmacol; 16(8):557-577.

Parrott AC, Buchanan T, Scholey AB, Heffernan T, Ling J, Rodgers J. (2002). Ecstasy/MDMA attributed problems reported by novice, moderate and heavy recreational users. Hum Psychopharmacol; 17(6):309-12.

Parrott AC, Buchanan T, Scholey AB, Heffernan T, Ling J, Rodgers J. (2003). Ecstasy/MDMA attributed problems reported by novice, moderate and heavy recreational users. Hum Psychopharmacol; 17(6):309-12.

Parrott AC, Gouzoulis-Meyfrank E, Rodgers J, Solowij N. (2004). Ecstasy/MDMA and cannabis: the complexities of their interactive neuropsychobiological effects. J Psychopharmacol; 18(4):572-5.

Parrott AC. (2005). Chronic tolerance to recreational MDMA (3,4-methylenedioxymethamphetamine) or Ecstasy. J Psychopharmacol; 19(1):71-83. Review.

Parrott AC. (2009). Cortisol and 3,4-methylenedioxymethamphetamine: neurohormonal aspects of bioenergetic stress in ecstasy users. Neuropsychobiology; 60(3-4):148-58.

Parrott AC. (2011). MDMA and temperature: A review of the thermal effects of 'Ecstasy' in humans. Drug Alcohol Depend. Online.

Peluso MA, Hatch JP, Glahn DC, Monkul ES, Sanches M, Najt P, Bowden CL, Barratt ES, Soares JC. (2007) Trait impulsivity in patients with mood disorders. J Affect Disord; 100(1-3):227-31.

Passchier J, van Waarde A, Vaalburg W, Willemsen AT. (2001) On the quantification of [18F]MPPF binding to 5-HT1A receptors in the human brain. J Nucl Med; 42(7):1025-31.

Peraile I, Torres E, Mayado A, Izco M, Lopez-Jimenez A, Lopez-Moreno JA, Colado MI, O'Shea E. (2010). Dopamine transporter down-regulation following repeated cocaine: implications for 3,4-methylenedioxymethamphetamine-induced acute effects and long-term neurotoxicity in mice. Br J Pharmacol; 159(1):201-11.

Peroutka SJ, Price SC, Wilhoit TL, Jones KW. (1998). Comorbid migraine with aura, anxiety, and depression is associated with dopamine D2 receptor (DRD2) NcoI alleles. Mol Med; 4(1):14-21.

Perrine SA, Ghoddoussi F, Michaels MS, Hyde EM, Kuhn DM, Galloway MP. (2010). MDMA administration decreases serotonin but not N-acetylaspartate in the rat brain. Neurotoxicology; 31(6):654-61.

Piechatzek M, Indlekofer F, Daamen M, Glasmacher C, Lieb R, Pfister H, Tucha O, Lange KW, Wittchen HU, Schütz CG. (2009). Is moderate substance use associated with altered executive functioning in a population-based sample of young adults? Hum Psychopharmacol; 24(8):650-65.

Pifl, C, Nagy, G, Berenyi, S, Kattinger, A, Reither, H. & Antus, S. (2005). Pharmacological characterization of ecstasy sythesis byproducts with recombinant human monoamine transporters. Journal of pharmacology and experimental therapeutics; 314(1), 346-354.

Piper BJ, Meyer JS. (2004). Memory deficit and reduced anxiety in young adult rats given repeated intermittent MDMA treatment during the periadolescent period. Pharmacol Biochem Behav; 79(4):723-31.

Piomelli D, Stella N, Schweitzer P. (1997). A second endogenous cannabinoid that modulates long-term potentiation. Nature; 388(6644):773-8.

Plant M, Plant M. (1992). Risk-takers - Alcohol, drugs, sex and youth. Routledge.

Pope, H.G, Ionescu-Pioggia, M. & Pope, K.W. (2001). Drug Use and Life Style Among College Undergraduates: A 30-Year Longitudinal Study. American Journal of Psychiatry; 158(9), 1519-1521.

Quednow BB, Jessen F, Kuhn KU, Maier W, Daum I, Wagner M. (2006). Memory deficits in abstinent MDMA (ecstasy) users: neuropsychological evidence of frontal dysfunction.J Psychopharmacol; 20(3):373-84.

Quednow BB, Kühn KU, Hoppe C, Westheide J, Maier W, Daum I, Wagner M. (2007). Elevated impulsivity and impaired decision-making cognition in heavy users of MDMA ("Ecstasy"). Psychopharmacology (Berl); 189(4):517-30.

Ramaekers JG, Kuypers KP, Wingen M, Heinecke A, Formisano E. (2009). Involvement of inferior parietal lobules in prospective memory impairment during acute MDMA (ecstasy) intoxication: an event-related fMRI study. Neuropsychopharmacology; 34(7):1641-8.

Ramsey JD, Johnston A, Holt DW. (1999) Death rate from use of ecstasy or heroin. Lancet; 354(9196):2166.

Ramsey J, Winstock AR, Wolff K. (2001) Ecstasy pill testing: harm minimization gone too far? Addiction; 96(8):1139-48.

Ramo DE, Grov C, Delucchi K, Kelly BC, Parsons JT. (2010). Typology of club drug use among young adults recruited using time-space sampling. Drug Alcohol Depend; 107(2-3):119-27.

Randall S, Johanson CE, Tancer M, Roehrs T (2009). Effects of acute 3,4-methylenedioxymethamphetamine on sleep and daytime sleepiness in MDMA users: a preliminary study. 32(11):1513-9.

Reneman L, Hurley RA, Taber KH. (2002). Ecstasy in the brain: a model for neuroimaging. J Neuropsychiatry Clin Neurosci; 14(2):125-9.

Rezvani AH, Levin ED. (2001). Cognitive effects of nicotine. Biol Psychiatry; 49(3):258-67. Review.

Riedlinger TJ, Riedlinger JE. (1994). Psychedelic and entactogenic drugs in the treatment of depression. J Psychoactive Drugs; 26(1):41-55. Review.

Reinoso-Suárez F, de Andrés I, Garzón M. (2011). Functional anatomy of the sleep-wakefulness cycle: wakefulness. Adv Anat Embryol Cell Biol; 208:1-128.

Rendell PG, Gray TJ, Henry JD, Tolan A. (2007). Prospective memory impairment in "ecstasy" (MDMA) users. Psychopharmacology (Berl); 194(4):497-504.

Reneman L, Booij J, Schmand B, van den Brink W, Gunning B. (2000a). Memory disturbances in "Ecstasy" users are correlated with an altered brain serotonin neurotransmission. Psychopharmacology (Berl); 148(3):322-4.

Reneman L, Habraken JB, Majoie CB, Booij J, den Heeten GJ. (2000b). MDMA ("Ecstasy") and its association with cerebrovascular accidents: preliminary findings. AJNR Am J Neuroradiol; 21(6):1001-7.

Reneman L, Booij J, de Bruin K, Reitsma JB, de Wolff FA, Gunning WB, den Heeten GJ, van den Brink W. (2001a). Effects of dose, sex, and long-term abstention from use on toxic effects of MDMA (ecstasy) on brain serotonin neurons. Lancet; 358(9296):1864-9.

Reneman L, Lavalaye J, Schmand B, de Wolff FA, van den Brink W, den Heeten GJ, Booij J. (2001b). Cortical serotonin transporter density and verbal memory in individuals who stopped using 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy"): preliminary findings. Arch Gen Psychiatry; 58(10):901-6.

Reneman L, Booij J, Majoie CB, Van Den Brink W, Den Heeten GJ. (2001c). Investigating the potential neurotoxicity of Ecstasy (MDMA): an imaging approach. Hum Psychopharmacol; (8):579-588.

Reneman L, Booij J, Habraken JB, De Bruin K, Hatzidimitriou G, Den Heeten GJ, Ricaurte GA. (2002). Validity of [123I]beta-CIT SPECT in detecting MDMA-induced serotonergic neurotoxicity. Synapse; 46(3):199-205.

Reneman L, Schilt T, de Win MM, Booij J, Schmand B, van den Brink W, Bakker O. (2006). Memory function and serotonin transporter promoter gene polymorphism in ecstasy (MDMA) users. J Psychopharmacol; 20(3):389-99.

Reuter M, Esslinger C, Montag C, Lis S, Gallhofer B, Kirsch P. (2008). A functional variant of the tryptophan hydroxylase 2 gene impacts working memory: a genetic imaging study. Biol Psychol; 79(1):111-7.

Rezvani AH, Levin ED. (2001). Cognitive effects of nicotine. Biol Psychiatry; 49(3):258-67. Review.

Ricaurte, G.A, Forno, L.S, Wilson, M.A, DeLanney, L.E, Irwin, I, Molliver, M.E. & Langston, J.W. (1988). 3,4-Methylenedioxymethamphetamine Selectively Damages Central Serotoneric Neurons in Nonhuman Primates. JAMA; 260, 51-56.

Ricaurte GA, Markowska AL, Wenk GL, Hatzidimitriou G, Wlos J, Olton DS. (1993). 3,4-Methylenedioxymethamphetamine, serotonin and memory. J Pharmacol Exp Ther; 268(1):529.

Ricaurte, G.A, McCann, U.D, Szabo, Z. & Scheffel, U. (2000a). Toxicodynamics and long-term toxicity of the recreational drug, 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy). Toxicology Letters; 112-113, 143-146.

Ricaurte, G.A, Yuan, J. & McCann, U.D. (2000b). 3,4-Methylenedioxymethamphetamine (Ecstacy)-Induced Serotonin Neurotoxicty: Studies in Animals. Neuropsychobiology, 42(1), 5-10.

Ricaurte, G.A. & McCann, U.D. (2001). Assessing long-term effects of MDMA (Ecstasy). Lancet; 358, 1831-2.

Ricci LC, Wellman MM. (1990). Monoamines: biochemical markers of suicide? J Clin Psychol. 1990 Jan;46(1):106-16.

Riedel WJ, Sobczak S, Schmitt JA. (2003). Tryptophan modulation and cognition. Adv Exp Med Biol; 527:207-13. Review.

Risch SC, Nemeroff CB. (1992). Neurochemical alterations of serotonergic neuronal systems in depression. J Clin Psychiatry; 53 Suppl:3-7. Review.

Rissanen AM. (1994). Food and mood: relationship between food, serotonin and affective disorders. Acta Psychiatr Scand Suppl; 377:36-40. Review.

Roberts GM, Garavan H. (2010). Evidence of increased activation underlying cognitive control in ecstasy and cannabis users Neuroimage; 52(2):429-35.

Roberts AD, Pearce JM, Good M. (1998). Hippocampal lesions disrupt navigation based on cognitive maps but not heading vectors. Nature; 396(6706):75-7.

Robbins TW, Roberts AC. (2007). Differential regulation of fronto-executive function by the monoamines and acetylcholine. Cereb Cortex; 17 Suppl 1:i151-60. Review.

Roehrs T, Roth T. (2001). Sleep, sleepiness, sleep disorders and alcohol use and abuse. Sleep Med Rev; 5(4):287-297.

Rodgers J. (2000). Cognitive performance amongst recreational users of "ecstasy". Psychopharmacology (Berl); 151(1):19-24.

Roman V, Walstra I, Luiten PG, Meerlo P. (2005). Too little sleep gradually desensitizes the serotonin 1A receptor system. Sleep; 28(12):1505-10.

Roiser JP, Sahakian BJ. (2004). Relationship between ecstasy use and depression: a study controlling for poly-drug use. Psychopharmacology (Berl); 173(3-4):411-7.

Rolls ET. (1996). A theory of hippocampal function in memory. Hippocampus; 6(6):601-20.

Saadat KS, Elliott JM, Green AR, Moran PM. (2006). High-dose MDMA does not result in long-term changes in impulsivity in the rat. Psychopharmacology (Berl); 188(1):75-83.

Sachs C, Jonsson G. (1975). 5,7-Dihydroxytryptamine induced changes in the postnatal development of central 5-hydroxytryptamine neurons. Med Biol; 53(3):156-64.

Sahakian B, Jones G, Levy R, Gray J, Warburton D. (1989). The effects of nicotine on attention, information processing, and short-term memory in patients with dementia of the Alzheimer type. Br J Psychiatry; 154:797-800.

Sala M, Braida D. (2005). Endocannabinoids and 3,4-methylenedioxymethamphetamine (MDMA) interaction. Pharmacol Biochem Behav; 81(2):407-16. Review.

Sanchez, V, O'shea, E, Saadat, K.S, Elliott, J.M, Colado, M.I. & Green A.R. (2004). Effect of repeated ('binge') dosing of MDMA to rats housed at normal and high temperature on neurotoxic damage to cerebral 5-HT and dopamine neurones. Journal of Psychopharmacology; 18(3), 412-416.

Saunders, N. (1995) The chance of getting a good E in Britain. http://ecstasy.org/testing/purity.html.

Series HG, Cowen PJ, Sharp T. (1994). p-Chloroamphetamine (PCA), 3,4-methylenedioxy-methamphetamine (MDMA) and d-fenfluramine pretreatment attenuates d-fenfluramine-evoked release of 5-HT in vivo. Psychopharmacology (Berl); 116(4):508-14.

Schacter DL (1987). Implicit expressions of memory in organic amnesia: learning of new facts and associations. Hum Neurobiol; 6(2):107-18.

Scheffel, U, Szabo, Z, Mathews, W.B, Finley, P.A, Dannals, R.F, Ravert, H.T, Szabo, K, Yuan, J. & Ricaurte, G.A. (1998). In vivo detection of short- and long-term MDMA neurotoxicity – A positron emission tomography study in the living baboon brain. Synapse; 29, 183-192.

Schifano F. (1991). Chronic atypical psychosis associated with MDMA ("ecstasy") abuse. Lancet; 338(8778):1335.

Schifano F, Di Furia L, Forza G, Minicuci N, Bricolo R. (1998). MDMA ('ecstasy') consumption in the context of polydrug abuse: a report on 150 patients. Drug Alcohol Depend; 52(1):85-90.

Schifano F, Oyefeso A, Webb L, Pollard M, Corkery J, Ghodse AH. (2000a). Review of deaths related to taking ecstasy, England and Wales, 1997-2000. BMJ; 326(7380):80-1.

Schifano F. (2000b). Potential human neurotoxicity of MDMA ('Ecstasy'): subjective self-reports, evidence from an Italian drug addiction centre and clinical case studies. Neuropsychobiology; 42(1):25-33. Review.

Schilt T, de Win MM, Koeter M, Jager G, Korf DJ, van den Brink W, Schmand B. (2007). Cognition in novice ecstasy users with minimal exposure to other drugs: a prospective cohort study. Arch Gen Psychiatry; 64(6):728-36.

Schilt T, Goudriaan AE, Koeter MW, van den Brink W, Schmand B. (2009). Decision making as a predictor of first ecstasy use: a prospective study. Psychopharmacology (Berl); 203(3):519-27.

Schilt T, Koeter MW, Smal JP, Gouwetor MN, van den Brink W, Schmand B (2010). Long-term neuropsychological effects of ecstasy in middle-aged ecstasy/polydrug users. Psychopharmacology (Berl); 207(4):583-91.

Schneider GE (1973). Early lesions of the superior colliculus: factors affecting the formation of abnormal retinal projections. Brain Behav Evol; 8:73–109.

Scholey AB, Parrott AC, Buchanan T, Heffernan TM, Ling J, Rodgers J. (2004). Increased intensity of Ecstasy and polydrug usage in the more experienced recreational Ecstasy/MDMA users: a WWW study. Addict Behav; 29(4):743-52.

Scholey AB, Owen L, Gates J, Rodgers J, Buchanan T, Ling J, Heffernan T, Swan P, Stough C, Parrott AC (2011). Hair MDMA samples are consistent with reported ecstasy use: findings from a study investigating effects of ecstasy on mood and memory. Neuropsychobiology; 63(1):15-21.

Scott RM, Hides L, Allen JS, Burke R, Lubman DI. (2010). Depressive and anxiety symptomatology in ecstasy users: the relative contribution of genes, trauma, life stress and drug use. Psychopharmacology (Berl); 209(1):25-36.

Selvaraj S, Hoshi R, Bhagwagar Z, Murthy NV, Hinz R, Cowen P, Curran HV, Grasby P. (2009). Brain serotonin transporter binding in former users of MDMA ('ecstasy'). Br J Psychiatry; 194(4):355-9.

Senathi-Raja D, Ponsford J, Schönberger M. (2010). Impact of age on long-term cognitive function after traumatic brain injury. Neuropsychology; 24(3):336-44.

Sharp and Miech R. (2001). The formation of a socioeconomic health disparity: the case of cocaine use during the 1980s and 1990s. J Health Soc Behav; 49(3):352-66.

Shallice, 1982 cited in Culbertson WC, Zillmer EA. (1998). The Tower of London(DX): a standardized approach to assessing executive functioning in children. Arch Clin Neuropsychol; 13(3):285-301.

Shankaran M, Gudelsky GA. (1998). Effect of 3,4-methylenedioxymethamphetamine (MDMA) on hippocampal dopamine and serotonin. Pharmacol Biochem Behav; 61(4):361-6.

Silberg JL, Heath AC, Kessler R, Neale MC, Meyer JM, Eaves LJ, Kendler KS. (1990). Genetic and environmental effects on self-reported depressive symptoms in a general population twin sample. J Psychiatr Res; 24(3):197-212.

Simić I, Malicević Z. (2008). The acute effects of 3,4-methylenedioxymethamphetamine on oxidative stress in rat brain. Med Pregl; 61(5-6):222-5. Translated.

Simon NG, Mattick RP. (2002). The impact of regular ecstasy use on memory function. Addiction; 97(12):1523-9.

Slikker W Jr, Holson RR, Ali SF, Kolta MG, Paule MG, Scallet AC, McMillan DE, Bailey JR, Hong JS, Scalzo FM. (1989). Behavioral and neurochemical effects of orally administered MDMA in the rodent and nonhuman primate. Neurotoxicology; 10(3):529-42.

Smith GE, Petersen RC, Ivnik RJ, Malec JF, Tangalos EG. (1992). Subjective memory complaints, psychological distress, and longitudinal change in objective memory performance. Psychol Aging; 11(2):272-9.

Smith GB, Bezon J. (1997). Case management guideline. Major depression in adults and older adults. Nurs Case Manag; 2(6):246-54; quiz 255-6. Review.

Smith CN, Hopkins RO, Squire LR. (2006a). Experience-dependent eye movements, awareness, and hippocampus-dependent memory. J Neurosci; 26(44):11304-12.

Smith JC, Löw A, Bradley MM, Lang PJ. (2006b). Rapid picture presentation and affective engagement. Emotion; 6(2):208-14.

Sumnall HR, Tyler E, Wagstaff GF, Cole JC. (2004). A behavioural economic analysis of alcohol, amphetamine, cocaine and ecstasy purchases by polysubstance misusers. Drug Alcohol Depend; 76(1):93-9.

Sumnall HR, Cole JC. (2005) Self-reported depressive symptomatology in community samples of polysubstance misusers who report Ecstasy use: a meta-analysis. J Psychopharmacol; 19(1):84-92.

Soar K, Turner JJ, Parrott AC. (2001). Psychiatric disorders in Ecstasy (MDMA) users: a literature review focusing on personal predisposition and drug history. Hum Psychopharmacol.; 16(8):641-645.

Soar K, Parrott AC, Fox HC. (2004). Persistent neuropsychological problems after 7 years of abstinence from recreational Ecstasy (MDMA): a case study. Psychol Rep; 95(1):192-6.

Soloff, P.H, Lynch, K.G. & Moss, H.B. (2000). Serotonin, impulsivity, and alcohol use disorders in the older adolescent: a psychobiological study. Alcoholism: Clinical and Experimental Research; 24(11), 1609-1619.

Sowell ER, Thompson PM, Tessner KD, Toga AW. (2001a). Mapping continued brain growth and gray matter density reduction in dorsal frontal cortex: Inverse relationships during postadolescent brain maturation. J Neurosci; 21(22):8819-29.

Sowell ER, Delis D, Stiles J, Jernigan TL. (2001b). Improved memory functioning and frontal lobe maturation between childhood and adolescence: a structural MRI study. J Int Neuropsychol Soc; 7(3):312-22.

Squire LR.(1994). Memory and forgetting: long-term and gradual changes in memory storage. Int Rev Neurobiol; 37:243-69; discussion 285-8. Review.

Stalnaker TA, Takahashi Y, Roesch MR, Schoenbaum G. (2009). Neural substrates of cognitive inflexibility after chronic cocaine exposure. Neuropharmacology; 56 Suppl 1:63-72. Review.

Stanford MS, Wan L, Baldridge RM, Colby AM. (2009). Enhanced intensity dependence and aggression history indicate previous regular ecstasy use in abstinent polydrug users. Prog Neuropsychopharmacol Biol Psychiatry; 33(8):1484-90.

Steriade M. (1996). Awakening the brain. Nature; 383(6595):24-5.

Stone, D.M, Stahl, D.C, Hanson, G.R. & Gibb, J.W. (1986). The effects of 3,4-methylenedioxymethamphetamine (MDMA) and 3,4-methylenedioxyamphetamine (MDA) on monoaminergic systems in the rat brain. European Journal of Pharmacology; 128(1-2), 41-8.

Stuss DT and Alexander MP. (2000). Disorders of frontal lobe functioning. Semin Neurol; 20(4):427-37. Review.

Swann AC, Dougherty DM, Pazzaglia PJ, Pham M, Moeller FG. (2004). Impulsivity: a link between bipolar disorder and substance abuse. Bipolar Disord; 6(3):204-12.

Tabachnick BG, Fidell LS. (2001). Using Multivariate Statistics. Allyn and Bacon: Boston.

Tan BL. (2009). Profile of cognitive problems in schizophrenia and implications for vocational functioning. Aust Occup Ther J; 56(4):220-8. Review.

Taylor JR, Jentsch JD. (2001). Repeated intermittent administration of psychomotor stimulant drugs alters the acquisition of Pavlovian approach behavior in rats: differential effects of cocaine, d-amphetamine and 3,4-methylenedioxymethamphetamine ("Ecstasy"). Biol Psychiatry; 50(2):137-43.

Thompson M.Eisenberg N, Spinrad TL, Fabes RA, Reiser M, Cumberland A, Shepard SA, Valiente C, Losoya SH, Guthrie IK. (2004a). The relations of effortful control and impulsivity to children's resiliency and adjustment. Child Dev; 75(1):25-46.

Thompson JP. (2004b). Acute effects of drugs of abuse. Clin Med; (2):123-6.

Thompson MR, Li KM, Clemens KJ, Gurtman CG, Hunt GE, Cornish JL, McGregor IS. (2004c). Chronic fluoxetine treatment partly attenuates the long-term anxiety and depressive symptoms induced by MDMA ('Ecstasy') in rats. Neuropsychopharmacology; 29(4):694-704.

Toker L, Amar S, Bersudsky Y, Benjamin J, Klein E. (2010). The biology of tryptophan depletion and mood disorders. Isr J Psychiatry Relat Sci; 47(1):46-55.

Toates F. (2001). Biological Psychology. Pearson Education. Open University. Prentice Hall.

Topp L, Hando J, Dillon P, Roche A, Solowij N. (1999). Ecstasy use in Australia: patterns of use and associated harm. Drug Alcohol Depend; 55(1-2):105-15.

Tröster AI, Butters N, Salmon DP, Cullum CM, Jacobs D, Brandt J, White RF. (1993). The diagnostic utility of savings scores: differentiating Alzheimer's and Huntington's diseases with the logical memory and visual reproduction tests. J Clin Exp Neuropsychol; 15(5):773-88.

Tucker GT, Lennard MS, Ellis SW, Woods HF, Cho AK, Lin LY, Hiratsuka A, Schmitz DA, Chu TY. (1994). The demethylenation of methylenedioxymethamphetamine ("ecstasy") by debrisoquine hydroxylase (CYP2D6). Biochem Pharmacol; 47(7):1151-6.

United Nations reports. (2003/2008). www.unodc.org.

Valdes IH, Steinberg JL, Narayana PA, Kramer LA, Dougherty DM, Swann AC, Barratt ES, Moeller FG. (2006). Impulsivity and BOLD fMRI activation in MDMA users and healthy control subjects. Psychiatry Res; 147(2-3):239-42.

Vaiva G, Boss V, Bailly D, Thomas P, Lestavel P, Goudemand M. (2001). An "accidental" acute psychosis with ecstasy use. J Psychoactive Drugs; 33(1):95-8.

van den Buuse M, Becker T, Kwek P, Martin S, Ruimschotel E, Risbrough V. (2011) Disruption of prepulse inhibition by 3,4-methylenedioxymethamphetamine (MDMA): comparison between male and female wild-type and 5-HT1A receptor knockout mice. Int J Neuropsychopharmacol; 1-6.

van Nuijs AL, Castiglioni S, Tarcomnicu I, Postigo C, de Alda ML, Neels H, Zuccato E, Barcelo D, Covaci A. (2010). Illicit drug consumption estimations derived from wastewater analysis: A critical review. Sci Total Environ.

Verdejo-García AJ, López-Torrecillas F, Aguilar de Arcos F, Pérez-García M. (2005). Differential effects of MDMA, cocaine, and cannabis use severity on distinctive components of the executive functions in polysubstance users: a multiple regression analysis. Addict Behav; 30(1):89-101.

Verdejo-García A, Pérez-García M. (2007). Ecological assessment of executive functions in substance dependent individuals. Drug Alcohol Depend; 90(1):48-55.

Verheul R. (2001). Co-morbidity of personality disorders in individuals with substance use disorders. Eur Psychiatry; 16(5):274-82. Review.

Verheyden SL, Hadfield J, Calin T, Curran HV. (2002). Sub-acute effects of MDMA (+/-3,4-methylenedioxymethamphetamine, "ecstasy") on mood: evidence of gender differences. Psychopharmacology (Berl); 161(1):23-31.

Verheyden SL, Henry JA, Curran HV. (2003). Acute, sub-acute and long-term subjective consequences of 'ecstasy' (MDMA) consumption in 430 regular users. Hum Psychopharmacol; 18(7):507-17.

Verheyden SL, Hadfield J, Calin T, Curran HV. (2006). Sub-acute effects of MDMA (+/-3,4-methylenedioxymethamphetamine, "ecstasy") on mood: evidence of gender differences. Psychopharmacology (Berl); 161(1):23-31.

Verkes RJ, Gijsman HJ, Pieters MS, Schoemaker RC, de Visser S, Kuijpers M, Pennings EJ, de Bruin D, Van de Wijngaart G, Van Gerven JM, Cohen AF. (2001). Cognitive performance and serotonergic function in users of ecstasy. Psychopharmacology (Berl); 153(2):196-202.

Virkkunen ME, Horrobin DF, Jenkins DK, Manku MS. (1987). Plasma phospholipid essential fatty acids and prostaglandins in alcoholic, habitually violent, and impulsive offenders. Biol Psychiatry; 22(9):1087-96.

Virden TB, Baker LE. (1999). Disruption of the discriminative stimulus effects of S(+)-3,4-methylenedioxymethamphetamine (MDMA) by (+/-)-MDMA neurotoxicity: protection by fluoxetine. Behav Pharmacol; 10(2):195-204.

Vollenweider FX, Gamma A, Liechti M, Huber T. (1998). Psychological and cardiovascular effects and short-term sequelae of MDMA ("ecstasy") in MDMA-naïve healthy volunteers. Neuropsychopharmacology; 19(4):241-51.

Ward J, Hall K, Haslam C. (2006). Patterns of memory dysfunction in current and 2-year abstinent MDMA users. J Clin Exp Neuropsychol; 28(3):306-24.

Wareing M, Fisk JE, Murphy PN. (2000). Working memory deficits in current and previous users of MDMA ('ecstasy'). Br J Psychol; 91 (Pt 2):181-8.

Wareing M, Fisk JE, Murphy P, Montgomery C. (2005a). Verbal working memory deficits in current and previous users of MDMA. Hum Psychopharmacol; 19(4):225-34.

Wareing M, Fisk JE, Murphy P, Montgomery C. (2005b). Visuo-spatial working memory deficits in current and former users of MDMA ('ecstasy'). Hum Psychopharmacol; 20(2):115-23.

Wang X, Baumann MH, Xu H, Rothman RB. (2004) 3,4-methylenedioxymethamphetamine (MDMA) administration to rats decreases brain tissue serotonin but not serotonin transporter protein and glial fibrillary acidic protein. Synapse; 53(4):240-8.

Wechsler, 1987 cited in Loring DW, Papanicolaou AC. (1987) Memory assessment in neuropsychology: theoretical considerations and practical utility. J Clin Exp Neuropsychol; 9(4):340-58.

Willem Van der Merens W, Does AJ, Spinhoven P (2007). The effects of serotonin manipulations on emotional information processing and mood. Journal of Affective Disorders; 103:43–62.

Williamson S, Gossop M, Powis B, Griffiths P, Fountain J, Strang J. (1997). Adverse effects of stimulant drugs in a community sample of drug users. Drug Alcohol Depend; 44(2-3):87-94.

Wiklund L, Björklund A, Nobin A. (1978). Regeneration of serotonin neurons in the rat brain after 5,6-dihydroxytryptamine-induced axotomy. Ann N Y Acad Sci; 305:370-84. Review.

Winstock AR, Mitcheson LR, Deluca P, Davey Z, Corazza O, Schifano F. (2010). Mephedrone, new kid for the chop? Addiction; 106(1):154-61

Wurtman JJ. Carbohydrate craving, mood changes, and obesity. (1988). J Clin Psychiatry; 49 Suppl:37-9. Review.

Wurtman JJ. (1990). Carbohydrate craving. Relationship between carbohydrate intake and disorders of mood. Drugs; 39 Suppl 3:49-52. Review.

Xie T, Tong L, McCann UD, Yuan J, Becker KG, Mechan AO, Cheadle C, Donovan DM, Ricaurte GA. (2004). Identification and characterization of metallothionein-1 and -2 gene expression in the context of (+/-)3,4-methylenedioxymethamphetamine-induced toxicity to brain dopaminergic neurons. J Neurosci; 24(32):7043-50.

Yacoubian GS Jr, Miller S, Pianim S, Kunz M, Orrick E, Link T, Palacios WR, Peters RJ. (2003a). Toward an ecstasy and other club drug (EOCD) prevention intervention for rave attendees. J Drug Educ; 34(1):41-59.

Yacoubian GS Jr, Boyle C, Harding CA, Loftus EA. (2003b). It's a rave new world: estimating the prevalence and perceived harm of ecstasy and other drug use among club rave attendees. J Drug Educ; 33(2):187-96.

Yao K, Fang J, Yin YL, Feng ZM, Tang ZR, Wu G. (2011). Tryptophan metabolism in animals: important roles in nutrition and health. Front Biosci (Schol Ed); 3:286-97. Review.

Yücel M, Lubman DI, Solowij N, Brewer WJ (2007).Understanding drug addiction: a neuropsychological perspective. Aust N Z J Psychiatry; 41(12):957-68. Review.

Zakzanis KK, Young DA. (2001a). Executive function in abstinent MDMA ('ecstasy') users. Med Sci Monit; 7(6):1292-8.

Zakzanis KK, Young DA. (2001b). Memory impairment in abstinent MDMA ("Ecstasy") users: a longitudinal investigation. Neurology; 56(7):966-9.

Zakzanis KK, Campbell Z. (2006). Memory impairment in now abstinent MDMA users and continued users: a longitudinal follow-up. Neurology; 66(5):740-1.

Zhou, J.F, Chen, P, Zhou, Y.H, Zhang, L. & Chen, H.H. (2003). 3,4-Methylenedioxymethamphetamine (MDMA) Abuse may cause oxidative stress and potential free radical damage. Free Radical Research, 37(5), 491-497.

Zouk H, McGirr A, Lebel V, Benkelfat C, Rouleau G, Turecki G. (2007). The effect of genetic variation of the serotonin 1B receptor gene on impulsive aggressive behavior and suicide. Am J Med Genet B Neuropsychiatr Genet; 144B(8):996-1002.

Zuckermann (1984) cited in Zuckerman M. (1996). The psychobiological model for impulsive unsocialized sensation seeking: a comparative approach. Neuropsychobiology; 34(3):125-9. Review.