PROBLEMATIC AND NON-PROBLEMATIC ECSTASY (MDMA) USAGE: COGNITIVE AND PSYCHOPATHOLOGICAL ASPECTS

KIRSTIE SOAR

A thesis submitted in partial fulfilment of the requirements of the University of East London for the degree of Doctor of Philosophy

March 2005

ACKNOWLEDGEMENTS

I would like to take this opportunity to thank Professor Andy Parrott and Dr John Turner for supervising my PhD thesis over the past years and for their useful comments and corrections. Thanks also go to Margherita Milani and Helen Fox for their valuable advice and support; providing a forum for discussion, and for commenting on some chapters; as well as their friendship and support during the earlier years of this research.

Special thanks go to my parents Graham and Anne Soar for their love and support when the times were bad and especially for keeping me financially afloat for the first years of this thesis. Additional thanks to Graham for proof-reading the final version of my thesis. Thanks also go to Professor Irvine Gersch for the part-time work, which helped the financial situation, but also for the valuable moral support he has provided throughout the years.

Thanks to all my colleagues in the School of Psychology at the University of East London for their encouraging support, especially the 'girls' (you know who you are) and Alan Martin from room GN141. Lastly, I would also like to thank everyone who volunteered to participate in these research studies and those at the Big Issue magazine for facilitating contact with many participants through allowing me advertising space.

ABSTRACT

This research thesis aimed to explore the apparent dichotomy of ecstasy (MDMA) users who report cognitive and psychopathological problems which they attribute to their use of this drug ("problematic" users), and those who report no adverse ecstasy-related effects ("non-problematic" users). In the first study, possible psychological sequalae linked to past ecstasy use were assessed in problematic and non-problematic ecstasy users using the modified Brief Symptom Inventory, aspects of the Rivermead Behavioural Memory Test, Tower of London and Auditory Verbal Learning Task. Problematic ecstasy users displayed higher psychopathological symptoms and a small number of selective cognitive deficits compared to non-problematic ecstasy users and polydrug controls. However, problematic ecstasy use did not appear to be related to patterns of ecstasy use or polydrug use. Using the same assessment measures, a case study based on a heavy problematic ecstasy user (RW), who had been abstinent for seven years, was presented. RW displayed cognitive deficits and extensive psychological problems suggesting that heavy ecstasy consumption may be associated with irreversible problems. The persistence of possible psychological and cognitive problems was further investigated in the second group study, using the same battery of tests. However no significant differences in cognitive and psychopathological performances were found between polydrug controls, current and ex-ecstasy users. It is argued that impairments in performance were possibly masked by poor cognitive performance in polydrug controls. The validity of the polydrug control group was addressed (in the third study) by assessing 20 drug-naïve participants on the same measures. The introduction of a drug-naïve control group only suggested that problematic and non-problematic ecstasy users were exhibiting more errors on the Tower of London task compared to polydrug and drug-naïve controls. The final study assessed psychopathological symptoms in problematic and non-problematic ecstasy users relative to drug-naïve and polydrug controls, and explored factors which may be integral in the development of problematic ecstasy use, including certain pre-existing factors. Users were assessed on the BSI and Locus of Control scale. Pre-existing psychiatric histories, the intensity of ecstasy dosing and the role of polydrug use in relation to ecstasy use, appeared to contribute in higher psychopathological symptoms in problematic ecstasy users. Together these studies suggest that only self-reported problematic ecstasy users consistently display cognitive and psychopathological problems. For these vulnerable individuals the intensity of ecstasy use, patterns of other drug use and pre-existing psychiatric histories are thought to contribute to the development of these problems.

CONTENTS

FIGURES AND TABLES

APPENDICES

ABBREVIATIONS:

AVLT	Auditory Verbal Learning Task
BDI	Beck Depression Inventory
BSI	Brief Symptom Inventory
BZs	Benzodiazepines
CANTAB	Cambridge Neuropsychological Test Automated Battery
mCPP	1(3-Chlorophenyl)piperazine dihydrichloride
(r)CSF	Cerebrospinal fluid
DNMS	Delayed non-matching to samples test
DNTMP	Delayed non-match to place procedure
DXM	pheneylethylamine dextromethorphan
EEG	Electroencephalogram
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EMQ	Everyday Memory Questionnaire
ERBMT	Extended Rivermead Behavioural Memory Test
GC/MS	Gas chromatography/mass spectrometry
GH	Growth Hormone
GHB	Gamma-hydroxybutyrate
H-MRS	Proton Magnetic Resonance Spectroscopy
IVE	Impulsivity, Venturesomeness and Empathy Questionnaire
IMS	ion mobility spectrometry
LOC	Locus of Control Scale
LSD	d-lysergic acid
MDA	3,4-methlyenedioxyamphetamine
MDEA	3,4-methylenedioxy-N-ethylamphetamine
MDMA	3,4-methlenedioxymethamphetamine
MHLC	Multi-dimensional Locus of Control
MI	Myo-inositol
MFFT 20	Matching Familiar Figures Test 20
MR	Magnetic Resonance Imaging
NART	National Adult Reading Test
OCD	Obsessive-compulsive disorder
PET	Positron Emission Tomography
PMQ	Prospective Memory Questionnaire
RBMT	Rivermead Behavioural Memory Test
SCL-90	Symptom Checklist
SCL-90-R	Revised Symptom Checklist
SERT	Serotonin transporter
SPECT	Single Photon Emission Computed Tomography
SPSS	Statistical Package for the Social Sciences
SOSS	Self-ordered spatial search task
STAI	State-trait anxiety inventory
STAXI	State-trait anger expression inventory
TOL	Tower of London
VMAT	Vesicular monoamine transporters
WAIS-R	Wechsler Adult Intelligence Scale, Revised.
WMS-R	Wechsler Memory Scale, Revised
5-HIAA	5-hydroxyindoleacetic acid
5-HT	5-hydroxytryptamine (Serotonin)

CHAPTER 1

The History, Culture and Chemistry of MDMA (Ecstasy)

HISTORY OF MDMA/ECSTASY

3,4-methlyenedioxymethamphetamine (MDMA) was first synthesised and patented by Merck in 1914. Many believe it was patented as an appetite suppressant, but according to Holland (2001) there was no use mentioned for MDMA within this patent application and such claims probably arose from MDMA's chemical cousin MDA (3,4-methlyenedioxyamphetamine), which was patented by SmithKline French in 1958 and tested as an appetite suppressant in humans.

MDMA was never marketed due to the lack of commercial interest and therefore did not become available on the public market. It resurfaced briefly during the 1950's, in a toxicological and behavioural report from a study conducted by the US Army Chemical Centre when they secretly tested a number of psychoactive chemicals for military application (Shulgin & Nichols, 1978). It was not until 1976, that Alexander Shulgin synthesised MDMA and suggested its potential use in psychotherapy (Holland, 2001). From Shulgin's experiences, it was suggested that MDMA's subtle mood modifying characteristics could be used as a adjunct to psychotherapy, with the strengthening of the therapeutic alliance by enhancing trust, freeing patients from defensive anxiety and making them more emotionally open. Its success in fostering introspection and verbalisation during therapy led to a slow spread of its use in underground psychotherapeutic work in the late 70s and early 80s (Greer and Tolbert, 1986). The drug's ability to alter consciousness and induce such subtle mood changes leaked out of the therapeutic community, and as a result MDMA was being used amongst students throughout the US under its new name ecstasy.

In 1977 MDMA and other similar psychedelic amphetamines such as MDA and MDEA (3,4-methlyenedioxyethylamphetamine) were listed as class A drugs under the Misuse of Drugs Act 1971, in the United Kingdom (UK). In the United States (US) the drug was still legal until the mid 1980s. However due to numerous reports of misuse in conjunction with a widely publicised report of brain damage in rats caused by a similar drug, MDA, the US Department of Justice's Drug Enforcement Agency (DEA) followed the British Government and placed MDMA and related derivatives on the list of substances under international control schedule 1 (equivalent to UK Class A schedule).

Despite ecstasy's illegality within the UK, towards the end of the 1980s, it started to become a popular drug of choice at all-night dance parties, commonly known as 'raves', due to its modulation of emotional state; inducing feelings of relaxation, fearlessness and happiness which, along with its stimulant properties, enhanced the ability and enjoyment of dancing. Since then ecstasy has grown in popularity as a recreational drug and according to Saunders (1997), has been used by about one to five million people within Britain.

EPIDEMIOLOGY

Worldwide estimates of ecstasy use within the general population are hard to establish, but according to Holland (2001) nearly one million people take ecstasy every weekend. Ecstasy along with amphetamine is the second most commonly used drug in Europe (EMCDDA, 2001). Since the re-emergence of ecstasy in the late 80s, its use increased in the 1990s but now appears to be stabilising (EMCDDA, 2001). In 1998 prevalence rates in the general population of EU (European Union) adults were 0.5-3% (EMCDDA, 1998) and by 2002 this had only risen to 5% (EMCDDA, 2002).

The UK accounts for most of the ecstasy use in the EU, with rates at 11% (EMCDDA, 2002). Outside the UK the highest European rates appear in Ireland 8.9% (EMCDDA, 2001) and Latvia 6% (ESPAD, 2001). Similar rates to the EU have been reported elsewhere in the world. In Australia, for example, the National Drug Strategy Household Survey reports rates at 3%, (Commonwealth Department of Health and Family Services, 1996).

In the US, ecstasy has also been reported as the second most frequently tried illicit drug after cannabis (Pope et al, 2001). However, despite the prevalence rates stabilising in the EU, reports from America indicate a dramatic increase in use in the later part of the 90s amongst 16-26 year olds (Johnston et al, 2002). Amongst American college students, rates increased significantly by 69% between 1997 and 1999, from 2.8% to 4.7% (Strote et al, 2002). Whilst one study showed an increase in prevalence rates from 4.1% in 1989 to 10.1% in 1999 (Pope et al, 2001), however these rates were based on usage within just the one college.

Prevalence rates are higher in younger more specific age groups, with 6% of 15-34 years olds having used the drug. In a school survey 5% of 15-16 year olds reported its usage (EMCDDA, 2001). At the end of the 90s there was a marked rise in ecstasy use at the ages of

16/17 years (Measham et al, 1998), which is thought to reflect the shift in leisure activities of the youth as they start reaching the age to attend licensed clubs, bars and pubs. This is reflected in the greater use amongst university students at 13% (Webb et al, 1996). Additionally, prevalence rates are again much higher amongst youngsters that attend the rave or 'party' scene, in which ecstasy is a popular drug of choice; this is fairly consistent across the world. Amongst rave attendees in the UK, reported use varied from 82% to 96% (Riley et al, 2001; Forsyth, 1996; Winstock et al, 2001). In Australia, reported use amongst people in the rave scene has been seen to vary between studies, with Topp et al (1999) reporting 76% compared to an earlier report of 89% (Lenton et al, 1997); in the US, Arria et al (2002) reported lifetime use by 89% of rave attendees; and in Canada rates were reported as 65.2% (Gross et al, 2002).

PATTERNS OF ECSTASY USE

Recreational ecstasy use has been commonly associated with the rave or dance scene, were its use has been seen as a dance drug, and has been used in this setting more than any other recreational drug (Forsyth, 1996). However, its usage in more recent times has been seen to be shifting away from large dance events to more geographically diffuse club, bar and private settings (EMCDDA, 2000). In particular, a sub-cultural music preference for house/techno music has been shown to be the greatest predictor of ecstasy use (Pederson & Skrondal, 1999).

The assumption that drug users are unemployed, uneducated and come from socially deprived backgrounds does not fit the profile of a common recreational ecstasy user. Ecstasy users are not academic underachievers (Strote et al, 2002), but are generally employed or in higher education (Riley et al, 2001). In one survey of recreational ecstasy users, 80% reported having been in further education (Forsyth, 1996), and another survey reported 65% of users were currently employed (Winstock et al, 2001).

The ecstasy user is more than likely to be white (Hammersley, 1999), with surveys reporting the average age to be late teens to early twenties (e.g. mean age 18.9 years (Lenton et al, 1997) and 24 years old (Winstock et al, 2001)). In addition, approximately half to two thirds of all users being male (62% - Forysth, 1996; 56% - Boys et al, 2001; 53% - Lenton et al, 1997).

The drug is usually consumed orally in multiple tablets (Winstock et al, 2001), but there is a subsample of users (16%), mostly found in Australia, that report injection of ecstasy (Topp et al, 1999). Boys et al (2001) examined the reasons why a sample of poly-substance users chose to use ecstasy, and they discovered that 91% of users reported that the main reason for using ecstasy was to 'keep going'. Also, 78% reported using for its euphoric/elation effects, 80% for its ability to enhance activity, 72% to stay awake and 68% to feel intoxicated.

Recreational ecstasy users rarely report sole use of the drug. In fact, Hammersley (1999) failed to find a single interviewee that reported sole use of ecstasy. Instead ecstasy users are more likely to be polydrug users, in that they often consume ecstasy in combination with other substances, such as tobacco, cannabis, speed, alcohol, d-lysergic acid (LSD), and amyl nitrate (Winstock et al, 2001; Topp et al, 1999; Arria et al, 2002). Ecstasy 'polydrug' users have also been shown to consume cannabis, alcohol, tobacco, amphetamine, heroin and benzodiazepines (BZs) whilst coming off the drug (Topp et al, 1999; Winstock et al, 2001). There are a number of potential reasons why people choose to consume ecstasy in the context of polydrug use. Firstly, taking several psychoactive compounds together may enhance the effects of ecstasy (Schifano, 2004). In particular, the use of alcohol prior to taking ecstasy is thought to enhance the 'high' from MDMA (Schifano, 2004), whilst stimulants, such as amphetamine and cocaine are thought to maintain the arousal and alertness of the ecstasy experience. Sedatives and relaxants, such as opiates, BZs and cannabis, are reported to relieve the unpleasant sub-acute effects of ecstasy (Scholey et al, 2004). Secondly, it has been repeatedly reported that there is a decrease in the desired effects of ecstasy following repeated use (Scholey et al, 2004; Parrott, 2005). This chronic tolerance to ecstasy may lead to the use of other stimulants and hallucinogens in order to try and achieve the initial ecstasy effects (Schifano, 2004). Some ecstasy users have indeed reported that this is the reason behind the need to consume other psychoactive drugs in the context of ecstasy use (Scholey et al, 2004).

ACUTE EFFECTS OF MDMA

The acute effects of MDMA begin approximately 30-60 minutes after ingestion and last for approximately 3-5 hours (Liechti & Vollenweider, 2001). Numerous controlled studies using single doses of pharmaceutical MDMA have shown consistent behavioural and physiological

effects in humans. The behavioural and psychological effects include increased positive mood, feelings of euphoria, increased physical and emotional energy, heightened sensual awareness, depersonalisation, derealisation, fear of loss of control, increased extroversion, mild perceptual alterations, increased self-confidence, accelerated thinking, thought blocking, difficulty in concentrating and impaired decision making (Downing, 1986; Liechti et al, 2000a; Liechti et al 2000b; Gamma et al, 2000; Cami et al, 2000; Liechti & Vollenweider, 2001). Reported physiological effects of MDMA include suppressed appetite, pupil dilation, jaw clenching (trismus), enhanced tendon reflexes, increased heart rate and blood pressure, increased peripheral body temperature, dry mouth, impaired balance and dizziness (Downing, 1986; Grob et al, 1996; Liechti et al, 2000a; Gamma et al, 2000; Liechti & Vollenweider, 2001).

The subjective psychological and physiological effects from pharmaceutical grade MDMA are similar to the subjective acute effects of ecstasy. It has been repeatedly reported that ecstasy users experience elation, agreeableness, euphoria, increased energy, confidence, exhilaration, warmth and friendliness, calmness and relaxation, increased perception of sound, colour and touch, confusion, increased heart rate, increased body temperature, sweating and dehydration, trismus, sexual arousal, papillary dilation, bruxism, lower back pain and nausea (Cohen, 1995; Davison & Parrott, 1997; Parrott & Stuart, 1997; Verheyden et al, 2003).

Following the acute effects of ecstasy, users report subacute effects in the following 24 to 48 hour period, which tend to be negative effects (Verheyden et al, 2003), characterised by symptoms such as muscle aches, lethargy, fatigue, moodiness, depression, anxiety, aggression, paranoia, irritability, difficulty in concentrating and headache (Curran & Travill, 1997; Davison & Parrott, 1997; Verheyden et al, 2002; Verheyden et al, 2003). Which of these adverse residual effects individuals experience, and to what degree, has been shown to be determined by the age of the user and the length of their ecstasy usage (Verheyden et al, 2003). Gender has also been shown to determine differences in sub-acute effects, with females being more susceptible to the depressive mood effects than men (Verheyden et al, 2002). This period is often referred to the as 'the come down' or 'crash' stage from ecstasy. Again, these subjective, subacute effects of ecstasy are similar to the subacute effects of MDMA. Leicht, Gamma and Vollenwider (2001) demonstrated post MDMA-treatment effects such as fatigue, muscle ache and headache in approximately half of the participants and up to a third reported lowering of mood, including emotional irritability, lack of energy,

brooding and bad dreams. The fact that the subjective effects of acute and subacute ecstasy use are similar to the acute and subacute effects of MDMA administration in placebo controlled studies, suggests that in most cases ecstasy contains the active compound MDMA more so than any other psychoactive drug.

PSYCHOPHARMACOLOGY OF MDMA

3,4-methylenedioxymethamphetamine (MDMA) is a completely synthetic substance. It is a ringed substituted amphetamine derivative, which resembles the structure of the hallucinogenic material mescaline. As a result its pharmacological effects are a blend of those from amphetamine and mescaline, affecting 5-hydroxytryptamine (Serotonin; 5-HT) and dopamine-containing neurons, and also other neurotransmitter systems; hence the frequent references to MDMA being a rather 'messy' drug.

MDMA acts as an indirect monoaminergic agonist, stimulating the release of 5-HT from the presynaptic neuron (Nixdorf et al, 2001) and inhibiting the reuptake of 5-HT (Iravani et al, 2000; Mechan et al, 2002), causing the synapse to be flooded with atypically large amounts of 5-HT. At the same time it also causes the release of dopamine; although this effect is weaker than the MDMA-induced efflux of 5-HT (Yamamoto and Spanos, 1988; Gough et al, 1991; Nixdorf et al, 2001) and, possibly, norepinephrine (Rothman et al, 2001). Additionally, MDMA produces a rapid inactivation of trytophan hydroxylase (Stone et al, 1989; Schmidt and Taylor, 1988), an enzyme necessary for the synthesis of 5-HT, thus slowing 5-HT replenishment. For a more comprehensive review of the pharmacology of MDMA see Green et al (2003).

The acute boost in monoamine activity generates the unique reinforcing effects of the drug. Selective blocking studies show that the subjective effects of MDMA (feelings of elation, euphoria and well-being, emotional closeness and sensory pleasure; Liechti et al, (2000a & 2000b) and Cami et al, (2000)), are largely dependent on carrier-mediated 5-HT release, whilst the stimulant-like mood effects appear to be related, at least in part, to dopamine D2 receptor stimulation (see Liechti & Vollenweider, 2001). The mild hallucinogenic like perceptual effects appear to be due to serotonergic 5-HT2-receptor stimulation (Liechti & Vollenweider, 2001). Because MDMA's dopaminergic actions are similar to those of amphetamine, whilst its serotonergic effects are closer to LSD, in behavioural terms MDMA

displays similarities to both amphetamine and LSD. However, its strong euphoric properties appear to be unique to MDMA itself.

MDMA NEUROTOXICITY IN ANIMALS

There is currently a large body of preclinical research, which shows that MDMA has neurotoxic effects on brain serotonin neurons in animals (for a comprehensive review see Ricaurte et al, 2000 and Green et al, 1995 & 2003). Evidence has arisen from studies using a variety of experimental techniques and neurochemical, neuroanatomcial and functional measures of 5-HT neurons, which have consistently demonstrated MDMA-induced serotonergic injury. These include long-term decreases in levels of 5-HT, the metabolite 5-HIAA, 5-HT transporters, tryptophan hydroxylase activity, anterograde transporters and vesicular monoamine transporters (VMAT) and histological evidence of 5-HT axon degeneration (Ricaurte, 2000). The areas of the rat brain that appear to be the most sensitive to these alterations in serotonergic activity are the striatum, hippocampus and prefrontal cortex, with smaller but significant effects in the brain stem and hypothalamus (Sabol et al, 1996).

This selective serotonergic neurotoxicity induced by MDMA has been demonstrated in a variety of animals, such as rats (Finnegan et al, 1988; Lew et al, 1996), guinea pigs (Battaglia et al, 1988), baboons (Scheffel et al, 1998) and monkeys (Ricaurte et al, 1988). Non-human primates have been shown to be considerably more sensitive to the serotonin depleting effects than rats (Ricaurte, 1989). The only animal to date that is resistant to this MDMA-induced serotonergic neurotoxicity is the mouse. In the mouse dopamine neurons are affected whilst serotonin neurons appear to be spared (Battaglia et al, 1988; O'Shea et al, 2001).

Studies have also suggested that regardless of the route of administration and dosage of MDMA, serotonin neurotoxicity is still evident. Orally administered MDMA has been seen to produce toxic effects that are comparable to those induced by subcutaneous administration in rats and monkeys (Finnegan et al, 1988; Ricaurte et al 1988). Serotonergic neurotoxicity also appears to be dose-dependent (Battaglia et al, 1988; Finnegan et al, 1988). However, even though multiple doses of MDMA are more effective than single doses at depleting serotonin, Ricaurte et al (1988) showed that even a single dose of MDMA could produce long-lasting depletions in monkey brain 5-HT.

These effects in animals produced by oral administration and single and multiple dosing of MDMA, often at concentrations analogous to MDMA amounts in ecstasy users (Ricaurte, 2000), has raised legitimate concerns about possible MDMA-induced neurotoxicity in humans (Parrott, 2000; Turner and Parrott, 2000). Furthermore, comparative animal data has shown that the level of neurotoxicity also increases in high ambient temperatures (Broening et al, 1995; Colado et al, 1998; Malberg and Seiden, 1980). However, caution needs to be taken in interpreting many of the animal findings and extrapolating to human MDMA use. The dosing regimens used in animals vary greatly between studies, and many studies look at amounts that actually cause neurotoxic effects, rather than looking at doses that are equivalent to those used by human recreational ecstasy users. Many animals employed in these studies also have been used in previous studies assessing the acute effects of several other psychoactive compounds (Frederick et al, 1995; Frederick et al, 1998; Taffe et al, 2001).

Behavioural consequences of MDMA-induced neurotoxicity in animals

Considering the evidence of MDMA-induced neurotoxicity in animals, it is important to determine whether such neurotoxicity has behavioural consequences, and if so, what areas of behaviour are affected. Compared to the number of animal studies demonstrating neurotoxicity, there is a somewhat limited behavioural data in animals. Studies investigating various regimens of MDMA on animal behaviour have consistently failed to find any baseline changes in performance across a number of behavioural tests, despite marked reductions in 5-HT and 5-HIAA (up to 80% decrease, in the study of Winsaur et al, 2002) in areas including the hippocampus, striatum, neocortex, caudate, and thalamus (Ricaurte et al, 1993; Seiden et al, 1993; Marston et al, 1999; Dornan et al 1991; Frederick et al, 1995; Winsaur et al, 1993), which have, in some studies, lasted up to 4-7 months (Ricaurte et al, 1993; Taffe et al, 2001; Frederick et al 1998).

In a majority of the studies that have demonstrated cognitive and behavioural dysfunction relative to control animals, this has not persisted longer than 7 days post-MDMA treatment (Slikker et al, 1989; McNamara et al, 1995; Robinson et al, 1993; Taffe et al, 2001; Maldonado & Navarro, 2001; Navarro et al, 2004). McNamara et al (1995) demonstrated behavioural changes in locomotor activity in rats, during the 4 days of MDMA administration, but following withdrawal of MDMA no changes were observed compared to

controls, despite MDMA-induced depletions of 5-HT and 5-HIAA in the frontal cortex and amygdala, 7 days after treatment. Similarly, rats who showed 73% depletion in serotonin concentrations in the neocortex and 32% in the caudate nucleus relative to controls, only demonstrated a mild impairment in developing an efficient search strategy, on a spatial-navigation learning set-task, on the first three days of training, after MDMA-treatment. However, once learnt, memory performance concerning this location was equivalent to that of controls (Robinson et al, 1993). Taffe et al (2001) reported behavioural impairments in rhesus monkeys treated with MDMA. Performance in memory, on the delayed non-matching to samples test (DNMS) and the self-ordered spatial search task (SOSS); reinforcer efficacy and sustained attention on a progressive-ratio (PR) schedule of responding task; fine motor control on a bimanual motor task reaction; and reaction time were all impaired relative to controls. Task performance returned to pre-treatment baseline levels within one week after MDMA treatment, despite reports of a 44% reduction in 5-HIAA concentrations which persisted for approximately 3 months after MDMA treatment. However, they did report one single animal's behavioural performance to be severely affected which persisted for up to two months.

These earlier studies suggest that any cognitive and behavioural dysfunction in MDMA treated animals is the result of the acute and sub-acute effects of MDMA, rather than functional consequences of neurotoxicity. This evidence also suggests that the neurotoxic effects of the drug may not be manifested behaviourally, despite the underlying neurochemical changes. However, more recent studies have shown behavioural effects related to MDMA-neurotoxicity. Martson et al (1999) reported a selective deficit in performance in rats on the delayed non-match to place procedure (DNTMP), 16 days following MDMA exposure. MDMA-treated rats did not show the improvement in performance at the longer delays, as seen in the control rats. In addition, MDMA treated rats showed reductions of 5-HT function upon post-mortem analysis. Memory impairments, on object recognition tasks, in MDMA treated rats have also been shown, one week (Piper & Meyer, 2004) and 10-12 weeks after drug treatment (McGregor et al, 2003). Taffe et al (2002) have showed lasting behavioural sensitivity in monkeys. When pharmacologically challenged with 1(3-Chlorophenyl)piperazine dihydrichloride (mCPP), vigilance and reaction time (5-choice reaction time), and reinforcer efficacy and sustained attention (PR), where disrupted in monkeys treated 13-months previously with MDMA . Taffe et al (2002) also

showed 50% reductions in 5-HIAA, 2-17 weeks post MDMA treatment. However, cognitive dysfunction was quite small compared to the magnitude of serotonin depletion.

Studies also indicate that social interaction and anxiety-related behaviours are disrupted in MDMA-treated animals, which are lasting after the cessation of MDMA administration. McGregor et al (2003) reported that rats pre-treated with MDMA displayed increased anxiety in a social interaction test and emergence test; demonstrating a shorter duration of social interaction and fewer social interaction bouts, and took longer to emerge in the open field compared to control groups 8-10, weeks following drug administration. In addition, rats were reported to have shown depressive symptoms in the forced swim test, displaying reduced escape attempts and increased immobility. However, these symptoms were only evident on the third day of testing. Ho et al, (2004) did not provide indications of anxiety, reduced social interaction and depressive symptoms, using similar testing paradigms (open field, plus maze and forced swim test). However, Ho et al (2004) only injected animals with a single dose (7.5mg/kg) of MDMA compared with a dosing regimen of 5 mg/kg every 4 hours on 2 consecutive days (20 mg/kg per day) in McGregor et al's study. This, together with the animal studies which have demonstrated small, if any, changes in behaviour compared to the relatively large amounts of serotonin depletion, suggests that it may be the magnitude of neurotoxicity produced by MDMA that is crucial in behavioural studies. The research data suggests that there may be a threshold effect of 5-HT, below which no behavioural consequences will be observed. In many of the studies which have not demonstrated behavioural disturbances or very limited and selective deficits, there may not have been sufficient neurotoxic damage over and above that 5-HT threshold, in order to interfere with behavioural and cognitive functioning.

The shortage and very selective nature of long-term behavioural dysfunction in these studies may be because of the specific tests employed and the differing paradigms: they may not be sensitive enough to detect changes in the 5-HT system; and the behaviour in question may not be influenced directly by the 5-HT system. What is certain is that the animal behaviour research has utilised various behavioural measures, covering numerous behavioural domains which are known to be sensitive to small changes in monoamine neurotransmitter concentrations (Seiden et al, 1993). One possibility to account for discrepancies in some of these tests is that the lasting effects of MDMA may depend on subject-dependent factors.

Taffe et al (2001) drew attention to one monkey of the six that they assessed, which demonstrated marked deficits in performance which lasted for up to 2 months. Ho et al (2004) also demonstrated behavioural impairments 3 weeks after MDMA-treatment only in animals with low anxiety levels, but not high anxiety levels. This demonstrates certain individual vulnerabilities to MDMA-induced effects.

Recovery from MDMA neurotoxicity in animals

Animal studies have shown that these neurodegenerative effects in the serotonin system are long lasting (up to one year). However, there is evidence which shows 'recovery' of this serotonergic function; although subsequent reorganisation and/or function may be abnormal. Recovery of serotonin reuptake sites has been shown in rats, with the concentration of 5-HT reuptake sites returning to control levels after 12 months (Battaligia et al, 1991; Sabol et al, 1996; Scheffel et al, 1998; Scanzello et al, 1993). Taffe et al (2001) demonstrated a 44% reduction in 5-HIAA concentrations and altered peak latencies in brainstem auditory evoked potentials in rhesus monkeys, which persisted for approximately 3 months post-MDMA treatment, yet in the fourth month both these measures normalised.

Ricaurte at al (1992) showed evidence of partial recovery in some brain regions of nonhuman primates (hippocampus, caudate nucleus, frontal cortex). However, after 18 months it was evident that recovery did not continue in all regions with the exception of the thalamus and hypothalamus. Thus the rate and degree of recovery appears to depend on the brain region (Lew et al, 1996; Battaglia et al, 1991; Sabol et al, 1996), with some brain regions showing an increase in 5-HT functioning, mainly the hypothalamus, but others showing persistent decreases (Ricaurte et al, 1992; Scheffel et al, 1998); also, recovery was not always normal. Fischer et al (1995) demonstrated that the pattern of some of the serotonin axonal sprouting in both rats and monkeys was abnormal, especially in the amygdala and hypothalamus where neuron axons were reinnervated or hyperinnervated, suggesting that MDMA actually lead to a reorganisation of the serotonin system. Such abnormal patterns were also evident in monkeys seven years after MDMA treatment, although some regions were less severely affected than those observed at 18 months (Hatzidimitriou et al 1999). This abnormal reorganisation of 5-HT axons and axon terminals is synonymous to the 'pruning effect' seen with a number of neurotoxins (Ricaurte et al, 2000), where nerve cells will often grow replacement terminals,

where there has been damage, resulting in a different dendritic pattern. This pruning effect provides further evidence of MDMA's neurotoxicity (Ricaurte, 2000), but also of potential attempts of the serotonergic system to recover from such damage.

Serotonergic recovery also depends on the animal treated. On inspection of experimental animals, Scanzello et al (1993) revealed a group of rats that did not show signs of recovery, whilst others did. Those that did not recover had severe and enduring serotonergic deficits in multiple brain regions. Thus, it appears that the recovery of serotonin neurons is region dependent and also varies between and within species. Monkeys tend to be more sensitive and damage appears to be permanent, whereas with rats there is some indication that recovery takes place, but the question is whether this is sustained? Such differences in recovery may be due to the severity of damage sustained from MDMA; the more severe the damage, or more highly arborized, the lower the probability of recovery (Fischer et al, 1995). Disparity may also be due to genetic differences, individual vulnerabilities and other parameters like age, health status, diet and fluid supply etc.

Whilst studies have demonstrated the potential for animals to show a certain level of recovery from neurotoxic effects of MDMA, this recovery is not always normal and there is a paucity of research indicating the behavioural consequences this has. As tests for neurotoxic effects become more refined, then the assessment of behavioural recovery should become possible.

HUMAN NEUROTOXITICY

That fact that nearly all animal species tested are sensitive to the neurotoxic potential of MDMA (with the exception of the mouse), suggests that humans too will be sensitive to the toxic effects. Applying the well-established principles of interspecies scaling also strengthens the case for human sensitivity to MDMA-induced serotonergic neurotoxicity. The principle of interspecies scaling is that smaller animals require higher doses of a psychoactive drug to achieve the equivalent effect. As demonstrated in the animal literature, rodents require higher doses of MDMA to produce the same neurotoxic effect as in non-human primates. Using this technique, the dosages of MDMA known to be neurotoxic in animals falls squarely in the range of dosages typically used by recreational ecstasy users: between 75-125mg of MDMA (Ricaurte et al, 2000). The fact that most recreational ecstasy users consume more than one

dose of ecstasy on one occasion (Winstock et al, 2001), and that the acute effects of ecstasy mimic these controlled effects of pharmaceutical MDMA (Leicht & Vollenweider, 2001), strongly suggests that recreational ecstasy users are ingesting neurotoxic doses of MDMA.

A number of lines of evidence to support the notion that MDMA-induced serotonergic neurotoxicity occurs amongst recreational ecstasy users has emerged in the last 10 years (see table 1). Methods of assessing serotonin neurotoxic changes in the living human brain include analysis of cerebrospinal fluid (CSF) 5-hydroxyindoleacetic acid (5-HIAA – a major metabolite of serotonin) concentrations and pharmacological challenges using 5-HT agonists. Less invasive methods of assessing changes have included Positron Emission Tomography (PET), Single Photon Emission Computed Tomography (SPECT), Proton Magnetic Resonance Spectroscopy (H-MRSI), Electroencephalograms (EEG) and assessment of auditory evoked potentials.

1. CSF Assessment

The first study which measured the concentration of 5-HIAA in cerebrospinal fluid (CSF) did not find any significant indication of neuronal alteration in ecstasy users compared to age-matched controls (Peroutka et al, 1987). However, subsequent studies using the same technique and larger participant numbers have consistently demonstrated significantly reduced concentration levels of CSF 5-HIAA in human ecstasy users compared to controls (Ricaurte et al, 1990; McCann et al, 1994; Bolla et al, 1998; McCann et al, 1999). Bolla et al, (1998) demonstrated a dose-response effect, with the concentration of 5-HIAA decreasing as the dose of reported ecstasy use increased. However, other studies which have looked at this correlation, have not found a significant relationship between the concentration levels of 5-HIAA and number of ecstasy exposures (Ricaurte at al, 1990; McCann et al, 1994). Measuring levels of CSF does not indicate which areas of the brain are potentially affected by ecstasy, if at all; because CSF can also be a consequence of psychological changes; (e.g CSF 5-HIAA is lower in depressed individuals (Becker et al, 1995)).

2. Pharmacological Challenges

Pharmacological challenges using 5-HT modulators, such as L-tryptophan, d-fenfluramine and M-chlorophenylpiperazine, have also been used to assess possible MDMA-induced

neuronal alterations but with less consistency in their findings. Price et al (1989) first demonstrated altered 5-HT functioning compared to healthy controls, using the precursor L-tryptophan. Ecstasy users showed blunted responses to the effects of L-tryptophan, as measured by prolactin concentration, yet the difference compared to healthy controls failed to reach significance. A subsequent study using L-tryptophan also did not find any significant differences in prolactin concentration between ecstasy users and controls (McCann et al, 1999). A more recent study by Curran & Verheyden (2003) showed that only ex-ecstasy users (who had used more than 20 tablets, but not within the last year), and not current ecstasy users (who had used more than 20 tables within the last year), showed significantly higher levels of total and free plasma tryptophan following tryptophan manipulation compared to polydrug controls. However, such differences in these ex-users may reflect pre-morbid differences in their 5-HT function.

The studies by Gerra et al (1998 & 2000) and Verkes et al (2001) have indicated alterations in serotonin functioning in ecstasy users compared to control participants using the agonist d-fenfluramine, with ecstasy users showing significantly reduced prolactin and cortisol responses compared to controls. Gouzoulis-Mayfrank et al (2002) failed to find any significant effects of d-fenfluramine. However, one of their control groups consisted of heavy cannabis users, which is thought to be an important confound in endocrinological studies of ecstasy users.

McCann et al (1999) also found evidence of possible serotonergic neurotoxic change using another 5-HT agonist, M-chlorophenylpiperazine, which caused significant blunting of both prolactin and cortisol responses in heavy ecstasy users compared to non-using controls. It therefore appears that differences in the studies involving pharmacological challenges are related to the 5-HT activating drug used, with L-tryptophan appearing to be the least sensitive probe for demonstrating brain serotonergic alteration induced by MDMA. None of these pharmacological challenge studies have demonstrated any significant correlation between prolactin responses and the amount of ecstasy used (Price et al, 1989; Gerra et al 1998 & 2000), such that in summary pharmacological challenge techniques seem a somewhat crude and indirect assessment measure of MDMA neurotoxicity in humans.

3. Neurological Assessment

More recently less invasive methods of evaluating the neurotoxic effects of MDMA in humans have been developed, using measurements of biological markers by *in vivo* imaging techniques (see Table 1; for a comprehensive review see Reneman et al, 2001). PET studies using the 5-HT transporter ligand McN-5652 have shown decreases in both global and regional 5-HT transporter binding in ecstasy users, compared with ecstasy-naïve controls (McCann et al, 1998) and polydrug controls (Thomasius et al, 2003). This would appear to indicate actual structural changes in the serotonin neurons within the brain. Also the decreases observed in the 5-HT labelled transporter sites correlated with the degree of previous MDMA exposure (McCann et al, 1998), indicate dose-related 5-HT neurotoxicity. Further, using the same transporter ligand, Buchert et al (2003) showed that ecstasy users had significantly reduced distribution volume ratios of SERT (presynaptic serotonin transporter) availability in the mesencephalon and thalamus, compared to drug naïve controls. However, Gamma et al (2001) did not find any indication of neuronal alterations using the same 5-HT ligand; although this method only used PET to detect possible deviant patterns of rCBF, not SERT densities or availability.

Neuronal activity using PET has also been studied by Obrocki et al (2000). They assessed alterations to the brain cerebral glucose metabolic rate using the ligand 2-[(18)F]-fluro-2-deoxy-D-glucose (FDG). They demonstrated lasting reductions in the metabolic uptake rate within the amygdala, hippocampus and Brodmann's area 11 in ecstasy users, compared to controls. However, no correlations were found between FDG uptake rates and cumulative ecstasy dosage. One further limitation of this study was that FDG PET does not selectively display activity of the serotonergic system; rather it reflects total neuronal activity and thus the possible effects of MDMA on other neurotransmitters in these areas, can not be established. In addition, it is as yet impossible to conclude whether any disruption to 5-HT or other neurotransmitters, is due to MDMA and/or other drug use.

SPECT has also been used to demonstrate selective serotonin neurotoxicity, using a number of different radioactive ligands; in particular [^{123}I]β-CIT and [^{123}I]R91150 which are good *in vivo* tracers for 5-HT transporters (Reneman et al, 2001). Using these markers, ecstasy users were shown to have significantly reduced cortical SERT, particularly in the primary sensory cortex, compared to polydrug controls, but there were no correlations between lifetime dose

and reductions in SERT binding (Semple at al, 1999). Such effects on cortical 5-HT receptor densities have been replicated by Reneman and colleagues (2000, 2001a, 2001b), who demonstrated significantly lower binding ratios in recent ecstasy users compared to controls. This suggests down-regulation of receptors caused by MDMA-induced 5-HT release. Reductions in receptor densities have also been demonstrated in all areas studied within the cerebral cortex (Reneman et al, 2002), but with no correlation between the level of cortical binding and extent of previous ecstasy use.

These alterations in SERT densities only appear to occur in heavy ecstasy users. In all of the above studies, reported lifetime consumption of ecstasy is above 140 tablets. Reneman et al (2001) only found significant decreases in overall binding ratios in heavy users (who had used over 50 ecstasy tablets) compared to non-ecstasy users, but not between binding ratios of moderate users (who reported use of a maximum of 50 ecstasy tablets) compared with non-users. This could be taken to suggest a possible dose-response effect shown in the previously discussed animal data. However, this could also be indicative of a neurotoxic 'threshold'. Below this threshold neurons can manage or self-protect against (or perhaps recover from) the neurotoxic effects of MDMA, but above this threshold neurons may sustain damage.

Magnetic resonance spectroscopic imaging (1H-MRSI) has also provided evidence for neuronal abnormality in human recreational ecstasy users. Reneman et al (2002) evaluated the MDMA-related alterations in metabolite ratios: N-Acetylaspartate (NAA) / creatine (Cr), NAA/Choline (Cho) and myo-inositol (MI)/Cr ratios (markers associated with neuronal loss or dysfunction) in the frontal cortex of ecstasy users. Neuronal abnormalities significantly correlated with the degree of ecstasy use: the higher the amount of ecstasy exposure the lower the metabolite ratios. Chang et al (1999) also demonstrated metabolic alterations in ecstasy users compared to normal controls using the same method. Cumulative lifetime dose showed significant effects on MI (a glial marker) in the parietal white matter and the occipital cortex of ecstasy users. However, using the same technique, Obergeisser et al (2001) failed to find any group differences in neuronal functioning in the hippocampus, between ecstasy users and controls, although they only assessed a small number of users (5) and also a differing region of the brain to that assessed by Reneman et al (2002), which might account for the difference in findings.

Neuroimaging techniques are not without their criticism, especially when it comes to data interpretation as evidence for MDMA neurotoxicity. The binding specificity of ligands has been questioned, potentially causing an under or overestimation of binding density (see Cole et al, 2003 for further discussion). Also, the loss of markers indicated in these neuroimaging techniques does not necessarily equate to actual cell loss. Certain polymorphisms in the 5-HT transporter gene have shown to have reduced 5-HT transport activity. As such, these possible pre-existing differences in ecstasy users in previous studies are unknown (Kish, 2002). Whilst there are limitations to neuroimaging studies, the converging line of evidence, using different techniques in conjunction with the preclinical animal data, does allow for a certain level of assessment of the potential effects of ecstasy.

4. Electrophysiological Assessment

Other evidence of MDMA-induced depletion of 5-HT functioning is provided by studies using electrophysiological assessment, involving the auditory evoked potentials and the intensity dependence paradigms. The intensity dependence of auditory evoked potentials is thought to be one index of 5-HT integrity. High intensity dependence has found to be associated with a low functioning of serotonergic neurotransmission (Hegerl and Juckel, 1993). Croft et al (2001) and Tuchtenhagen et al (2000) have both demonstrated serotonin neuronal alterations via this method in ecstasy users. Ecstasy users exhibited significant increases in amplitude of the tangential N1/P2 source activity with higher stimulus intensities compared to drug-naïve and cannabis users, indicating diminished serotonergic activity specifically in ecstasy users. In addition, Croft et al (2001) demonstrated a significant positive relation between ecstasy users' N1/P2 slopes and total ecstasy consumption independent of cannabis use, suggesting a causative link between ecstasy and 5-HT dysfunction.

Further evidence for dose-related neuronal alterations is provided by Dafters et al (1999). They investigated whether there was a correlation between quantitative EEG variables (Spectral power and coherence) and the level of prior ecstasy use. Reported ecstasy use positively correlated with absolute power in alpha and beta frequency bands and negatively correlated with EEG coherence.

Dopaminergic functioning

Most of the previously discussed studies addressing neurotoxicity have focused on the levels of serotonin within the brain of human recreational ecstasy users. Two further studies focused primarily on the long-term effects, MDMA exposure may have, on the dopamine system. Gerra et al (2002) investigated dopaminergic function in ecstasy users compared to control subjects. In a pharmacological challenge study using bromocriptine (a specific D-2 receptor agonist), they found a negative correlation between dopamine receptor sensitivity and ecstasy exposure. This suggested possible reduced dopaminergic receptor sensitivity in heavy ecstasy users. Within the same study, there were no significant group differences on prolactin response, but there was a significant difference in growth hormone (GH) responses. Ecstasy users showed significantly reduced GH response compared to controls. However, such alterations in dopamine could be related to the use of other drugs, which are known to affect dopaminergic neurons. Reneman et al (2002) demonstrated that the sole use of ecstasy was not related to dopaminergic neurotoxicity, but rather that the combined use of ecstasy and amphetamine were associated with reduced dopamine transporter densities. This appears to suggest that MDMA is not associated with human dopaminergic neurotoxicity; but rather it is a selective serotonergic neurotoxin.

Strength of evidence for neurotoxicity in ecstasy users

With the development of *in vivo* imaging in the human brain, there is now extensive evidence which suggests that MDMA may cause neuronal injury in some recreational ecstasy users. However, these human studies employ a retrospective design and thus evidence is indirect and based on associations. Experimental and/or longitudinal designs are needed to establish whether there is actually a causal link between neurotoxic changes and MDMA. There are a number of methodological flaws with the neuroimaging studies. Kish (2002) argues that evidence employing the radioligands used to bind to the serotonin neuron, over-rely on one component, that of the serotonin transporter (SERT). He questions the reliability and validity of the SERT measure and whether this is actually proof of brain damage; since it has been established that drug-induced changes in the levels of brain neurotransmitter transporters can occur independently of any changes in the number of serotonin neurones. As such, brain levels of SERT might change following exposure to some drugs independently of any changes in levels of nerve terminals. It is also suggested that SERT levels can also vary as a

function of oestrogen status, gender and variations in a SERT promoter gene polymorphism, which may be unrelated to the actual number of serotonin neurons. Thus studies involving measurement of brain SERT might be confounded to some extent.

However, there is other evidence, as discussed, which suggests there are alterations in neuronal functioning which have been associated with MDMA exposure, which mirrors findings found in the animal data. The notion that cell loss of markers equates to real 5-HT cell loss, within the human brain can be obtained from post-mortem brain examination and to date there is only one published study that has done this. Kish et al (2000) reported that striatal (putamen, caudate, nucleus accumbens) levels of serotonin and of its metabolite 5-HIAA were severely depleted by 50 to 80% in the brain of an ecstasy user compared to controls, but that there were generally normal dopamine concentrations. However, it still can not be determined whether 5-HT depletion was caused by ecstasy use or other polydrug use. Though all methodologies described are flawed, taken together with the animal data there is an increasingly compelling case for the theory of MDMA-induced 5-HT injury in recreational ecstasy users. Thus taken together the evidence strongly supports the earlier animal findings of reductions in brain serotonin in ecstasy users as a result of MDMA-induced neurotoxicity.

Recovery from MDMA neurotoxicity in humans

As outlined above there is strong evidence to suggest that recreational ecstasy use can cause serotonergic injury within the human brain. This also raises the question as to whether recovery of brain neurons can occur after continued abstinence from the drug or whether such changes are persistent. Theses questions have only been addressed in the last 5 years. Chang et al (1999) did not find a significant relationship between the recent timing of MDMA use and the concentration of any metabolites, nor did Reneman et al (2002). McCann et al (2000) also found no significant correlation between the duration of abstinence from MDMA and the extent of 5-HT transporter binding. However, Semple et al (1999) and Reneman et al (2002) observed a significant positive correlation between SERT binding and the duration of abstinence; suggesting possible recovery from serotonergic neurotoxic injury over time. Obrocki et al (2000) also focused on the reversibility of PET FDG uptake on brain glucose metabolism and found a correlation between uptake and the time since ecstasy was last ingested; though as mentioned before, PET FDG only reflects total neuronal activity levels

not selective serotonergic activity. The evidence of possible reversibility of MDMA neurotoxicity, is only based on associations using correlational analyses. Other studies though, have actually looked at group differences between current ecstasy users, former or ex-ecstasy users and controls.

Using SPECT, Reneman et al (2000a and b) compared ecstasy users and ex-ecstasy users who reported using similar amounts of ecstasy but had not used in the last 2 months, and controls. Cortical binding ratios were lower in current ecstasy users compared to ex-users and controls. There was also a significant correlation between cortical binding and duration of abstinence from ecstasy; suggesting possible neuronal recovery in ex-ecstasy users. They also demonstrated that there was higher cortical binding of the 5-HT ligand [^{123}I]R91150 in the ex-ecstasy users compared to controls (though not a significant effect), possibly suggesting an up-regulation of postsynaptic receptors. Reneman et al (2002) replicated these findings in a later study, but only in female ecstasy users. Binding ratios were significantly higher in ex-female users compared to current female users, but not controls; again suggesting that in several brain regions, MDMA-induced decreases in serotonin transporters could be reversible. This study also suggested a possible gender difference in recovery as this reversal was not observed in the male ecstasy users. Buchert at al (2003) have also indicated the reversibility of MDMA-induced SERT availability as measured by PET. Former users showed levels close to that of drug-naïve controls in all brain regions assessed. However, using a tryptophan challenge, as an indirect measure of central 5-HT function, Curran & Verheyden (2003) showed evidence of altered 5-HT functioning in ex-ecstasy users, but not current users, compared to controls. This indicates that neuronal alterations could further develop after cessation of ecstasy use. However, in light of previous research showing possible recovery, it is more than likely that such differences in 5-HT functioning in these users could reflect pre-morbid differences in 5-HT function.

When considering the persistence or reversibility of MDMA-induced neurotoxicity, there is a need for more longitudinal studies like that of Gerra et al (2000) who investigated possible reversibility of changes in the 5-HT system. They found that prolactin rises were significantly impaired in ecstasy users compared to controls both 3 weeks after discontinuing ecstasy use and after prolonged abstinence (12 months). But in contrast, cortisol rises in ecstasy users were significantly impaired compared to controls at 3 weeks, but were restored after 12 months. Thus, the restored responses of cortisol after 12 months may represent the

expression of an initial recovery of serotonergic functioning after MDMA-induced neurotoxicity.

Whether MDMA leads to irreversible or partly reversible impairment of serotonergic neurons within humans still remains controversial. The current studies do not allow for definite conclusions but do indicate that there are delayed changes in 5-HT function after abstinence of MDMA.

Table 1: Summary of pharmacological, imaging, physiological and CSF studies investigating neurotoxicity in human ecstasy users

	Assay	Number in ecstasy groups	Lifetime consumption of ecstasy	Duration of ecstasy use (years)	Significant indication of neuronal alteration-
Pharmacological challenges					
Price et al (1989)	L-tryptophan	9	13.3	5.1	NO
McCann et al (1994)	L-tryptophan	30	94.4	4.98	NO
Curran & Verheyden (2003)	L-tryptophan	32	Current[1] = 466[2] Ex[3] = 707	Current = 4.33 Ex = 3.49	YES[4]
Gerra et al (1998)	D-fenfluramine	15	62.7	14 months	YES
Gerra et al (2000)	D-fenfluramine	15	69.3	15 months	YES
Gouzoulis-Mayfrank et al (2002)	D-fenfluramine	24	Males = 78.2: Females = 81.4	Males = 29.3 mths Females =20.2 mths	NO
Verkes et al (2001)	D-fenfluramine	Moderate = 21 Heavy = 21	169 741	4.4 4.5	YES YES
McCann et al (1999)	M-chlorophenylpiperazine	25	196	5	YES
Brain imaging studies					
Chang et al (1999)	H-MRS	21	75	10	YES
Obergriesser et al (2001)	H-MRSI	5	100+	3-6	NO
Reneman et al (2002)	H-MRS	15	723	5.6	YES
Reneman et al (2001)	MRI	8	154	4.3	YES
Semple et al (1999)	SPECT: [^{123}I]β-CIT	10	672	-	YES
Reneman et al (2001)	SPECT: [^{123}I]β-CIT	22	485	5.5	YES
Reneman et al (2001)	SPECT: [^{123}I]β-CIT	Moderate = 15 Heavy = 23	28.6 530	4.1 4.6	NO YES
Reneman et al (2002)	SPECT: [^{123}I]β-CIT : DA transporters	29	324	5.1	YES
Reneman et al (2000)	SPECT: [^{123}I]R91150	5	218	-	YES
Reneman et al (2000)	SPECT: [^{123}I]R91150	10	139	-	YES

[1] Used over 20 ecstasy tablets within the last year
[2] estimated lifetime consumption (days/month x no. tablets per session x no. of months used)
[3] Used over 20 ecstasy tablets but not within the last year
[4] Ex-users showed significantly higher levels of total and free plasma tryptophan than current ecstasy users and controls

Table 1 (Cont…)	Assay	Number in ecstasy groups	Lifetime consumption of ecstasy	Duration of ecstasy use (years)	Significant indication of neuronal alteration-
Reneman et al (2001)	SPECT: [^{123}I]R91150	17	224	5.9	YES
Chang et al (2000)	SPECT: [^{99m}Tc] HMPAO	21	211	8.6	NO
Obrocki et al (1999)	PET: FDG	7	12-840	1-39 months	YES
Obrocki et al (2002)	PET: FDG	93	483	-	YES
McCann et al (1998)	PET: McN-5652	14	228	4.6	YES
Thomasius et al (2003)	PET: ^{11}C-(+)-McN5652	30	Males = 1034 Females = 600	Males = 45.5 mths Females= 60.5 mths	YES
Buchert et al (2003)	PET: ^{11}C-(+)-McN5652	30	827	54 mths	YES
Gamma et al (2001)	PET: rCBF	16	270	-	NO
Auditory Evoked Potentials					
Croft et al (2001)	Auditory Evoked Potentials	22	225.9	4.5	YES
Tuchtenhagen et al (2000)	Auditory Evoked Potentials	28	93.4	27 months	YES
Electroencephalography (EEG)					
Dafters et al (1999)	EEG: Spectral Power & Coherence Levels	23	14.04 (previous year only)	?	YES[5]
Cerebrospinal-fluid analysis					
Peroutka et al (1987)	CSF 5-HIAA	5	18	-	NO
Ricaurte et al (1990)	CSF 5-HIAA	33	52	3.5	YES
McCann et al (1994)	CSF 5-HIAA	30	94.4	4.98	YES
Bolla et al (1998)	CSF 5-HIAA	24	60	4.75	YES
McCann et al (1999)	CSF 5-HIAA	23	215	4.5	YES

CHAPTER 2

Possible Functional Consequences of Ecstasy-Induced Serotonergic Neurotoxicity

The previous chapter highlighted a substantial body of evidence that supports the idea that recreational ecstasy use induces neurotoxic effects on serotonergic neurons and alters brain serotonergic functioning. The fundamental question then, is whether or not this MDMA-induced neurotoxicity results in alterations in human behaviour.

The role of serotonin has been implicated in the regulation of mood (Young et al, 1985), depression (Delgado et al, 1990), anxiety (Garvey et al, 1995), aggression and impulsiveness (Brown et al, 1979; Coccaro, 1989; Reist et al, 1996; Askenazy et al, 2000), sexual activity, appetite (Fernstrom, 1987), sleep (Oswald et al, 1964), pain (Messing et al, 1977; Akunne and Soliman, 1994), circadian and seasonal rhythms (Penev et al, 1995), motor activity (Loubinoux et al, 2002) and body temperature (Blier et al, 2002). It is also thought to play a role in cognitive processes (Hunter, 1988), although the place of 5-HT in cognition is poorly understood. However, it has been proposed that serotonin may play an important modulating role in memory and attention and so it is possible that extreme deviations of 5-HT activity could result in biases in cognitive processing. Evidence to date suggests that 5-HT is involved in learning, visuo-spatial memory, visual discrimination, associative functions and aspects of planning and general memory.

The consequences, therefore, of alterations in serotonergic functioning in recreational ecstasy users are expected in these psychological and behavioural domains, which are related to serotonergic processes. This current chapter summarises the growing number of research reports which lend support to this notion, in particular concerning psychiatric, psychobiological, and also cognitive effects in recreational ecstasy users. The idea that these psychological effects are associated with altered serotonergic functioning is also discussed, along with a discussion regarding evidence concerning the reversibility or permanence of these effects.

Long-term psychopathological consequences associated with ecstasy use

The first evidence which indicated that ecstasy might lead to chronic psychiatric symptoms came from individual case studies, where psychiatric complaints were reported to have appeared to develop in the context of ecstasy use (see Table 2 for a summary of case reports from the last 15 years). These clinical reports suggest that certain individuals appeared to have developed psychopathological symptoms, which manifested in a range of psychiatric

Table 2: A summary of clinical case studies, where ecstasy appears to be a prominent feature.

Reference	Symptom/ Disorder	Age/ Sex	Psychiatric History	Psychiatric illness among 1st degree relatives	Ecstasy Use	Other drug use
Teggin (1992)	Hysterical dissociative state followed by mild expressive aphasia	32 F	?	?	1 occasion	?
Cohen & Cocores (1997)	Perpetual neuropsychotic symptomatology	17 M	None	?	1 occasion	None
Cohen (1996)	Adverse symptomatology inc. persistent depressive episodes	22 F	None	?	6 years	Alcohol & cannabis
McGuire & Fahy (1991)	Paranoid symptoms	28 M	Amphetamine psychosis	Schizophrenia	2-10 per night for 18 months	Used other drugs
McGuire & Fahy (1991)	Paranoid delusions	22 M	None	Unknown/ adopted	2 years	Used other drugs
Cassidy & Ballard (1994)	Paranoid psychosis	21 M	None	None	1-2 per week for 6 months	Abused cannabis
Series et al (1994)	Paranoid psychosis	24 M	None	None	2 in 1 month	LSD & cannabis
Keenan et al (1993)	Paranoid Psychosis	17 M	None	None	1-2 per week for 5 months	Occasional cannabis use
Bone et al (2000)	Paranoid psychosis	24 M	Bad manners & violent conduct	?	5 every weekend	Cannabis, cocaine, alcohol & LSD
Ellis & Schimmel (1989)	Paranoid pychosis	? F	None	None	?	None
Van Kampen & Katz (2001)	Psychosis[i]	18 F	None	None	½ tablet one occasion prior this	Cannabis approx 10 occasions, Mushrooms in conjunction with MDMA
Williams et al (1993)	Psychosis	18 M	None	Psychotic depression with paranoid delusions	¼ tablet on occasions	Cannabis
Creighton et al (1991)	Psychosis	22 M	None	None	4-7 per week for 4 months	Moderate but prolonged cannabis use
Vaiva et al (2001)	Acute Psychosis	26 M	Moderate anxiety disorder	?	1 tablet	Alcohol
Schifano (1991)	Chronic atypical psychosis	24 M	None	None	150 over 4 years	Sporadic use alcohol, BZ's cannabis, cocaine.
Schifano & Magni (1994)	Atypical psychosis	28 M	None	None	20 occasions weekly over 4 months	Opiates
Schifano & Magni (1994)	Atypical psychosis	28 M	None	None	20 occasions weekly over 5 months	Opiates, cannabis & alcohol
Schifano & Magni (1994)	Atypical psychosis and major depression	22 M	None	None	35 occasions in 4 years	Opiates & cannabis
Milas (2000)	Acute psychosis with aggressive behaviour	26 ?	?	?	?	?
Spatt, Glawar & Mamoli (1997)	Psychotic episode with ongoing pure amnesic syndrome	20 F	None	None	½ tablet	Occasional cocaine & heroin use
Alciati et al (1999)[ii]	Delirium	22 M	None	Paranoid disorder & narcissistic personality disorder	Weekly for 8 months	Cocaine in conjunction with ecstasy
Alciati et al (1999)[ii]	Delirium	21 M	None	None	Weekly for 6 months	Cannabis weekly 6 months
Alciati et al (1999)[ii]	Delirium	21 M	?	Schizophrenia	3 tablets	History of intravenous opioid abuse for 4 years and currently on methadone
Cassidy & Ballard (1994)	Hallucinogenic delusional disorder	17 M	None	None	2-3 per week for 4-6 months	Abused cannabis[iii]
McGuire et al (1994)[iv]	Depersonalisation /hallucinations	19 M	Cannabis & LSD induced hallucinations	Drug abuse	Less than 1 week	Used other drugs
McGuire et al (1994)	Delusions/hallucinations	26 M	None	Alcohol abuse	2 years	Used other drugs
McGuire et al (1994)	Delusions	24 M	Paranoid ideation	None	7 months	Used other drugs
McGuire et al (1994)	Delusions	30 M	None	Personality disorder & drug abuse	13 months	Used other drugs

Reference	Symptom/ Disorder	Age/ Sex	Psychiatric History	Psychiatric illness among 1st degree relatives	Ecstasy Use	Other drug use
McGuire et al (1994)	Delusions/illusions	21 M	Transient paranoid psychosis	Depression	1 year	Used other drugs
McGuire et al (1994)	Delusions/hallucinations	20 M	Paranoid ideation	None	2 years	Used other drugs
McGuire et al (1994)	Illusions/hallucinations	18 F	None	None	6 months	Used other drugs
Creighton et al (1991)	Flashbacks and anxiety symptoms	22 F	None	None	2 in one week	Regular cannabis use & occasional use of LSD, heroin & amphetamine.
Creighton et al (1991)	Flashbacks and anxiety symptoms	17 M	None	None	1 occasion	?
McGuire et al (1994)	Delusions/panic attacks	32 M	Paranoid ideation	Depression	3 months	Used other drugs
McGuire et al (1994)	Panic attacks/flashbacks	18 F	None	None	4 months	Used other drugs
McGuire et al (1994)	Panic attacks/depersonalisation	22 F	None	Panic disorder	3 years	Used other drugs
Pallanti & Mazzi (1992)[v]	Panic disorder & agoraphobic avoidance	27 M	None	None	20 in 10 months	Alcohol
Pallanti & Mazzi (1992)[v]	Panic disorder & agoraphobic avoidance	21 M	None	None	3 in 6 months	?
Pallanti & Mazzi (1992)[v]	Panic disorder & agoraphobic avoidance	28 M	None	None	1 per 2 months for 2 years	Cocaine
McCann & Ricaurte (1992)	Panic disorder	23 M	None	None	Single low dose	Sporadic use of cannabis
Windhaber et al (1998)	Panic disorder	23 M	None	None	Over 5 months, increased use to 7 per day	None
Schifano & Magni (1994)	Panic disorder & major depressive episode	24 M	None	None	Daily or every other for two 20-day periods (interval of 6 months)	Sporadic use of cannabis
Whitaker-Azmitia & Aronson (1989)	Panic attacks[vi]	26 F	None	None	1 occasion	Phenylpropanolamine (non-prescription anorexic medication)
Whitaker-Azmitia & Aronson (1989)	Panic attacks[vi]	25 M	None	None	6 occasions	?
Whitaker-Azmitia & Aronson (1989)	Panic attacks[vi]	22 F	None	None	?	?
Schifano & Magni (1994)	Major depressive disorder & panic disorder (without agoraphobia)	23 M	None	None	Lifetime consumption of 2000 tablets over 2 periods (interval 24 months)	Sporadic use of BZ's & opiates
Series et al (1994)	Anxiety & depression	23 F	None	Depression	1-2 for 2 months	Cannabis, amphetamines & LSD
Teggin (1992)	Major Depressive Disorder	48 M	?	?	6 occasions	?
Schifano & Magni (1994)	Major depressive episode	20 F	None	None	45 occasions weekly for 1 year	Alcohol & cannabis
McGuire et al (1994)	Depression	38 M	None	Depression & drug and alcohol abuse	1 year	Occasional use of other drugs
Benazzi & Mazzoli (1991)	Depression with suicidal ideation	23 M	None	None	1 on 4 occasions	?
Cohen (1996)	Depression and suicide	17 M	?	?	1 tablet	?

Symptoms persisted for approx. 12 weeks until olanzapine treatment
[ii] Symptoms remitted within an average of 6 days
[iii] It is possible cannabis use may have augmented the propensity of MDMA to cause psychosis
[iv] Collected series of psychiatric cases where MDMA was the prominent feature
[v] Responded well to serotonergic antidepressant drugs
[vi] All cases attacks were time limited and did not recur despite subsequent use of the drug in two cases.
? – details not reported in paper

conditions, including panic attacks (Whitaker-Azmitia & Aronson, 1989), depression (Cohen, 1996), flashbacks (Creighton et al, 1991), psychosis (Vaiva et al, 2001), paranoid ideation (McGuire & Fahy, 1991) and suicidal ideation (Benazzi & Mazzoli, 1991). As table 2 indicates the most common symptoms thought to be associated with ecstasy use appear to be psychoticism, panic attacks and depression; behavioural domains that are putatively influenced by brain serotonin. In most cases individuals who reported these problematic effects of ecstasy had previous experience of using the drug (Cohen, 1996; McGuire & Fahy, 1991; Cassidy & Ballard, 1994; Keenan et al, 1993; Bone et al, 2000; Creighton et al, 1991; Schifano, 1991; Schifano & Magni, 1994; Alciati et al, 1999; McGuire et al, 1994; Pallanti & Mazzi, 1992; Windhaber et al, 1998) and thus these sequalae could not be considered to be acute reactions to the drug. Additionally, many of the individuals reported symptoms which persisted after the acute ecstasy withdrawal effects, and were also exacerbated or reoccurred after further ecstasy use (Series et al 1994; McGurie et al, 1994; Milas, 2000). Creighton et al (1991) reported a patient who was free of psychiatric symptoms for 8 months, but after taking a further 4 doses of ecstasy the psychological symptoms returned. Similarly, the individual reported by Cassidy and Ballard (1994) stated a close relationship between symptom improvement and ecstasy cessation.

The main limitation of using individual case studies as evidence for the possible neuropsychiatric effects of ecstasy is that such individual abreactions may be viewed as idiosyncratic or atypical. However, additional support for psychiatric consequences of ecstasy use comes from a clinical survey conducted by Schifano et al in 1998. This study examined the possible psychopathological consequences of ecstasy use in 150 patients who had taken ecstasy on at least one occasion. 53% of the sample were found to be affected by one or more psychopathological problems as diagnosed using the criteria of DSM-III-R (the diagnostic manual of the American Psychiatric Association version III Revised.). These patients specifically denied the presence of these psychiatric disturbances prior to ecstasy usage. The most frequent psychopathological problems were depression, psychotic disorders, cognitive disturbances, bulimic episodes, impulse control disorders, panic disorders and social phobia. Again these are areas of behaviour/pathology thought to be influenced by serotonin and, in addition, parallel the disorders seen in the individual case study reports. The key limitation of this study is that participants were all clients at a clinical unit. This self-referred psychiatric group may not have been typical recreational ecstasy users, since many reported high use of cocaine and heroin; drugs which when used in isolation can cause long-term

psychiatric complications. There was nonetheless a significant correlation between severity and extent of symptoms and level of ecstasy use. Those that had used larger doses of ecstasy, both acutely and cumulatively were found to have more severe symptoms.

The notion of ecstasy-related psychiatric symptoms and disorders has not only been shown in a clinical sample. Recent research suggests that there may be other ecstasy users who experience milder psychiatric disturbances who do not contact health professionals. There is a growing body of evidence to suggest this from studies employing recreational users that do not present themselves to clinicians, but show evidence of psychopathological symptoms on numerous measures of clinical indicators compared to people who do not use illicit drugs and/or participants who have used other illicit drugs but not ecstasy (see table 3 for a summary of these studies). The method of comparing ecstasy users to other drug using groups has been used in order to try to eliminate the confounding effects of these other drugs on psychological performance. It is difficult to ascertain which, if any, of the drugs previously used by recreational ecstasy users is responsible for the manifestation of psychological problems. Epidemiological studies have failed to identify sole ecstasy users. Instead ecstasy users are more likely to be polydrug users (Webb et al, 1996; Pederson & Skrondal, 1999; Topp et al, 1999; Winstock et al, 2001; Strote et al, 2002; Arria et al, 2002). All of the drugs reported in these studies are capable of producing strong psychoactive effects and may also have longer-term psychological effects if used alone (Rodgers & Robbins, 2001). Thus interpretation of the findings from many of the empirical studies into the functional effects of MDMA-induced neurotoxicity, is limited. The solution of employing a research design that incorporates valid control groups with matched levels of drug use other than ecstasy (often referred to in the literature as polydrug users) and/or cannabis use, addresses this interpretative difficulty. Any findings in group differences can then be attributed more to ecstasy and not polydrug or cannabis use. Also, evidence for any dose-related* effects between levels of ecstasy consumption and levels of reported psychopathology can further strengthen the associations with ecstasy use and potential psychological effects.

---

* The term "dose-related" (response) will be used in a loose fashion throughout this thesis to allude to possible relationships between consumption of ecstasy and possible effects. This differs from the stricter use of this terminology which is normally applied in psychopharmacology (i.e. in controlled trials).

Table 3: Summary of empirical research assessing the long-term psychopathological effects associated with ecstasy use.

	Assessment Measure	Lifetime consumption of ecstasy	Significant group effect: Ecstasy v's Drug naïve	Cannabis	Polydrug
Depression					
Curran & Travill (1997)	Beck Depression Inventory	?[1]	-	-	**YES**[2]
MacInnes et al (2001)	Beck Depression Inventory	527	**YES**	-	-
Verheyden et al (2002)	Beck Depression Inventory	Males = 1172, Females = 397	-	-	**YES**[3]
Curran & Verheyden (2003)	Beck Depression Inventory	Current[4] = 466[5], Ex[6] = 707	-	-	**NO**
Curran et al (2004)	Beck Depression Inventory	207.87[7]	-	-	**YES**[8]
Gamma et al (2001)	Hamilton Rating Scale	270	-	-	**YES**
Verheyden et al (2002)	HADS (Hospital anxiety & depression scale (trait depression))	Males = 1172, Females = 397	-	-	**NO**
Parrot, Sisk & Turner (2000)	SCL-90	Light = 6.7, Heavy = 371	-	-	**NO**
Parrott et al (2001)	SCL-90	Light = 1-20, Heavy = 20+	**NO**	**NO**	**NO**
Dughiero et al (2001)	SCL-90	233	**NO**	**NO**	**NO**
Daumann et al (2001)	SCL-90-R & D-S (Depression Scale)	25+	**NO**		-
Morgan et al (2002)	SCL-90-R	Males = 513, Females = 93	**YES**	-	**YES**
Thomasius et al (2003)	SCL-90-R	Males = 1034, Females = 600	**YES**	-	**NO**
Somatisation					
Parrott, Sisk & Turner (2000)	SCL-90	Light = 6.7, Heavy = 371	-	-	**YES**
Parrott et al (2001)	SCL-90	Light = 1-20, Heavy = 20+	**YES**	**YES**	**YES**
Dughiero et al (2001)	SCL-90	233	**NO**	**NO**	**NO**
Daumann et al (2001)	SCL-90-R	25+	**NO**	**NO**	-
Morgan et al (2002)	SCL-90-R	Males = 513, Females = 93	**YES**	-	**YES**
Thomasius et al (2003)	SCL-90-R	Males = 1034, Females = 600	**NO**	-	**NO**
Psychosis/psychoticism					
Parrott, Sisk & Turner (2000)	SCL-90	Light = 6.7, Heavy = 371	-	-	**YES**
Parrott et al (2001)	SCL-90	Light = 1-20, Heavy = 20+	**YES**	**YES**	**YES**
Dughiero et al (2001)	SCL-90	233	**YES**	-	**YES**

[1] Lifetime consumption not recorded. 2 reported using ecstasy once a week, 6 reported approx. one per month and 4 only occasionally.
[2] Day 5 ecstasy scored higher than alcohol control group
[3] Females more susceptible than males compared to polydrug controls
[4] Used over 20 ecstasy tablets within the last year
[5] Lifetime consumption not reported therefore an estimate is provided based on the following calculation [(days/month x no. tablets per session) x no. of months used]
[6] Used over 20 ecstasy tablets but not within the last year
[7] Lifetime consumption not reported therefore an estimate is provided based on the following calculation – 12 (days a month x tablets in typical session) x number of years
[8] Lower BDI scores than controls on day 0, higher on day 4, no different day 7

Table 3 (cont…)					
Daumann et al (2001)	SCL-90-R	25+	YES	NO	-
Thomasius et al (2003)	SCL-90-R	Males = 1034, Females = 600	NO	-	NO
Phobic Anxiety					
Parrott, Sisk & Turner (2000)	SCL-90	Light = 6.7, Heavy = 371	-	-	YES
Parrott et al (2001)	SCL-90	Light = 1-20, Heavy = 20+	YES	YES	YES
Dughiero et al (2001)	SCL-90	233	YES	-	YES
Daumann et al (2001)	SCL-90-R	25+	YES	NO	-
Morgan et al (2002)	SCL-90-R	Males = 513, Females = 93	YES	-	YES
Thomasius et al (2003)	SCL-90-R	Males = 1034, Females = 600	NO	-	NO
Obsessive-compulsive					
Parrott, Sisk & Turner (2000)	SCL-90	Light = 6.7, Heavy = 371	-	-	YES
Parrott et al (2001)	SCL-90	Light = 1-20, Heavy = 20+	YES	YES	YES
Dughiero et al (2001)	SCL-90	233	YES	-	YES
Daumann et al (2001)	SCL-90-R	25+	YES	NO	-
Morgan et al (2002)	SCL-90-R	Males = 513, Females = 93	YES	-	YES
Thomasius et al (2003)	SCL-90-R	Males = 1034, Females = 600	YES	-	NO
Interpersonal sensitivity					
Parrott, Sisk & Turner (2000)	SCL-90	Light = 6.7, Heavy = 371	-	-	NO
Parrott et al (2001)	SCL-90	Light = 1-20, Heavy = 20+	NO	NO	NO
Dughiero et al (2001)	SCL-90	233	NO	NO	NO
Daumann et al (2001)	SCL-90-R	25+	NO	NO	-
Morgan et al (2002)	SCL-90-R	Males = 513, Females = 93	YES	-	YES
Thomasius et al (2003)	SCL-90-R	Males = 1034, Females = 600	YES	-	NO
Anxiety					
Morgan (1998) Study 1	State-trait Anxiety Inventory (STAI)	35.6	NO	NO	NO
Verheyden et al (2002)	HADS (Hospital anxiety & depression scale (trait depression))	Males = 1172, Females = 397	-	-	NO
Curran & Verheyden (2003)	State Anxiety Inventory (STAI)	Current = 466, Ex = 707	-	-	NO
Wareing et al (2001)	State Anxiety	101.2	YES	-	-
Parrott, Sisk & Turner (2000)	SCL-90	Light = 6.7, Heavy = 371	-	-	YES
Parrott et al (2001)	SCL-90	Light = 1-20, Heavy = 20+	YES	YES	YES
Dughiero et al (2001)	SCL-90	233	NO	NO	NO
Daumann et al (2001)	State-trait Anxiety Inventory (STAI) & SCL-90-R	25+	YES	NO	-
Morgan et al (2002)	SCL-90-R	Males = 513, Females = 93	YES	-	YES
Thomasius et al (2003)	SCL-90-R	Males = 1034, Females = 600	NO	-	NO
Paranoia					
Parrott, Sisk & Turner (2000)	SCL-90	Light = 6.7, Heavy = 371	-	-	YES
Parrott et al (2001)	SCL-90	Light = 1-20, Heavy = 20+	NO	NO	NO

Table 3 (cont…)					
Dughiero et al (2001)	SCL-90	233	**NO**	**NO**	**NO**
Daumann et al (2001)	SCL-90-R	25+	**YES**	**NO**	-
Morgan et al (2002)	SCL-90-R	Males = 513, Females = 93	**YES**	-	**YES**
Thomasius et al (2003)	SCL-90-R	Males = 1034, Females = 600	**NO**	-	**NO**
Aggression					
Daumann et al (2001)	FAF (Aggressiveness Factors)	25+	**NO**	**YES**	-
Verheyden et al (2002)	AQ (Trait Aggression Questionnaire)	Males = 1172, Females = 397	-	-	**NO**
	Aggression rating scale		-	-	**YES**
Curran & Verheyden (2003)	AQ (Trait Aggression Questionnaire)	Current = 466, Ex = 707	-	-	**YES**[9]
Curran et al (2004)	Aggression Rating Scale	207.87[10]	-	-	**YES**[11]
Curran et al (2004)	Interpretative Bias Task	207.87[5]	-	-	**YES**
Anger/Hostility					
Parrott, Sisk & Turner (2000)	SCL-90	Light = 6.7, Heavy = 371	-	-	**YES**
Parrott et al (2001)	SCL-90	Light = 1-20. Heavy = 20+	**YES**	**YES**	**YES**
Dughiero et al (2001)	SCL-90	233	**NO**	**NO**	**NO**
Daumann et al (2001)	STAXI (State-trait anger expression inventory)	25+	**NO**	**NO**	-
Thomasius et al (2003)	SCL-90-R	Males = 1034, Females = 600	**YES**	-	**NO**
Alter sleep/disturbed sleep					
Parrott, Sisk & Turner (2000)	SCL-90	Light = 6.7, Heavy = 371	-	-	**NO**
Dughiero et al (2001)	SCL-90	233	**YES**	-	**YES**
Morgan et al (2002)	SCL-90-R	Males = 513, Females = 93	**YES**	-	**YES**
Altered appetite					
Parrott, Sisk & Turner (2000)	SCL-90	Light = 6.7, Heavy = 371	-	-	**YES**
Negative psychobiology					
Parrott et al (2001)	SCL-90	Light = 1-20, Heavy = 20+	**NO**	**NO**	**NO**
MDMA side effects					
Parrott et al (2001)	SCL-90	Light = 1-20, Heavy = 20+	**YES**	**YES**	**YES**
General Health					
Morgan (1998) Study 2	GHQ (General Health questionnaire)	49.6	**YES**	-	**NO**
Morgan et al (2002)	GHQ (General Health questionnaire)	Males = 513, Females = 93	**NO**	**NO**	**NO**
Sociability					
Parrott et al (2001)	SCL-90	Light = 1-20, Heavy = 20+	**NO**	**NO**	**NO**

[9] ex-users scored higher than current users and controls
[10] Lifetime consumption not reported by authors therefore an estimate is provided based on the following calculation - 12(days a month x tablets in typical session) x number of years
[11] higher only on day 4, no longer persisted on day 7

Positive moods					
Parrott et al (2001)	SCL-90	Light = 1-20, Heavy = 20+	**YES**	**YES**	**YES**
Positive psychobiology					
Parrott et al (2001)	SCL-90	Light = 1-20, Heavy = 20+	**NO**	**NO**	**NO**
Positive life experiences					
Parrott et al (2001)	SCL-90	Light = 1-20, Heavy = 20+	**NO**	**NO**	**NO**
Table 3 (cont…)					
SCL-90-R Global Severity Index					
Dughiero et al (2001)	SCL-90	233	**NO**	**NO**	**NO**
Daumann et al (2001)	SCL-90-R	25+	**YES**	**NO**	-
Morgan et al (2002)	SCL-90-R	Males = 513, Females = 93	**YES**	-	**YES**
Simon & Mattick (2002)	SCL-90-R	258	-	**NO**	-
Thomasius et al (2003)	SCL-90-R	Males = 1034, Females = 600	**YES**	-	**YES**
SCL-90-R Positive symptom distress index					
Daumann et al (2001)	SCL-90-R	25+	**NO**	**NO**	-
Morgan et al (2002)	SCL-90-R	Males = 513, Females = 93	**YES**	**YES**	**YES**

One of the first studies to report long-term psychological effects in recreational ecstasy users was Cohen (1995) who surveyed 500 ecstasy users. The most frequently reported psychological effects pertaining to the long-term effects of ecstasy were depersonalisation, insomnia, depression and flashbacks. However, findings were purely reliant on participant's subjective reports, with no supportive objective psychological assessment or any comparison to other non-drug/drug using groups. Additionally, he did not find any relationship between an individual's number of exposures to ecstasy and recurring symptomatology.

Curran and Travill (1997) reported one of the first studies showing elevated psychopathology in ecstasy users compared to a control group. They found elevated levels of depression as measured by the BDI (Becks Depression Inventory) in ecstasy users five days after ecstasy consumption compared to alcohol controls. Further still, Verheyden et al (2002) suggested that females may be more susceptible to this low mood effect than males, and in addition they demonstrated that aggression ratings, in both males and females, were increased 4 days after ecstasy use. Further support for these sub-acute psychopathological effects have been shown in a later study by Curran et al (2004) who reported that ecstasy users displayed higher scores on the BDI compared to polydrug controls on day 5, but by day 7 there were no differences in levels of depression. Together, these studies would appear to identify a number of sub-acute effects of ecstasy rather than the long-term effects of ecstasy (at least two weeks post-ecstasy use).

Long-term changes in psychopathological symptomatology in ecstasy users have been reported in studies such as that by Parrott, Sisk & Turner (2000). Using the SCL-90 they showed elevated psychopathological scores on a number of dimensions including somatisation, psychoticism, phobic anxiety, obsessive-compulsive symptoms, paranoid ideation, anger/hostility and altered appetite. Also, they demonstrated that heavier ecstasy users reported significantly higher scores on several of these dimensions compared to polydrug users. Light ecstasy users also scored significantly lower than heavy ecstasy users on anxiety, paranoid-ideation and appetite, but significantly higher on paranoid-ideation compared to polydrug users. It was suggested that this may be evidence that heavier ecstasy users exhibit a greater range of psychobiological problems, as a result of their greater exposure to the drug. Dugherio et al (2001) have also shown ecstasy users to exhibit higher psychopathological scores, on the same assessment measure, compared to drug-naïve and polydrug controls, but failed to find any differences between 'ecstasy abusers', experimental

users and controls; despite their definition of 'ecstasy abuser' being similar to that of a 'heavy' ecstasy user in Parrott, Sisk & Turner's (2000) study ('abusers' being those who took ≥ 27.5 tablets in their lifetime, 'heavy' users taking 30+ tablets). One possible reason for the discrepancy in these studies is that whilst they used similar criteria for defining 'heavy' or 'abuser' ecstasy use, mean ecstasy use in the two studies could have differed considerably. In Parrott, Sisk & Turner's study, mean ecstasy use in 'heavy' users was 371 times, where as mean usage of 'abusers' in Dugherio's study was not specified. Another possible account for the discrepancy in findings could be due to polydrug use, which has also been found to influence psychopathological profiles of ecstasy users (Parrott et al, 2001).

From a large-scale survey involving 768 volunteers from Italy and the UK, Parrott et al (2001) demonstrated that heavier ecstasy polydrug use was associated with higher psychopathology scores on the SCL-90. Whilst the heavy ecstasy using group was the most problematic and to a lesser extent the light ecstasy users, ecstasy users also displayed the heaviest polydrug use. Thus the high pathology scores for the heavier ecstasy users could simply be a profile of polydrug use in general. However, evidence to further suggest that higher psychopathology is associated with heavy ecstasy use, comes from a study by Milani et al (2000). They showed there was a significant positive correlation between the amount of ecstasy pills consumed and the scores on the anxiety, phobic anxiety and psychoticism scales of the SCL-90. A further study reported that of 234 ecstasy-polydrug users, 'problematic' users had higher pathology scores on several sub-scales of the SCL-90 compared with the 'non-problematic' users. These perceived problems were related to greater lifetime consumption of ecstasy and the number of pills taken in a single occasion (Milani et al, 2001).

Other studies have also shown elevated psychopathology in ecstasy users compared to drug-naïve and/or polydrug users (Gamma et al, 2001; Wareing et al, 2001; Daumann et al, 2001; Morgan et al, 2002 and Thomasius et al, 2003). Simon and Mattick (2002) also reported elevated levels of general psychopathology in ecstasy users compared to drug-naïve and polydrug controls, as measured by the SCL-90-R Global Severity Index, but they failed to identify any specific psychopathological symptoms in these ecstasy users compared to cannabis users. However, this particular study has been criticised for its design in comparing ecstasy users with heavy concomitant use of cannabis, with cannabis users that also reported some use of ecstasy (Parrott et al, 2003).

Which areas of psychopathology are affected?

Areas of psychopathology which have consistently been shown to be elevated in ecstasy users include psychoticism (Parrott, Sisk & Turner, 2000; Parrott et al, 2001; Dugherio et al, 2001; Daumann et al, 2001), phobic anxiety (Parrott, Sisk & Turner, 2000; Parrott et al, 2001; Dugherio et al, 2001; Daumann et al, 2001; Morgan et al, 2002), obsessive-compulsive symptomatology (Parrott, Sisk & Turner, 2000; Parrott et al, 2001; Dugherio et al, 2001; Daumann et al, 2001; Thomasius et al, 2003) and sleep (Dugherio et al, 2001; Morgan et al, 2002). Table 3 summarises these findings.

Depression and anxiety have been the most extensively studied psychopathological symptom amongst ecstasy users, however, findings have not always been consistent. MacInnes et al (2001) reported elevated levels of depression as measured by the BDI in ecstasy users compared to drug-naïve controls. Further still, they reported that these levels of depression positively correlated with the maximum amount of ecstasy consumed in 12 hours (i.e. binge consumption). Other studies have shown long-term changes in depression in ecstasy users relative to drug-naïve controls (Morgan et al, 2002) and compared to polydrug controls (Gamma et al, 2001; Morgan et al, 2002). Thomasius et al (2003) found significant differences in depression between ecstasy users and drug-naïve controls but not between ecstasy users and polydrug users. However, it is notable that other studies did not find any significant group differences in levels of depression (Parrott, Sisk & Turner, 2000; Parrott et al, 2001; Dugherio et al, 2001; Daumann et al, 2001). As for anxiety, using the STAI, Morgan et al (1998) did not find any significant group differences between ecstasy users, polydrug controls, drug naïve controls and cannabis users. However, in later studies assessing state anxiety, Wareing et al (2001) and Daumann et al (2001) found ecstasy users to have elevated anxiety scores compared to drug-naïve controls, although they did not differ from cannabis users (Daumann et al, 2001). Using the SCL-90 and SCL-90-R, several studies have reported ecstasy users to exhibit significantly higher anxiety scores compared to drug naïve and polydrug controls, but not cannabis users (Parrott, Sisk & Turner, 2000; Parrott et al, 2001; Daumann et al, 2001; Morgan et al, 2002). However, Thomasius et al (2003) and Dugherio et al (2001) did not replicate this finding despite heavier use of ecstasy in their participants.

Other areas of psychopathology, which have shown less consistent findings in ecstasy users, include somatisation, paranoia, aggression, anger/hostility and interpersonal sensitivity (see Parrott, Sisk & Turner, 2000; Parrott et al, 2001 and Morgan et al, 2002; Dugherio et al, 2001; Daumann et al, 2001; Thomasius et al, 2003; Curran & Veryheyden, 2003 and Curran et al, 2004; Table 3). Such inconsistencies in the research could be partly related to the variation in the assessment measures used. For example, both studies by Parrott's group (Parrott el al, 2001 and Parrott, Sisk & Turner, 2000) used the older version of the SCL-90 and demonstrated elevated anger/hostility scores in ecstasy users compared to polydrug controls and/or drug-naïve controls. This version of the SCL-90 has been criticised for its psychometric properties (see Cole et al, 2002). Conversely, Thomasius et al (2003) used the newer revised version of this scale (the SCL-90-R) and only found elevated anger/hostility scores compared to drug-naïve controls, but not the polydrug controls. Further still, Daumann et al (2001) assessed anger using the State-Trait Anger Expression Inventory (STAXI) and found that anger levels did not differ in ecstasy users compared to cannabis and drug-naïve controls.

Ecstasy use or polydrug use?

Whether or not the elevated psychopathological symptoms in these ecstasy users are due to ecstasy use or general polydrug use has still to be fully addressed. Many differences in ecstasy user's psychopathological symptoms have only been shown relative to drug-naïve controls. MacInnes et al (2001) reported elevated depression in ecstasy users relative to drug-naïve controls. Thomasius et al (2003) report elevated levels of depression, anger/hostility, obsessive-compulsive and interpersonal sensitivity symptoms compared to drug-naïve, but not polydrug controls. Daumann et al (2001) reported elevated phobic anxiety, obsessive-compulsive symptoms, anxiety, paranoia and aggression in ecstasy users relative to cannabis and drug-naïve controls, but not polydrug controls. This could suggest that psychopathological symptomatology in these ecstasy users may be more an artefact of polydrug use in general.

Studies such as Parrott et al (2001), Gamma et al (2001) and Parrott, Sisk & Turner (2000) have shown elevated psychopathological symptoms in ecstasy users compared to polydrug controls. Morgan et al (2002) showed that ecstasy users displayed significantly elevated

scores on a majority of the scales of the SCL-90-R compared to drug-naïve controls as well as polydrug controls, who were matched on levels of other drugs besides ecstasy. This suggests that the group differences were a result of ecstasy use rather than polydrug use. However, no measure of past ecstasy use predicted the psychopathology scores in these ecstasy users, whereas measures of cannabis use and some other drug use (e.g. poppers, speed, cocaine) did significantly predict psychopathological levels. Similar confounding effects of cannabis on psychopathological scores were found by Daumann et al (2001). Parrott et al (2001) also confirmed that psychological problems were not specific to ecstasy users, since higher psychopathology scores were evident in heavy polydrug users who had not consumed ecstasy, and that as the amounts of drug use increased, so too did the levels of psychopathology. This strongly suggests that drug use in general, in particular cannabis, is associated with psychopathology rather than ecstasy alone.

Perhaps the strongest evidence to date for psychological effects linked to ecstasy is from the only longitudinal study into the effects of ecstasy functioning on humans. Gerra et al (2000) assessed a group of ecstasy users over a period of a year compared to a group of control subjects. Levels of aggression/hostility, as measured by the Buss Durkee Hostility Inventory, were significantly higher in ecstasy users compared to controls after three weeks of abstinence from ecstasy. After 12 months of abstinence the ecstasy users no longer showed higher scores on aggression, and such a reduction in scores was significant compared to levels of aggression at 3 weeks. However, this study was limited in numbers and by the absence of a control group; this work also only measured one aspect of behaviour.

Interim Summary

In summary it appears that studies demonstrate elevated levels of psychopathology in ecstasy users compared to drug-naïve controls and polydrug users. Dose-related findings between levels of psychopathology and levels of ecstasy use further suggest that there may certainly be an association between ecstasy use and psychopathological symptoms. The psychopathological symptoms that appear to be the most consistently elevated in ecstasy users are: - psychoticism, phobic anxiety, obsessive-compulsive symptoms and often anxiety and depression. All of these psychopathological dimensions, highlighted in these recreational ecstasy users are those which are prevalent in the individual case studies reported earlier. However, there is evidence to suggest that drug use in general is associated with

psychopathology, in particular cannabis use. As such, interpreting any association or specifically any causative link between ecstasy use and psychopathology should be made with caution.

Long-term cognitive consequences associated with ecstasy use

In contrast to individual case study reports of psychiatric complaints associated with ecstasy use, there are a limited number of case studies focusing on adverse neurological and cognitive effects associated with ecstasy consumption. Teggin (1992) reported a 32-year-old female who developed an hysterical dissociative state followed by mild expressive aphasia, which lasted up to six weeks after ingesting a single tablet of ecstasy. Spatt et al (1997) also reported a case of a female aged 26 who developed a pure amnestic syndrome after exposure to ecstasy. Following a psychotic episode, which resolved, she was left with ongoing memory problems which persisted for two months. Nine months later there was only a slight improvement in her memory performance. A neurological examination showed bilateral hyperintense lesions, in the globus pallidus, which partly disappeared 2 months later. This is an area rich in serotonin releasing neurons and intimately connected to the basal ganglia (Feldman et al, 1997) and to basal structures of forebrain mnemonic systems (Dunnett et al, 2001).

More recently Kopelman et al (2001) reported severe and persisting cognitive and neurological abnormalities in a 26-year-old female after she had consumed two ecstasy tablets on a single occasion. There was no known history of adverse reactions to ecstasy use from previous occasions when she took the drug. She exhibited severe anterograde memory problems, with evidence of executive/frontal lobe impairments, whilst immediate memory span, card sorting performance and various aspects of semantic memory remained intact. Kopelman and colleagues observed some improvement during an 8-year follow-up period, particularly in verbal recognition memory and performance IQ, but severe deficits still remained. However, with this case, and others of its nature, it is impossible to be certain whether the patient's brain damage and subsequent cognitive problems resulted directly from neurotoxic effects of ecstasy. For example, in this study, damage could have arisen indirectly from a disseminated intravascular coagulation and brief respiratory arrest that the woman

suffered at the initial time of the adverse reaction to ecstasy. In addition, such adverse reaction case studies are, by their very nature, highly atypical.

The most extensive body of research concerning the long-term cognitive effects associated with ecstasy are from empirical studies. A brief summary of findings by specific area of cognitive processing can be found in Table 4.

Memory deficits are the most consistently reported long-term cognitive problem associated with ecstasy use. Parrott et al (1998) was one of the first to show memory deficits in ecstasy users compared to drug-naïve controls. Since then, numerous studies have supported this finding, demonstrating memory impairments in ecstasy users relative to drug-naïve controls (Wareing et al, 2000; Milani & Schifano, 2000; Reneman et al, 2000; Reneman et al, 2001; Gouzoulis-Mayfrank et al, 2000; Croft et al, 2001), cannabis users (Rodgers, 2000) and also polydrug controls (Morgan, 1998; Morgan, 1999; McCann et al, 1999; Bhattachary & Powell, 2001; Fox et al, 2001b; Fox et al, 2001c; Verkes et al, 2001; Heffernan et al, 2001).

However, there are studies which do not demonstrate memory impairments in ecstasy users relative to polydrug controls or even cannabis users. For example, Semple at al (2001) showed relatively heavy ecstasy users (average lifetime consumption of 672 ecstasy tablets) performed at comparable levels to that of polydrug controls on CANTAB working memory tasks and the FAS word generation task. Simon and Mattick (2002) also failed to find any differences in memory between ecstasy and cannabis users on immediate and delayed memory recall, and also on a working memory test (WASI III). Again, interpretation of this finding should be made with caution because of the methodological flaws previously mentioned.

Even with those studies that show memory deficits in ecstasy users, the consistency of memory impairments differs considerably between and within studies (see Table 4). The inconsistencies between studies may, in part, be due to the wide range of assessment methods that have been employed and the type of memory being assessed. Everyday memory, including prospective memory has been consistently shown to be impaired in ecstasy users relative to drug-naïve and polydrug controls (Schifano et al, 1998; Milani & Schifano, 2000; Rodgers, 2000; Heffernan et al, 2001; Rodgers et al, 2001).

Table 4: Summary of empirical research assessing the long-term cognitive effects associated with ecstasy use.

	Assessment Measure	Lifetime consumption of ecstasy	Significant group effect: Ecstasy v's Drug naïve	Cannabis	Polydrug
Verbal Recall					
Reneman et al (2001)	AVLT - recall	485	**YES**[1]	-	-
Reneman (2000)	AVLT - recall	218	**YES**[2]	-	-
Fox et al (2001c)	AVLT – recall	Short-term = 223.6; Long-term = 811.5	-	-	**YES** [1]
Thomasius et al (2003)	AVLT – recall	Female = 600; Male = 1034	**NO**	-	**NO**
Thomasius et al (2003)	RBMT: prose recall	Female = 600; Male = 1034	**NO**	-	**NO**
Morgan (1999)	RBMT: prose recall	50	**YES**[1]	-	**YES**[1]
Morgan (1998) Study 2	RBMT: prose recall	49.6	**NO**	-	**NO**
Morgan et al (2002)	RBMT: prose recall	Male = 513; Female = 93	**YES**	-	**YES**
Curran & Verheyden (2003)	RBMT: prose recall	Current[2] = 466[3], Ex[4] = 707	-	-	**YES**[5]
Curran & Verheyden (2003)	BSRT (Bushke selective reminding task) delayed recall	Current = 466, Ex = 707	-	-	**YES**[5]
Fox et al (2001b)	WMS: (LM-O) Prose recall	356.9	-	-	**NO**
Rodgers (2000)	WMS-R: recall	69 = 1-9; 66=10-99; 20=100+	**YES**	**YES**[6]	-
Simon & Mattick (2002)	WMS-III: auditory immediate & delayed	258	-	**NO**	-
Bhattachary & Powell (2001)	Prose recall	Novice = 1-5; Regular = 16+	-	-	**YES** [1]
Parrott et al (1998)	CDR: Word recall	Novice = 1-9; Regular = 10+	**YES** [1]	-	-
Parrot & Lasky (1998)	Auditory word recall	10+	-	-	**NO**
Fox et al (2001)	Matched verbal recall	356.9	-	-	**NO**
Wareing et al (2000)	Word span	101.2 days consumer per year	**NO**	-	-
Gouzoulis-Mayfrank (2000)	WASI-R: digit span	93.4	**YES**	**NO**	-
McCann et al (1999)	WRAIR PAB: delayed recall	215	-	-	**YES**
Verbal Learning					
Fox et al (2001c)	AVLT	Short-term = 223.6; Long-term = 811.5	-	-	**YES**
Thomasius et al (2003)	AVLT	Female = 600; Male = 1034	**NO**	-	**NO**

[1] Immediate & delayed recall
[2] Used over 20 ecstasy tablets within the last year
[3] estimated lifetime consumption (days/month x no. tablets per session x no. of months used)
[4] Used over 20 ecstasy tablets but not within the last year
[5] only ex-ecstasy users scored significantly worse on delayed recall compared to current and polydrug controls
[6] delayed recall only

Table 4 (Cont…)

Curran & Verheyden (2003)	(BSRT) Bushke selective reminding task	Current = 466, Ex = 707	-	-	**YES**[7]
Croft et al (2001)	Coughlan List	41.9	**YES**	**NO**	-
Semple et al (1999)	CVLT (California verbal Learning Test)	672	-	-	**NO**
Gouzoulis-Mayfrank (2000)	VLMT (Verbal Learning & memory test)	93.4	**YES**	**NO**	-
Verbal Recognition					
Reneman et al (2001)	AVLT - recognition	485	**YES**	-	-
Reneman (2000)	AVLT - recognition	218	**YES**	-	-
Croft et al (2001)	Warrington recognition memory test	41.9	**YES**	**NO**	-
Fox et al (2001b)	Matched verbal recognition	356.9	-	-	**NO**
Simon & Mattick (2002)	WASI-III	258	-	**NO**	-
McCann et al (1999)	WRAIR PAB: logical reasoning	215	-	-	**YES**
Visuo-spatial Recall					
Rodgers (2000)	WMS-R: recall	69 = 1-9; 66=10-99; 20=100+	**NO**	**NO**	-
Simon & Mattick (2002)	WMS-III	258	-	**NO**	-
Gouzoulis-Mayfrank (2000)	VIG: Visuo-spatial memory (immediate)	93.4	**YES**	**NO**	-
Morgan (1998) Study 1	CANTAB: Spatial span	35.6	**YES**	-	**YES**
Bhattachary & Powell (2001)	RCF	Novice = 1-5; regular = 16+	-	-	**NO**
Wareing et al (2000)	Visual Memory Task	101.2 days consumer per year	**NO**	-	-
Wareing et al (2000)	Brooks Spatial Matrix Task	101.2 days consumer per year	**NO**	-	-
Visuo-spatial Learning					
Croft et al(2001)	Spatial & non-spatial associative learning	41.9	**YES**	**NO**	-
Croft et al (2001)	Design Learning	41.9	**NO**	**NO**	-
Fox et al (2002)	CANTAB: paired associates	172	-	-	**NO**
McCann et al (1999)	WRAIR PAB: code subsitution	215	-	-	**YES**
Visuo-spatial Recognition					
Fox et al (2002)	CANTAB: pattern recognition	172	-	-	**YES**
Fox et al (2002)	CANTAB: spatial recognition	172	-	-	**NO**
Semple et al (1999)	CANTAB: delayed matching to sample	672	-	-	**NO**
Milani & Schifano (2000)	Gollin Visual Reognition Test	?	**NO**	-	-
McCann et al (1999)	WRAIR PAB: Manikin task	215	-	-	**NO**
Executive functioning / working memory					
Bhattachary & Powell (2001)	Digit span	Novice = 1-5; regular = 16+	-	-	**NO**

[7] both current and ex-ecstasy users showed poorer learning that controls

Table 4 (Cont...)

Verkes et al (2001)	Sternberg: Recognition of words	Moderate = 169, Heavy = 741	-	-	**YES**
Verkes et al (2001)	Sternberg: Recognition of figures	Moderate = 169, Heavy = 741	-	-	**YES**
Wareing et al (2000)	Baddeley Random letter generating task	101.2 days consumer per year	**YES** [8]	-	-
Curran & Verheyden (2003)	Serial Sevens	Current = 466, Ex = 707	-	-	**YES**[9]
Morgan et al (2002)	SSS (Subtracting serial sevens test)	Male = 513; Female = 93	**YES**	-	**NO**
Morgan et al (2002)	MFF20	Male = 513; Female = 93	**YES**	-	**YES**
Morgan (1998) Study 1	CANTAB: MFFT	35.6	**YES**	-	**YES**
Morgan (1998) Study 2	CANTAB: MFFT	49.6	**NO**	-	**YES**[10]
Morgan (1998) Study 1	CANTAB: TOL	35.6	**NO**	-	**NO**
Morgan (1998) Study 2	CANTAB: TOL	49.6	**NO**	-	**NO**
Fox et al (2002)	CANTAB: TOL	172	-	-	**NO**
Fox et al (2001b)	TOL (manual version)	356.9	-	-	**YES**
Schifano et al (1998)	TOL	Problematic (cps) = 47, Non-problematic (cps) = 3	-	-	**YES**
Milani & Schifano (2000)	TOL	?	**YES**	-	-
Morgan et al (2002)	Digit cancellation	Male = 513; Female = 93	**NO**	-	**NO**
Curran & Verheyden (2003)	Single & double digit cancellation	Current = 466, Ex = 707	-	-	**NO**
Croft et al (2001)	Forward and backward digit span	41.9	**YES**	**NO**	-
Gouzoulis-Mayfrank (2000)	Benton Verbal fluency	93.4	**NO**	**NO**	-
Wareing et al (2000)	Verbal fluency	101.2 days consumer per year	**NO**	-	-
Croft et al (2001)	Verbal fluency	41.9	**YES**	**NO**	-
Bhattachary & Powell (2001)	Verbal fluency	Novice = 1-5; regular = 16+	-	-	**YES**
Heffernan et al (2001) Study 2	Verbal fluency	5.6 per month	-	-	**YES**
Curran & Verheyden (2003)	Verbal fluency	Current = 466, Ex = 707	-	-	**NO**
Heffernan et al (2001) Study 2	Combined verbal/semantic fluency	5.6 per month	-	-	**NO**
Morgan et al (2002)	COWA (Controlled Oral Word Association Test)	Male = 513; Female = 93	**NO**	-	**NO**
Morgan et al (2002)	Category fluency	Male = 513; Female = 93	**NO**	-	**NO**
Fox et al (2002)	Semantic & letter category	172	-	-	**YES**[11]
Fox et al (2002)	CANTAB: Decision making task	172	-	-	**NO**
Fox et al (2002)	CANTAB: Spatial working memory	172	-	-	**YES**
Semple et al (1999)	CANTAB: Spatial working memory	672	-	-	**NO**

[8] more vowel intrusions
[9] ex-users carried out fewer subtractions than current users or controls, only at phase 1
[10] total errors committed
[11] only for letter category

Table 4 (Cont...)

Fox et al (2001b)	Spatial working memory	356.9	-	-	**YES**
Fox et al (2001b)	Wisconsin card sorting task	356.9	-	-	**NO**
McCann et al (1999)	WRAIR PAB: matching to sample	215	-	-	**NO**
Semple et al (1999)	Trials B test	672	-	-	**NO**
Semple et al (1999)	FAS word generation task	672	-	-	**NO**
Thomasius et al (2003)	WSCT – preservative errors	Female = 600; Male = 1034	**NO**	-	**YES**
Simon & Mattick (2002)	WASI-III	258	-	**NO**	-
Curran & Verheyden (2003)	RVIP (Rapid visual information processing	Current = 466, Ex = 707	-	-	**YES**[12]
Prospective Memory					
Heffernan et al (2001) Study 1	PMQ		-	-	**YES**
Heffernan et al (2001) Study 2	PMQ		-	-	**YES**
Rodgers et al (2001)	PMQ	69 = 1-9; 66=10-99; 20=100+	-	**NO**	**YES**
Measure of Everyday / General Memory					
Schifano et al (1998)	RBMT	Problematic (cps) = 47, Non-problematic (cps) = 3	-	-	**YES**
Milani & Schifano (2000)	RBMT	?	**YES**[13]	-	-
Rodgers et al (2001)	EMQ (everyday memory questionnaire)	69 = 1-9; 66=10-99; 20=100+	-	**YES**	-
Rodgers (2000)	WMS-R: general memory	20+	**YES**	**NO**	-
Simon & Mattick (2002)	WASI-III	258	-	**NO**	-
Reaction					
Verkes et al (2001)	Visual, auditory & binary reaction time	Moderate = 169, Heavy = 741	-	-	**YES**
Parrott et al (1998)	CDR: Simple and choice reaction time	Novice = 1-9; Users = 10+	**NO**	-	-
Rodgers (2000)	Visual, auditory & complex reaction time	20+	**NO**	**NO**	-
Fox et al (2001b)	Reaction time	356.9	-	-	**NO**
Semple et al (1999)	CANTAB: reaction time	672	-	-	**NO**
Croft et al (2001)	Grooved Peg	41.9	**YES**	**NO**	-
Attention/ Motor Tasks					
Gouzoulis-Mayfrank (2000)	TAP (subtest 1) Tonic & phasic attention	93.4	**NO**	**NO**	-
Gouzoulis-Mayfrank (2000)	TAP (subtest 6) Selective visual attention	93.4	**YES**	**YES**	-
Gouzoulis-Mayfrank (2000)	TAP (subtest 5) Divided attention	93.4	**NO**	**YES**	-
Gouzoulis-Mayfrank (2000)	TAP (subtest 8) Intermodal attention	93.4	**NO**	**YES**	-
Gouzoulis-Mayfrank (2000)	TAP (subtest 12): Visual scanning	93.4	**NO**	**NO**	-
Gouzoulis-Mayfrank (2000)	Stroop Test	93.4	**NO**	**NO**	-

[12] only ex-ecstasy users scored significantly worse on compared to current and polydrug controls
[13] only on appointment, message, date, route, and immediate and delayed recall components

Table 4 (Cont...)

Croft et al (2001)	Stroop Test	41.9	**YES**	**NO**	-
Morgan et al (2002)	Stroop Test	Male = 513; Female = 93	**NO**	-	**NO**
Semple et al (1999)	Stroop Test	672	-	-	**NO**
Milani & Schifano (2000)	Stroop Test	?	**NO**	-	-
Milani & Schifano (2000)	Simon effect	?	**NO**	-	-
Milani & Schifano (2000)	Posner effect	?	**YES**[14]	-	-
Rodgers (2000)	WMS-revised: attention & concentration	69 = 1-9; 66=10-99; 20=100+	**NO**	**NO**	-
Semple et al (1999)	WMS – digit span	672	-	-	**NO**
Zakzanis et al (2002)	TEA (Test of Everyday Attention)	22.3	-	-	**YES** [15]
Parrott et al (1998)	Number vigilance	Novice = 1-9; Users = 10+	**NO**	-	-
Parrott et al (1998)	Sternberg task	Novice = 1-9; Users = 10+	**NO**	-	-
Wareing et al (2000)	Information processing speed	101.2 days consumer per year	**YES**	-	-
Fox et al (2002)	CANTAB: 3D IDED Attentional shift	172	-	-	**YES**
Fox et al (2002)	CANTAB: Go/no go	172	-	-	**NO**
Parrot & Lasky (1998)	Visual Search	10+	-	-	**YES**
Morgan et al (2002)	Trail making test (B)	Male = 513; Female = 93	**YES**	-	**YES**
Semple et al (1999)	Trials A Test	672	-	-	**NO**
Verkes et al (2001)	Corsi Block Tapping Test	Moderate = 169, Heavy = 741	-	-	**YES**
Gouzoulis-Mayfrank (2000)	Corsi Block Tapping Test	93.4	**NO**	**NO**	-
McCann et al (1999)	WRAIR PAB: time wall task	215	-	-	**NO**
McCann et al (1999)	WRAIR PAB: serial add & subtract	215	-	-	**YES**
Thomasius et al (2003)	Go/no go	Female = 600; Male = 1034	**NO**	-	**NO**
Thomasius et al (2003)	Divided attention	Female = 600; Male = 1034	**NO**	-	**NO**
Gamma et al (2001)	CPT: Visual Vigilance	270	-	-	**NO**
Cognitive Failures Questionnaire					
Rodgers (2000)	Cognitive Failures Questionnaire	20+	**NO**	**NO**	-
Heffernan et al (2001)	Cognitive Failures Questionnaire	Average 20	**NO**	**NO**	-
Fox et al (2001b)	Cognitive Failures Questionnaire	356.9	-	-	**NO**

[14] only on congruent-incongruent condition
[15] Only on one of 8 subscales: Map search 2

Less consistent findings have been found regarding immediate and delayed memory, and working memory. Reneman et al (2000 & 2001) have shown immediate and delayed memory impairments on the AVLT compared to drug-naïve controls. Similar deficits have also been shown relative to polydrug controls, using the same and different methods of assessment (Fox et al, 2001c; Morgan, 1999; Morgan et al, 2002; Bhattachary & Powell, 2001; McCann et al, 1999). However, these findings have not always been supported. Parrot and Lasky (1999) did not find any significant differences in word recall between ecstasy and polydrug users. This finding was supported by Thomasius et al (2002) who also did not find any differences in ecstasy users compared to polydrug controls or even drug-naïve controls on prose and word recall, despite their ecstasy users having reported considerably large amounts of ecstasy use (average lifetime consumption was reported as 600 for females and 1034 for males).

Executive functioning/working memory deficits in ecstasy users have also been inconsistent. A number of studies have demonstrated significant deficits in ecstasy users relative to drug-naïve controls (Wareing et al, 2000; Milani & Schifano, 2000; Croft et al, 2001) and also polydrug controls (Verkes et al, 2001; Morgan, 1998; Fox et al, 2001b & 2001c; Bhattachary & Powell, 2001; Fox et al, 2002). Nonetheless, other studies have not found any working memory deficits in ecstasy users (Morgan et al, 2002; McCann et al, 1999; Gouzoulis-Mayfrank et al, 2000). Even within the same studies impairments in working memory depend on the assessment measure employed. For example, Fox et al (2002) showed ecstasy users to be impaired on a spatial working memory task and semantic and letter category task, but not on the CANTAB Tower of London test. Likewise, Morgan et al (2002) showed working memory performance decrements in ecstasy users on the MMF20 and Subtracting Serial Sevens task, but not on the Controlled Oral Word Association Test. These studies clearly demonstrate that research showing memory deficits in ecstasy users is dependent on the type of memory being assessed and also the assessment measures used. These outcomes appear to demonstrate that memory problems are clearly not profound, but are instead more subtle phenomena.

Research findings demonstrating learning deficits in ecstasy users have been relatively more consistent. Croft et al (2001) and Gouzoulis-Mayfrank et al (2000) have reported learning deficits in ecstasy users compared to drug-naïve controls but not cannabis users. Deficits have also been shown relative to polydrug controls (Fox et al, 2001c & McCann et al, 1999). However, Croft et al (2001) showed that learning deficits may again be task dependent. In

their study, ecstasy users were impaired on visuo-spatial learning as measured using a design learning task, but not on verbal learning using the Coughlan list.

More consistent cognitive deficits have been shown in relation to attention/motor abilities. Ecstasy users have demonstrated impaired performances on a number of attentional tasks relative to drug-naïve controls (Gouzoulis-Mayfrank et al, 2000; Croft et al, 2001; Milani & Schifano, 2000; Wareing et al, 2000; Morgan et al, 2002), cannabis users (Gouzoulis-Mayfrank et al, 2000) and polydrug controls (Zakzanis et al, 2002; Fox et al, 2002; Parrott & Lasky, 1998; Morgan et al, 2002; Verkes et al, 2001). Semple et al (1999), Gamma et al (2001) and Parrott et al (1998) did not show ecstasy users to be impaired on similar tasks, even though most of these studies actually employed heavier ecstasy users. Once again the discrepancy in findings between these and the former studies could be due to the differing measures employed in assessing this cognitive ability. Even within the same study, performance was dependent on the type of attention looked at and the assessment measure. For example, Gouzoulis-Mayfrank et al (2000) demonstrated deficits in ecstasy users on divided attention, selective visual attention and intermodal attention, but not on tonic and phase attention and visual scanning, nor on the Stroop test.

Ecstasy use or polydrug use?

Amongst the studies discussed, a number of cognitive deficits in ecstasy users have been shown relative to polydrug users, suggesting that these deficits are associated with ecstasy use rather than just general polydrug use. However, further clarification of the potential confounding effect of polydrug use, especially cannabis use, on cognitive performance is necessary.

Fox et al (2001c) found that ecstasy users were still cognitively impaired, even after covarying for other drugs such as cannabis, cocaine, LSD and magic mushrooms. Similar findings were also shown by Morgan (1999) and Bhattachary & Powell (2001). However, in a study by Croft et al (2001), they found that cannabis was an important confound in studies of ecstasy-induced cognitive impairments, because covarying for indices of cannabis consumption removed most of the significant cognitive differences previously evident in their sample of ecstasy users.

Further evidence suggests that there are certain cognitive deficits that are more pronounced or unique to ecstasy users. Rodgers (2000) found that deficits in logical memory were a feature of both ecstasy and cannabis use rather than ecstasy use alone. However, the ecstasy using group experienced additional impairments over and above those witnessed in the cannabis only control group. Rodgers et al (2001) tried to isolate the contribution of individual drugs to the overall variance in prospective memory performance scores in groups of ecstasy and cannabis users. They found a double dissociation between the impact of cannabis and ecstasy. Cannabis, but not ecstasy, was found to be associated with short-term and internally cued prospective memory; whilst ecstasy use, but not cannabis, was associated with long-term memory deficits. Thus, it appears that some selective cognitive deficits can be attributed to ecstasy use, but other drug use, specifically cannabis use, is certainly an important confound in these studies. Even though cannabis use alone is not sufficient to impair the performance in many of these tasks, the concomitant use of cannabis can certainly contribute to a cognitive impairment (Gouzoulis-Mayfrank et al, 2000).

Dose-related Effects

Further support for the role of ecstasy use and associated cognitive deficits, and an attempt to infer causation between ecstasy and its possible long-term cognitive effects, comes from studies which have reported dose-related type effects. This has been attempted, within cognitive studies, in one of two ways: Firstly, by employing different ecstasy using groups dependent on the level of drug use. For instance, assessing novice users who had only consumed ecstasy on 1-9 occasions, compared to regular ecstasy users who had used the drug on ten or more occasions (Parrott et al, 1998; Parrott & Lasky, 1998). Or comparing low ecstasy users (0-100 occasions), to medium (100-500 occasions) and high (500+ occasions) ecstasy users as well as polydrug controls (Fox et al, 2001b). The second method employed is to use statistical techniques such as regression, correlation or co-variant analysis to control for levels of ecstasy consumption and thus demonstrate possible dose-related findings (Morgan et al, 2002; Fox et al, 2001c; Morgan, 1999)

Parrott et al (1998) were one of the first research teams to employ a research design involving ecstasy groups with varying levels of drug use, as defined above. Despite finding significant cognitive deficits in immediate and delayed recall compared to drug-naïve controls, they failed to find any differences in recall between novice and regular ecstasy users. However,

they did find a difference between these two ecstasy-using groups on reaction time as measured by the Sternberg task. A further study by Parrott & Lasky (1998), which employed the same criteria for their novice and regular ecstasy using groups, found regular ecstasy users displaying the worst memory scores; though they did not differ significantly from the novice users.

A similar research design was used by Bhattachary & Powell (2001), comparing novice users, (1-5 occasions and never more than once a month), with regular ecstasy users (at least 5 times and twice in the last 21 days). Again, despite finding differences in performance between both ecstasy using groups and non-users, they did not find any differences between novice and regular users. However, statistically controlling for the amounts of ecstasy use, they found that heavier ecstasy use predicted poorer memory scores, with lifetime use emerging as the strongest predictor for immediate and delayed recall performance.

Level of ecstasy use was also found to influence performance on word recognition (Verkes et al, 2001), with heavy ecstasy users (defined as using on at least 48+ occasions, but had used on average 741 times), being affected significantly more than moderate ecstasy users (12-48 occasions). Executive functioning decrements as a function of the level of ecstasy have also been demonstrated. Fox et al (2001b) found that their higher user group (500+ occasions) demonstrated significantly poorer performance on an executive functioning task compared to low ecstasy users (0-100 occasions).

There is a greater amount of evidence demonstrating dose-related effects shown by statistically controlling for levels of ecstasy consumption. Bolla et al (1998) were one of the first research teams to demonstrate that impairments in immediate and verbal memory recall were associated with higher doses of ecstasy. Support for this dose-related effect on verbal memory recall also comes from Morgan et al (2001) and Reneman et al (2001), who both showed that greater lifetime use of ecstasy, negatively correlated with verbal memory performance. More recently, Thomasius et al (2003) demonstrated that the average number of words recalled on the AVLT was best predicted by the typical number of ecstasy tablets consumed in a year.

Other areas of cognitive performance deficits shown to be associated with ecstasy dosage include spatial working memory (Semple et al, 1999), working memory (McCann et al,

1999), reaction times (Gouzoulis-Mayfrank (2000), attentional abilities (Gouzoulis-Mayfrank et al, 2000; Zakzanis et al, 2002) and executive functioning (Zakzanis & Young, 2001). The latter study also showed that the frequency and duration of ecstasy use was also associated with lower scores on many subtests of the Behavioural Assessment Dysexecutive Syndrome test. Collectively, these results suggest that increasing ecstasy consumption may lead to more pronounced impairment in cognitive functioning.

However, Simon and Mattick (2002) did not show any significant effects between the relationship of lifetime exposure and memory performance on the WMS-II. More recently, a meta-regression analysis did not indicate support for a linear relationship between the mean effect size and total lifetime consumption (Verbaten, 2003). However, there was the possibility of a stepwise relationship which may account for most of the research findings discussed earlier.

Interim Summary

There is a fairly large amount of empirical research into the possible cognitive impairments associated with ecstasy use. Areas of relatively consistent cognitive dysfunction in current ecstasy users compared to non-ecstasy using groups are immediate and delayed memory, executive functioning, working memory, including prospective memory, and attentional abilities. Whilst cannabis use is thought to have a potential confounding effect on some of these cognitive functions, there are some selective cognitive deficits found to be associated with ecstasy alone. Conclusions concerning dose-related effects of ecstasy on cognitive impairments are more difficult to come to because of the inconsistencies in research findings and the differences in approaches in trying to demonstrate dose-related findings. It is possible that such inconsistencies and discrepancies between research studies may indicate that ecstasy-induced effects are very subtle, rather than overtly profound global impairments in cognition.

Cognition and altered serotonin functioning

In addition to dose-related effects between cognitive impairment and levels of ecstasy consumption, further support for the association between ecstasy and its possible functional consequences, on cognitive functioning, comes from studies which have measured alterations

in serotonin functioning, as well as corresponding cognitive performance in ecstasy users compared to controls.

Cognitive deficits in ecstasy users have been shown to be correlated with decreases in the concentration of 5-HIAA (McCann et al, 1999; Bolla et al, 1998). Bolla et al (1998) also showed an additional negative association between ecstasy dosage and 5-HIAA concentrations. This suggests that the higher the dose of ecstasy the greater the subsequent decrement in memory function and the lower the level of CSF-5-HIAA (an indirect measure of central 5-HT function).

Other markers of serotonergic neuronal injury and corresponding cognitive deficits have also been demonstrated. Krystal et al (1992) found a correlation between ecstasy user's performance on the delayed figural subtest of the Wechsler memory scale, and prolactin response to an $_{L}$-tryptophan pharmacological challenge. However, there is a limit concerning the degree to which one can derive conclusions from this finding since there were no age-matched controls and the sample size was small. Curran & Verheyden (2003) found elevated levels of plasma tryptophan following an $_{L}$-tryptophan pharmacological challenge, which strongly correlated with performance on a prose recall task. However, this was only found in ex-ecstasy users (those who had not used for at least one year) and not current ecstasy users. Verkes et al (2001) found that following a d-fenfluramine challenge, cortisol levels in moderate and heavy users significantly differed to that of polydrug controls. This study also showed cognitive deficits in both ecstasy using groups on a variety of tasks.

Further still, Reneman et al (2000) demonstrated that 5-HT cortical binding significantly correlated with verbal recall on the AVLT in ecstasy users. In a follow-up study they also showed significant group differences in cortical 5-HT neuron binding and also immediate and delayed recall on AVLT; though here memory performance was not associated with the extent of cortical binding and they failed to replicate the dose-related findings from the previous study (Reneman et al, 2001).

Although most of these studies addressing cognitive dysfunction and altered serotonergic activity are limited in someway or another (i.e. small sample sizes, cross reference comparisons only), they at least suggest an intriguing relationship between markers of serotonergic brain damage and memory performance in ecstasy users. This pattern of

cognitive decrement is consistent with the animal data illustrating serotonin neurotoxicity in the frontal cortex and hippocampus; brain areas that are important for planned actions and memory functioning (see chapter 1).

Recovery of cognitive abilities

Despite extensive empirical evidence suggesting serotonergic alterations and associated cognitive dysfunction as a result of recreational ecstasy use, there has been very little research into whether these cognitive deficits remain after abstinence from ecstasy, or if ex-users show signs of functional recovery. The recovery, if any, of cognitive functioning in humans might suggest a recovery of central 5-HT functioning, as documented in the case of animals.

Tentative evidence of the recovery of memory performance was shown in a small group of ecstasy users who had abstained from the drug for more than 6 months (Morgan, 1998). However, further evidence suggests that cognitive deficits are more persistent, as shown by Wareing, et al (2000). In their study, current and previous ecstasy users (defined as those who had stopped taking ecstasy at for at least six months), were found to have deficits on some aspects of central executive functioning compared to a control group of non-ecstasy users. Thomasius et al (2003) showed impairments on immediate and delayed verbal recall that were persistent in ex-ecstasy users. However, they had only been abstinent for at least 5 months (males on average 485.4 $\pm$ 533.09 days and females 545.13 $\pm$ 470.74 days), and their current ecstasy users failed to show any impairments relative to controls. Curran & Verheyden (2003) showed ex-ecstasy users demonstrated a number of cognitive impairments in working and episodic memory a year after ecstasy cessation compared to current ecstasy users and polydrug controls. However, like Thomasius et al (2003), their current ecstasy users did not show any impairments on the same tasks relative to controls. Further support for the persistency of selective cognitive impairments, come from a study by Morgan et al, (2002). Here ex-ecstasy users showed significant impairments on the RBMT story recall task and committed a significant number of errors on the MFFT-20 relative to polydrug users. These deficits remained after an average of two years of abstinence (Morgan et al, 2002).

It is also worth noting here that the data on the persistency of cognitive impairments in abstinent ecstasy users, does not necessarily reflect that serotonergic recovery does not occur. Reneman et al (2001) demonstrated that the neurotoxic effects on 5-HT in the cortex may be

reversible in ex-ecstasy users, yet despite these indications of recovery in cortical binding, cognitive impairment still remained in ex-ecstasy users compared to controls. AVLT performances showed that both ecstasy and ex-ecstasy users differed to that of controls. This suggests that although the neurotoxic effects may appear reversible at the neurological level, the effects on memory function may be long-lasting. This would tie in with the animal data (Fischer et al, 1995; Hatzidimitriou et al, 1999) showing 'sprouting' of serotonin axons i.e. serotonergic recovery, but not necessarily normal organisation or functioning. As such, it could be argued that memory testing is a more valid indicator of injury or recovery than measuring ecstasy effects on SERT densities, though this still remains to be proven.

Other important confounds/contributory factors

Caution is needed when interpreting some of the research findings discussed, as sequalae reported as long-term effects of ecstasy could instead be the subacute effects. Parrott et al (1998), Morgan et al (1999), Croft et al (2001), Heffernan et al (2001), Verkes et al (2001), Bhattachary and Powell (2001) and Daumann et al (2001), all reported effects of ecstasy after a short abstinence period of only 1-7 days. Therefore any effects could potentially be acute partial residual effects or drug withdrawal effects of the ecstasy, rather than the long-term effects. Also, many studies do not even report any abstinence criteria for ecstasy use before testing or the time since the last ecstasy ingestion (e.g. Schifano et al, 1998; Parrott et al, 2000 & 2001; Dughiero et al, 2001; Morgan et al, 2002). Again making it difficult to infer whether the findings are about the long-term effects of the drug. However, support suggesting that these problems are long-term effects associated with ecstasy use comes from studies which did utilise a minimum two-week abstinence period prior to assessment (e.g. Bolla et al, 1998; Zakzanis & Young, 2001; Zakzanis et al, 2002; Renemen et al, 2001; McCann et al, 1999).

In trying to interpret a causative link between recreational ecstasy use and the development of cognitive and psychological problems there is always the confounding variable of pre-existing problems that ecstasy users may have prior to their ecstasy use. Most empirical research into the long-term effects of ecstasy is retrospective and thus baseline (premorbid) levels of function, both cognitively and psychologically, are difficult to establish. Any differences between ecstasy users and control groups could reflect a number of pre-existing neurochemical, genetic and personality differences between the two groups rather than the

effects of using ecstasy. It has been repeatedly shown that, in a number of studies, ecstasy users display higher scores on impulsiveness, venturesomeness, sensation seeking and novelty seeking scales, compared to controls (Morgan et al, 1998; Parrott et al, 2000; Morgan et al, 2000; Montgomery & Butler, 2001a; Daumann et al, 2001; Dugherio et al, 2001). It is well established that childhood problems and personality traits such as sensation seeking and impulsivity, are associated with an increase risk of experimenting with controlled drugs and developing substance abuse problems (Bardo et al, 1996; Hawkins et al, 1992; Zuckerman et al, 1994; Hatzitaskos et al, 1999; Clark et al, 1998). These secondary personality factors are also associated with lower serotonergic functioning (Linnoila et al, 1993; Virkkunen et al, 1995) and alone may account for the psychopathological scores and cognitive deficits in the ecstasy users, since many of these personality traits, independent of drug use, are also associated with poorer cognitive performance and increased risk of developing adult psychopathology (Zuckerman & Neeb, 1979; Hawkins & Trobst, 2000). Thus, premorbid states, especially ones that are known to be related to low 5-HT function, could contribute to a misleading impression that cognitive deficits and increased psychopathology are caused by ecstasy use or, at the very least, may limit the interpretation of the functional effects of ecstasy.

There is also the confounding factor of the individuals having a pre-existing diathesis, especially concerning studies assessing the psychopathological status of ecstasy users. The classic diathesis model for mental health, proposes that the combined impact of genetic predisposition and an environmental stressor, produces a given negative mental health outcome (Gabbard & Goodwin, 1996). However, it may be that in ecstasy using individuals, their ecstasy use may have constituted this significant external stressor by negatively modulating normal brain function. Even though many empirical studies exclude participants with current or past psychiatric and medical illnesses (e.g. Verkes et al, 2001; Bolla et al, 1998; Reneman 2000; Zakzanis et al, 2002; Fox et al, 2002; Simon & Mattick, 2002), few studies actually report family psychiatric history, which might suggest a possible genetic predisposition to psychiatric illness in participants. Thus, evidence in terms of any causative link between ecstasy and MDMA-induced neurotoxicity from psychiatric reports and experienced psychopathology following ecstasy use, is therefore the weakest, because of the mediating factor of a pre-existing diathesis. Therefore interpretation should be limited to

mere associations between ecstasy use and these cognitive and psychological effects which have been discussed.

Finally, another pre-existing genetic difference that could possibly account for differences in ecstasy users, and/or determine possible individual vulnerabilities in ecstasy users, is the individual metabolic handling of certain drugs. Polymorphic enzyme cytochrome P450 2D (CYP2D6) is involved in the metabolism of a broad array of drugs. Kreth et al (2000) and Ramamoorthy et al (2002) have shown that individuals who lack fully functioning CYP2D6 enzymes have a reduced ability to metabolise MDMA. Since about 5-9% of caucasians are deficient in this enzyme (Tucker et al, 1994), it has been suggested that this genetic polymorphism may explain some of the inter-individual differences in MDMA toxicity (Schifano, 2004). Additionally, the enzyme COMT is also involved in the metabolism of MDMA and its metabolites, and approximately 25% of the caucasian population have low COMT activity (Zhu, 2002). Thus a reduced ability to metabolise MDMA and its metabolites due to genetic differences, may contribute to the toxic effects of MDMA in some individuals, and potentially long-term ecstasy-related neurotoxicity and its cognitive and psychological consequences (Schifano, 2004).

Problematic ecstasy use

To date there is an extensive body of research that demonstrates the possible functional consequences of ecstasy-induced serotonergic neurotoxicity, with supportive dose-related type effects and associated alterations in serotonergic functioning. The literature suggests that ecstasy is associated with long-term cognitive and psychopathological effects, but little attention has been given to establishing whether these effects develop to such an extent that ecstasy users consider them to be problematic. Clinical case studies demonstrate that these effects of ecstasy can be problematic. However, these are limited in number compared to the numbers of people reported using ecstasy. Research concerning the extent of ecstasy-related effects in non-clinical ecstasy users has been limited.

According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA; 2001), ecstasy use is the main drug of those in treatment in only a few cases. However, reports focusing solely on ecstasy users demonstrate a different picture. In an Australian

survey, Topp et al (1999) showed that one fifth of ecstasy users had received treatment for an ecstasy-related problem, mainly from a GP or a natural therapist, 7% were currently in treatment and a further 15% wanted formal treatment for difficulties perceived to be related to ecstasy use.

In a UK survey of ecstasy users, 55% reported continuing to use ecstasy despite reporting problems (Winstock et al 2001). In the same study 15% of ecstasy users fell into the problematic range, as defined by using the severity of dependence scale. These studies indicate that there are recreational ecstasy users that are developing chronic problems associated with their ecstasy use, but do not indicate what specific type of problems these ecstasy users are exhibiting. Hammersley et al (1999) noted that the heaviest users of ecstasy were more likely to report having experienced paranoia and memory problems, but were also more likely to report having been an inpatient in the last year, making it difficult to determine whether their problems were a result of their ecstasy use.

To try and establish whether the effects of ecstasy develop to such an extent that users considered the effects to be problematic, Parrott et al (2002) aimed to assess the incidence of ecstasy-attributed problems in relation to the level of ecstasy use. Volunteer ecstasy users (n = 763) were divided into novice (n = 109), moderate (n = 136) and heavy users (n = 36), depending on their lifetime ecstasy consumption (1-9 occasions, 10-99 occasions and 100+ occasions respectively). They were asked to indicate whether or not they had experienced a list of problems 'off-drug' that they attributed to ecstasy; these included psychological, cognitive, medical and physiological problems. Depression, memory problems, anxiety, mood fluctuations, poor concentration, infections, tremors/twitches and weight loss were all significantly associated with the extent of ecstasy use. One limitation of this study is that it was web-based, which potentially means that these problematic ecstasy users are self-selected and are an unrepresentative cohort of ecstasy users. However, despite the reliance on self-report data, with no objective measure of these problems, it does argue that the diversity of problems experienced by these particular ecstasy users and their incidence, is a direct function of the number of occasions on which the drug has been consumed.

However, Fox et al (2001b) reported that psychological symptoms in "problematic" ecstasy users were unrelated to ecstasy use. This study examined the differences between self-reported problems (psychological, emotional and somatic problems) and "non-problem"

ecstasy users in relation to both consumption and premorbid life adjustment variables. Those problem ecstasy users who reported problems which they attributed to their ecstasy use, had significantly higher scores on all scales of the SCL-90 compared to the non-problem group. Yet their self-perceived problematic use was not related to their drug use but to negative interpersonal relationships prior to taking the drug and less socially orientated motivations for using the drug. Winstock et al (2001) argues that it is speculative to suggest that ecstasy per se can cause such problems or even an ecstasy dependence syndrome, because of social and behavioural constructs, which are key issues. This is supported by the findings of Fox et al (2001a), in that the role of premorbid data and self-perception of problematic drug use is integral to issues relating to cause and effect in the ecstasy use/pathology relationship. There are inconsistencies in the literature focusing on the problematic nature of these ecstasy-related effects, but evidence does suggest that some ecstasy users do consider themselves to have developed problems which are associated with past ecstasy use. This issue of problematic ecstasy use lends support to the MDMA induced serotonergic neurotoxicity model; in that, these ecstasy users have incurred serotonergic injury and are displaying the functional impairments associated with such damage. Individuals, who are not considered as problematic, may not have experienced sufficient neurotoxic injury for the effects to have developed to such an extent that they have become behaviourally problematic. However, there are inconsistencies in the evidence for this model, since not all ecstasy users become problematic. Not all deficits become problematic, some are more subtle than others and other behavioural capacities seem to be spared.

Taken together with anecdotal evidence, it is clear that many ecstasy users are not problematised by their ecstasy use. The question is, whether this is because the effects in these ecstasy users are so subtle they are not perceived as being problematic? Or, that they have not taken enough ecstasy to have incurred serotonergic damage to have caused behavioural problems? Or even, that there are some ecstasy using individuals who are impervious to the potential harmful effects of the drug, be that for genetic, biological and/or, personality reasons. It is for this reason that further empirical research is needed into the extent and nature of problems associated with ecstasy use and whether such problems are a result of ecstasy per se and/or a combination of other behavioural and social issues.

SUMMARY

This chapter provides an overview of the current research which demonstrates the possible cognitive and psychological effects associated with ecstasy use. It appears that there is evidence from both clinical and empirical studies to suggest that ecstasy users demonstrate elevated psychopathology and cognitive impairments. Studies have consistently shown that ecstasy has been associated with elevated levels of psychoticism, phobic anxiety, and obsessive-compulsive and anxiety symptoms. Whilst there is evidence to suggest that ecstasy users show elevated levels of interpersonal sensitivity, paranoia, aggression and anger, and depression, not all studies have shown consistent significant group differences. Research concerning cognitive abilities in ecstasy users, points to selective deficits: in particular verbal memory, prospective memory, working memory and executive functioning, and attentional abilities; even in studies which have accounted and controlled for polydrug use. However, not all findings have been consistent, with some studies only showing impairments in one of these cognitive domains and not others. Some studies have only indicated deficits relative to drug-naïve controls and not cannabis and/or polydrug users and some cognitive deficits are dependent on the specific cognitive task employed. Dose-related effects of ecstasy in relation to both cognitive impairment and psychopathology, strengthens the association with ecstasy use and these functional consequences, as well as associated alterations in serotonergic functioning. The question pertaining to whether or not any of these long-term problems develop to an extent that they become problematic to the user, and are a direct function of their past ecstasy use has yet to be resolved.

RATIONALE

Animal research strongly suggests that MDMA (ecstasy) induces serotonergic neurotoxicity. Human research, whilst less consistent, also provides support for possible serotonergic neurotoxicity, by showing altered brain serotonergic functioning in recreational ecstasy users. The possible psychological consequences of these neuronal alterations therefore are thought to be within areas that are regulated by serotonin. These include:- mood, anxiety, aggression, appetite, sleep, motor activity and areas of cognition such as learning, visuo-spatial memory, associative functions and aspects of planning and general memory consolidation and retrieval. Whilst a number of case studies and empirical evidence strongly point to this proposition, there still remain inconsistencies concerning which areas of cognition and which specific psychopathological domains are affected. More importantly, research concerning the extent of these problems is limited. Clinical case studies demonstrate that these effects of ecstasy can be problematic. However, these are limited in number compared to the numbers of people reported using ecstasy. There is also a paucity of literature on problematic ecstasy use in non-clinical population samples, with little attention given to establishing whether there are differences in ecstasy users who develop problems, to those ecstasy users who do not. Little research has addressed personality factors in relation to problematic ecstasy use. It may be that perceived problems relate to certain personality factors. In response to this shortage of research differentiating between problematic and non-problematic ecstasy use, the broad aim of this thesis was to corroborate and expand upon prior research, by identifying ecstasy users who have developed problems which they attributed to their past ecstasy and compare them to ecstasy users who do not report problems attributable to their ecstasy use, in order to identify any potential differences between these two distinct ecstasy using groups. In order to achieve this aim, this thesis intends on focusing on the two main areas which, in the current literature, have shown to be affected in ecstasy users relative to non-ecstasy users – that of cognitive problems and psychological health. To assess potential differences in problematic and non-problematic ecstasy users in relation to one another and compared to polydrug controls within these two areas, tests known to demonstrate ecstasy-related impairments will be used, these include the AVLT, TOL, RBMT and a measure of psychopathology using the brief version of the SCL-90-R; the BSI.

CHAPTER 3

Cognitive and psychological profiles of non-problematic and problematic ecstasy users

INTRODUCTION

This study aimed to assess whether ecstasy polydrug users are more susceptible to cognitive and psychopathological[1] problems compared to polydrug controls. More specifically, whether there are relationships between the cognitive and psychopathological effects, drug dosage and problematic ecstasy use (adverse psychological problems attributed to past ecstasy use).

To date a few studies have addressed the issue of problematic ecstasy use in relation to cognitive and psychological functioning. Schifano et al (1998) conducted a large scale clinical survey examining 150 patients who had used ecstasy on at least one occasion, and who had presented themselves, for various reasons, to an addiction treatment unit. Seventy-nine patients were diagnosed as problematic, with the presence of one or more psychopathological disorders as assessed by the DSM-III-R. Those individuals that had used ecstasy for a longer period of time, and had consumed a greater amount in their lifetime were more likely to show co-morbidity and/or present with more severe symptoms.

A sub-sample of these problematic ecstasy users (n=10) were assessed for cognitive impairment, by comparison with a group of 20 (age and education matched) normal subjects who did not report any lifetime consumption of illegal drugs (Milani, 1997). The problematic ecstasy users showed significant cognitive impairments compared to these drug-naïve controls. However, interpretation of the cognitive impairments in these problematic ecstasy users was limited since no comparison was made with ecstasy users that were not diagnosed with psychopathological disorders, or with age-matched drug-naïve psychiatric patients. Additionally, cognitive abilities were compared with a control group that consisted of drug-naïve subjects. Since 78% of the problematic ecstasy users reported opiate use and 30% reported other drug use (nitrates, LSD); cognitive deficits might be the result of polydrug use rather than ecstasy per se.

These limitations were addressed in the first non-clinical study to examine the interaction between ecstasy use and self-reported problematic drug use in relation to cognitive

[1] Psychopathology will be used as a term to refer to the manifestation of behaviours and experiences which may be indicative of mental distress / illness or psychological impairment.

impairment. Fox et al (2001b) assessed whether cognitive deficits in recreational ecstasy users were related to the awareness of problematic ecstasy use or actual drug dosage, by comparing problematic ecstasy users, non-problematic ecstasy users and polydrug controls on a number of cognitive tests. Despite the fact that the two ecstasy groups differed markedly in reported problems attributed to ecstasy use, both groups (problematic and non-problematic) showed similar cognitive impairments compared to polydrug controls on two executive tasks, as well as similar drug consumption profiles, duration and lifetime consumption of ecstasy use. Thus there were differences in perceived problems between groups yet they exhibited similar cognitive deficits and patterns of drug use. To further assess the interaction of drug dosage and cognitive functioning, Fox et al (2001b) combined both ecstasy-using groups together and further divided them into low, medium and high users. High ecstasy users exhibited significantly greater cognitive impairment than medium and low ecstasy users. Hence, decrements in cognitive functioning were demonstrated as a function of drug dosage rather than problematic ecstasy use, which further suggests that individual's awareness of problematic ecstasy use may not be necessarily dose-related. However, this study did not formally assess the psychopathological status of these recreational ecstasy users. Rather subjects were just asked to indicate whether they had or had not experienced problems which they attributed to their past use of ecstasy.

This current study aimed to expand and improve upon prior research into the cognitive functioning and psychopathological status in relation to drug dosage in problematic ecstasy users, by employing a non-problematic ecstasy using group and also looking at a clinical sample of problematic ecstasy users. In order to achieve this, the current study employed recreational ecstasy users who reported psychobiological problems that they attributed to their past ecstasy use (problematic ecstasy users) and a second group of recreational ecstasy users who were problem free (non-problematic ecstasy users), in addition to a polydrug control group. Problems in the 'problematic' ecstasy group were defined as problems that were clinically recognised and/or interfered sufficiently in their life functioning that they had sought some form of help for.

All three groups were assessed and compared on a battery of cognitive tasks which consisted of the Auditory Verbal Learning Task (AVLT), Tower of London (TOL) and Rivermead Behavioural Memory Test (RBMT). These tasks have previously demonstrated sensitivity to ecstasy-induced effects (see literature review). The AVLT assesses problems specifically

with immediate and delayed verbal recall. Ecstasy users have been shown to perform significantly worse than drug naïve and polydrug controls on the immediate recall component of this task (Reneman et al, 2001 and Fox et al, 2001c) and the delayed recall component (Reneman et al, 2001, Reneman et al, 2000 and Fox et al, 2001c). Additionally, AVLT verbal recall has been shown to significantly correlate with 5-HT cortical binding (Reneman et al, 2000). Ecstasy users may also be susceptible to frontal executive problems (Verkes et al, 2001; Morgan et al, 2002; Fox et al 2002). The TOL measures planning abilities, one aspect of executive functioning. This assessment measure has also revealed impairments in ecstasy users (Fox et al, 2001b; Schifano et al, 1998). The RBMT was employed because it is an ecologically valid battery of psychological tests which indicate impairments in everyday memory functioning and has also been used previously in this research area (Schifano et al 1998). The aim of the study was therefore to try and identify cognitive deficits in ecstasy users compared to polydrug controls and, more specifically, whether those that reported problematic ecstasy use were more sensitive to detrimental cognitive effects compared to ecstasy users that did not report problems.

Psychopathological status was assessed in all three groups, using a modified version of the Brief Symptom Inventory (BSI) (Derogatis & Melisaratos, 1983). This is a self-report clinical rating scale, covering nine distinct subscales; including somatisation, obsessive-compulsive-like behaviour (OCD), interpersonal sensitivity, depression, anxiety, anger/hostility, phobic anxiety, paranoid ideation and psychoticism (see appendix for further detailed definitions of these subscales). The BSI is a shortened version of the SCL-90-R (Derogatis et al, 1976), designed to assess the psychological symptom status across nine primary dimensions in psychiatric and medical patients, as well as individuals who are not patients (Derogatis & Melisaratos, 1983). This shortened version of the SCL-90-R seemed suitable to employ in conjunction with other assessment measures as psychometric evaluation has shown it to be an acceptable, reliable and valid alternative to the longer complete scale (Derogatis & Melisaratos, 1983). The use of this scale was to establish whether ecstasy users reported higher psychopathological scores than polydrug controls. Previous studies using the SCL-90-R have demonstrated elevated psychopathology compared to controls (Parrott et al, 2001; Morgan et al, 2002, Parrott et al, 2000; Daumann et al, 2001; Dugherio et al, 2001). Further still the BSI allows for formal assessment of psychopathology in the 'problematic' ecstasy users, to establish whether they do exhibit psychopathological problems, or whether

there is just a difference in awareness and perception of problematic ecstasy use as demonstrated previously by Fox et al (2001b).

The scale was modified with the addition of items reflecting sexual functioning, cognitive failures; known MDMA side effects and the addition of four positive dimensions: feeling content with life, positive psychobiology, sociability and mood state (items previously added to the SCL-90 in the studies by Parrott et al (2001) and Milani et al (2001)). The cognitive failures subscale was added to allow subjective assessment of cognitive performance, whilst the sexual functioning and MDMA side effects dimensions were added to tailor the scale to areas specifically related to ecstasy problems (Cohen, 1995). The four positive items were added in answer to criticism from advocates of recreational ecstasy use who frequently state that researchers are biased and focus solely on the negative effects rather than the positive effects of the drug (Parrott et al, 2001).

Another objective to the study was to examine whether there were any cognitive and psychological dose response effects of ecstasy use, in order to confirm previous findings (e.g. Schifano et al, 1998; Parrott, Sisk & Turner, 2000; MacInnes et al, 2001; Fox et al, 2001b; Reneman et al, 2001). In order to achieve this psychopathological and cognitive test scores in all ecstasy users (both problematic and non-problematic) were correlated with ecstasy use patterns; including lifetime consumption, average dose consumed on any one occasion and largest dose consumed on one occasion. To date a number of conclusions have been drawn relating to the total level of ecstasy consumption (Fox et al, 2001b; Parrott et al, 2001), the number of pills taken in a single occasion (Milani et al, 2001) or maximum amount of ecstasy consumed in 12 hours i.e. binge consumption (MacInnes et al, 2001). This will hopefully help to establish further which aspects of ecstasy consumption are important in inducing cognitive and/or psychopathological problems.

The study also aimed to explore further, a number of other variables such as, patterns of ecstasy use and levels of polydrug use and other self-rating variables, focusing on perceived positive and negative effects of ecstasy, which have been briefly examined in previous investigations (Liechti et al 2000b; Gamma et al, 2000; Cami et al, 2000; Liechti & Vollenweider, 2001; Cohen et al, 1995; Parrott et al, 2002). The study also explored a record of individual and family psychiatric histories. 'Ecstasy' problems may be influenced in whole or part by pre-existing pathology or predisposition, which in turn, might be reflected from

such individual and family histories, or more intense ecstasy use in combination with heavier polydrug use.

There is a multiple of case reports involving ecstasy induced toxicity that exhibit features and in some cases fit the diagnostic criteria for the serotonin syndrome[2] (Demirkan et al, 1996; Mueller & Korey, 1998). It has been argued that the serotonin syndrome represents a continuum of responses from mild to severe (Gillman, 1998), with the greater the elevation of 5-HT concentration the greater and more severe the symptoms (Gillman, 1997). Thus it has been proposed that the mechanism of ecstasy intoxication produces the serotonin syndrome (Gillman, 1997). Some individuals develop severe responses, as demonstrated by reported case studies and others reporting a milder version of the syndrome. Many of the negative acute effects of ecstasy (e.g. reduced body temperature, excessive sweating, confused thought, dilated pupils), are in part, mild symptoms that constitute the serotonin syndrome. Susceptibility to the long-term neurotoxic effects could be reflected by, or be a direct result of acute negative effects (Parrott, 2002). There is very little data on this relationship, therefore the current study also aims to explore whether this is possibly the case, by comparing problematic and non-problematic ecstasy user's scores on a self-rating questionnaire based on the acute physiological and psychological effects of ecstasy (Cohen, 1995; Davison and Parrott, 1997).

The working hypotheses were as follows: Firstly, ecstasy using individuals would demonstrate cognitive deficits and higher psychopathology compared to polydrug controls. In addition, it is predicted that there will be a significant difference in cognitive and psychopathological status between the two more 'clinically' defined ecstasy using groups; those who reported problems from ecstasy use and those who did not. Secondly, it is predicted that patterns and levels of ecstasy use would vary between the problematic and non-problematic ecstasy user groups. It is expected that problematic ecstasy users would report greater lifetime consumption and average use than non-problematic ecstasy users, and thirdly

---

[2] The serotonin syndrome is produced in the setting of the recent concurrent use of a serotonergic agent. It is characterised by alterations in cognition, behaviours, CNS function and neuromuscular activity. Diagnosis is usually established by a constellation of symptoms; confusion, shivering, diaphoresis, ataxia, hyperreflexia, diarrhoea, myoclonus, rigidity, agitation, restlessness, coma, autonomic instability, low-grade fever, nausea, flushing and rarely rhabdomyolysis and death (Sternbach, 1991; LoCurto, 1997).

the cognitive and psychopathological effects of the drug will vary with dose, i.e. the greater the dose the greater the impairment.

METHOD

Participants

Participants were recruited via the 'snowball' method (6%) (Solowij et al. 1992), word of mouth (35%), self-referrals from psychiatrists and clinical psychologists (3%), advertisements (appendix O) in a London based magazine called the Big Issue (15%) and posters (appendix Q) around the University of East London (28%). First year undergraduate psychology students, who volunteered for the study, did so as part of a course requirement (13%). All participants were assessed for ratings of health, age and number of years in education.

Fifty-four subjects participated in this study: 20 (13 male, 7 female) recreational ecstasy users who had used ecstasy on at least 20 occasions in their lifetime and had not experienced any long term problems attributable to its use, 14 (8 male, 6 female) recreational ecstasy users who reported problems which they attributed to past ecstasy use. These problems had to be clinically defined (e.g. clinical depression, psychosis, schizophrenia), and/or interfere sufficiently in the participants life functioning to the degree that they had sought some form of help. Finally, there were 20 (8 male. 12 female) polydrug controls that had no history of ecstasy exposure but otherwise had used other illicit drugs. Given that the half-life of MDMA in animals is between 1 and 2 hours, it was deemed appropriate to have a 2-week abstinence period of ecstasy prior to assessment, in order to rule out any withdrawal or possible residual effects of the drug. Participants were required to abstain from other drug use for 24 hours prior to assessment.

All participants were required to give details of personal history regarding their own and their immediate family's psychiatric history and details of their past drug history (appendix A). Ecstasy users were required to provide further information concerning, patterns of ecstasy use: including information on the duration of ecstasy use, the last time taken, the average number of ecstasy tablets consumed in one occasion, the largest number consumed in one occasion, whether they increased the number of ecstasy tablets taken on each successive occasion, whether they thought the effects of ecstasy had changed the more it was taken, whether they suffered if they went without ecstasy for sometime, whether they needed to take ecstasy regularly, whether they felt addicted or dependent on ecstasy, whether they considered themselves to be a stable user of ecstasy, whether they continued to use ecstasy and whether they used other drugs to alleviate any known ecstasy side effects (appendix B).

Both ecstasy-using groups were also asked to complete two additional sets of questions. The first consisted of a 4-point Likert scale on the acute effects of ecstasy (appendix C). Participants were asked to indicate which, of seventeen acute effects of ecstasy they had experienced, and if so, to what extent the acute effects were, from slightly too strongly. A mean acute effects score was calculated for each user. The list of acute effects was compiled from a review of empirical and subjective reports of the effects that were experienced whilst using ecstasy. The second set of questions ecstasy-using groups completed consisted of a 4-point self-report Likert scale on the positive and negative effects ecstasy has had on their experiences of life (appendix D). The scale comprised of twenty-eight long-term effects of ecstasy, seven positive effects and twenty-one negative effects. These effects were compiled from a review of empirical and subjective reports into the long-term effects of the drug. Ecstasy-users were asked to rate which, of these effects, they had noticed in their lives, from 'not at all' to 'strongly'. A separate mean positive and negative score was calculated for each ecstasy user. Participants were further asked whether any of these changes had led them to seek help and/or advice from a professional or organisation and to indicate which particular service (e.g. GP, Clinical psychologist, psychiatrist, drugs clinic/services or counselling) they sought this from. Participants were asked to abstain from using ecstasy for at least 2 weeks and any other drug for 24 hours prior to testing. The University of East London ethics committee approved the study (see appendix for application and confirmation of approval). All participants gave written informed consent (see appendix V) and were paid £10 each for participating.

Assessment Measures

Following completion of the above, psychopathological status and cognitive performance was then assessed using the following measures in the order presented below:

Modified Brief Symptom Inventory (BSI, Derogatis & Melisaratos, 1983). This scale is comprised of 53 items, each rated on a standard 5 point Likert Scale: not at all (0), a little bit (1), quite a bit (2), moderately (3) and extremely (4). The distinct items reflect nine primary symptom dimensions or subscales: somatisation, obsessive-compulsive behaviour (OCD), interpersonal sensitivity, depression, anxiety, anger/hostility, phobic anxiety, paranoid ideation and psychoticism. Additional items reflected sexual functioning, cognitive failures,

known MDMA side effects, and four positive dimensions: feeling content with life, positive psychobiology, sociability and mood state (Parrott et al, 2001 and Milani et al, 2001). See appendix for the full modified version and subscale definitions.

National Adult Reading Test (NART; Nelson, 1982). This test was a measure of premorbid verbal IQ, which involved participants reading out 50 words. These words allowed for assessment of the familiarity with the words rather than the ability to phonetically decode unfamiliar words (i.e. intelligent guess work alone would not result in a correct response). The number of correct pronunciations was recorded.

Choice reaction time tasks. A computerised choice reaction time task was utilised. Participants were presented with a fixation point that changed to either an X or Y, subjects had to press the corresponding key. Reaction time to each presentation was recorded in milliseconds (ms). There were 20 presentations and the mean latency response (ms) across all 20 trials was recorded along with the number of correct responses.

Auditory Verbal Learning Test (AVLT; Rey, 1964). The AVLT test was used as an assessment of immediate and delayed verbal recall. It began as immediate word span recall, with the participant recalling as many words from a 15-word list (list A) read aloud to them by the examiner at a rate of one word per second. The same list was read and immediately recalled for a further 4 trials. After trial 5, recall was then measured for a second new distractor word list (list B) – interference trial. After list B recall, the participant was then asked to recall as many words from the first list (list A), but without presentation – trial 6. Retention of the first word list was then measured after a 20-minute delay – delayed recall. All responses were taped for subsequent scoring. The score for each trial was the number of words correctly recalled. The number of repetitions and intrusion errors from list A and list B were also recorded.

Tower of London (TOL; Shallice, 1982). The TOL measures participants planning abilities, which is one aspect of executive functioning. Participants were instructed to arrange three different coloured balls (blue, green and red) on an abacus from a starting position to a "goal" position (as demonstrated on a second identical abacus) in a specified minimal number of moves. Participants were instructed to complete each trial in their own time and if they were to make a mistake they could start the trial again from the starting position, or move on to the

next trial. However, trials were terminated if problem solving exceeded one minute or if the participant was unable to solve the trail after 4 attempts. The test comprised of twelve trials which were tape recorded in order to calculate the "planning times" and "solution times" for each trial. Planning time represented the interval between the last verbalisation of the investigator to the first "click" of the apparatus. Solution time represented the duration of moves until completion of that particular trial. The mean total number of errors and total number of trials completed was also scored and then planning time and solution times were averaged across all completed trials.

Rivermead Behavioural Memory Test (RBMT; Wilson et al, 1991). The RBMT is a test battery consisting of a number of components that assess everyday memory functioning. Each component is described below.

Remembering a name. The subject was shown a photographic portrait and asked to remember the first and second name of the person in the photograph immediately after presentation of the name and after a delay. The duration of this delay was determined by the time it takes for the remaining RBMT components to be completed, and was tested at the end of the RBMT test.

Remembering a belonging. A possession belonging to the subject was borrowed and placed out of view of the participant. They were then requested to ask for their belonging when cued by the experimenter saying *"that is the end of the test"* and to remember where it had been hidden.

Remembering an appointment. The participant was required to ask a particular question relating to the near future (e.g. When will our next appointment be?) when an alarm sounded during the experiment.

Picture recognition. Line drawings of 10 common objects were shown one at a time, for approximately 5 seconds each. The participant was required to name each drawing and after a delay of a few minutes they were shown 20 pictures (the original 10 and 10 distractors) and asked to select which ones they had seen previously.

Remembering a story (immediate and delayed). After listening to a short prose passage read aloud by the experimenter, the participant was required to recall as much as possible immediately after the reading and again after a delay of approximately 10 minutes.

Face recognition. The participant was shown 5 portrait photographs, one at a time, for approximately 5 seconds. After a filled delay, the participant was required to select the original 5 from a set of 10 portraits (5 original and 5 distractors).

Remembering a new route (immediate and delayed). The experimenter traced a short path around the room. The path was composed of five sections. The participant was required to copy the route immediately after the experimenter and again after a 10-minute delay.

Delivering a message (immediate and delayed). When tracing a short route around the experimental room the participant was requested to pick-up an envelope marked with a message at one particular stage (e.g. when at the table) and leave it at the location indicated by the experimenter (e.g. ....) on both immediate and delayed routes.

Orientation. The participants were asked 10 questions regarding orientation in both time and place e.g. what month is it? What day of the week is it? What place are we in now?

For each component two scores were produced, a screening score (pass or fail) and a standardised profile score depending on the degree of deficit (0 = abnormal; 1 = borderline; 2 = normal). Thus, participant's scores on the RBMT were summarised by a total screening score of all components, ranging from 0-12, and a total Standardised Profile score, for all components, ranging from 0-24.

Statistical Analysis

Data analysis was conducted using the Statistical Package for the Social Sciences (SPSS) version 10 for windows. One-way between groups analysis of variance (ANOVA) tests were performed for all measures of the AVLT and TOL to assess whether there were any group differences between polydrug controls, non-problem ecstasy users and problematic ecstasy users. Post Hoc analysis included paired comparisons between groups using the Tukey's HSD range statistic.

ANOVAs were performed on the RBMT screening score, profile score and individual component scores. Where there were violations of homogeneity of variance on the individual component scores of the RBMT the non-parametric Kruskall-Wallis test was employed. Post Hoc analysis included paired comparisons between groups using the Tukey's HSD range

statistic and Mann-Whitney tests as the non-parametric equivalent; with a correction employed, to limit Type 1 errors, by dividing the standard 0.05 probability by the number of groups compared, in this case $\alpha/3 = 0.017$. The more usual Bonferroni adjustment was not employed as, with the large number of potential comparisons, this would have produced a p-value threshold that would have been difficult to estimate given the limitations of SPSS (ie. values of $p < 0.0001$ are presented as p=0.000). It is recognized however that the correction used here may have produced some Type 1 errors; so that although these results may be indicative of possible relationships between variables, such conclusions must be treated with a degree of caution.

The data from the BSI was positively skewed and had heterogeneous variances. As a result the square-root transformation was applied to stabilize the variances, allowing for an ANOVA to be performed assessing any differences in psychopathology between the three groups.

Drug use data violated the assumption of homogeneity of variance, despite attempts at transforming the data; therefore the Kruskall Wallis test was employed (with the exception of current tobacco and alcohol use in which an ANOVA was employed). An independent samples t-test was used to assess differences in patterns of ecstasy use between the two ecstasy groups (problematic and non-problematic). Chi-squared tests were used to establish any significant differences in responses to questions regarding the effects of ecstasy, gender, reported psychiatric history and family psychiatric histories.

After collapsing the two ecstasy using groups into one, Pearson correlational analyses were conducted to assess the association between patterns of ecstasy use and scores on the BSI, acute effects scale, negative and positive effects of ecstasy and cognitive performance. Where there were group differences in performance (between problematic and non-problematic ecstasy users), within group correlations were conducted; for example, for the 'remembering a name' component of the RBMT and certain subscales of the BSI. Additional analyses were conducted to assess whether the acute effect scores and the positive and negative effect scores correlated with scores on the BSI.

RESULTS

Group characteristics and drug data Tables 5-8

As part of the inclusion criteria to the problematic ecstasy-using group, participants had to have sought some form of help for their attributed problems. As shown in table 5, a majority of problematic ecstasy users sought help from either a GP, 93% (n = 13), a psychiatrist, 71% (n = 10) or a clinical psychologist, 57% (n = 8), whilst only 21% (n = 3) had approached a drugs service and 21% (n = 3) a counselling service.

There were no significant group differences for gender, education, verbal IQ, health and family psychiatric history. However, there was a significant group effect of age [$F(2,51) = 4.02$, $p = 0.024$]; problematic ecstasy users were significantly older than controls ($p=0.026$). There was a significant difference in reported psychiatric history ($\chi^2(2) = 11.31$, $p = 0.004$), with a greater number of problematic ecstasy users reporting a psychiatric history compared to non-problematic ecstasy users and controls.

Table 5: Professional organisations where help/advice was sought by problematic ecstasy users

	% of problem users reported contacting organisation
General Practitioner	93
Clinical Psychologist	57
Psychiatrist	71
Drugs clinic/services	21
Counselling	21
Other	21

There were no group differences with regard to alcohol and tobacco consumption, but there were significant group differences in other categories of illicit drug consumption (with the exception of GHB, solvents, opiates and crack). Polydrug controls reported using significantly less amphetamine, cocaine, cannabis, benzodiazepines, LSD, magic mushrooms,

poppers, ketamine and Prozac compared to non-problematic and problematic ecstasy users. Both ecstasy groups reported similar consumption of illegal drugs, with the exception of lifetime Prozac use (non-prescribed) and monthly cannabis use, where the problematic ecstasy group reported a significantly greater consumption ($p = 0.005$ and $p = 0.008$ respectively). There was no reported usage of any current prescription medicine in any of the participants.

Patterns of ecstasy use were similar across the two ecstasy using groups with the exception of 'continued use', whereby more problematic ecstasy users reported discontinued use compared to non-problematic ecstasy users. Other than this both ecstasy-using groups showed similar lifetime consumption, used similar amounts of ecstasy on each occasion, reported similar maximum dosage on any one occasion and had used for a similar period of time. Also both ecstasy-using groups reported similar acute effects from ecstasy. However, the two groups differed in their long-term self-reported positive and negative effects experienced from ecstasy (table 6). Problematic ecstasy users scored significantly higher on the questions regarding the positive effects of ecstasy [$t(80) = -4.56$, $p<0.001$] and scored significantly higher on the questions regarding the negative effects of ecstasy [$t(80) = -9.74$, $p<0.001$] compared to non-problematic ecstasy users.

Group differences

Measures of psychopathological symptoms Table 9.

For the modified BSI scores, there were significant group differences on a number of negative symptoms, including somatisation [$F(2,52) = 6.09$, $p = 0.004$] (figure 1), interpersonal sensitivity [$F(2,52) = 7.11$, $p = 0.002$] (figure 2), depression [$F(2,52) = 6.76$, $p = 0.002$] (figure 3), anxiety [$F(2,52) = 7.52$, $p = 0.001$] (figure 4), phobic anxiety [$F(2,52) = 9.43$, $p<0.001$] (figure 5), paranoid ideation [$F(2,52) = 9.33$, $p<0.001$] (figure 6) and psychoticism [$F(2,52) = 8.27$, $p = 0.001$] (figure 7) subscales[3]. Post hoc analysis revealed that problematic ecstasy users scored significantly higher than non-problematic ecstasy users and polydrug controls in all of these subscales. An adjusted ANCOVA was conducted on these BSI scores, with age entered as a covariate, as there was a significant age difference in groups (see

[3] The same group differences were found when analysing non-transformed data, and the addition of significant group differences on the anger/hostility [$F(2,51) = 4.124$, $p = 0.022$] and sexual dysfunction [$F(2,51) = 4.123$, $p = 0.022$] subscales.

above). This analysis revealed no change in the main effect of group on somatisation, interpersonal sensitivity, anxiety, phobic anxiety and psychoticism after co-varying for age (see table 43, appendix V for individual statistics).

Table 6: Participant demographics, levels of illicit drug use and patterns of ecstasy use consumption in polydrug controls, non-problematic and problematic ecstasy users (means and standard deviations).

	Polydrug Controls (C)	Non-problematic Ecstasy users (E)	Problematic Ecstasy users (P)	Group effect	Post Hoc Comparisons (p<0.05)
Age	25.15 ± 3.87	25.70 ± 3.45	28.93 ± 4.94	0.024	P > C
Education (number of years)	16.0 ± 2.13	16.60 ± 1.14	15.36 ± 2.41	0.183	
Verbal IQ	111.65 ± 6.53	113.35 ± 4.52	113.07 ± 6.40	0.624	
Current rating of health	3.45 ± 0.83	3.05 ± 0.76	2.86 ± 1.03	0.125	
Patterns of ecstasy use:					
Average dose		2.43 ± 1.37	2.86 ± 2.51	0.522	
Maximum dosage		5.33 ± 2.63	7.50 ± 7.36	0.306	
Total consumption		263.55 ± 299.54	367.36 ± 557.62	0.533	
Duration of ecstasy use (months)	-	83.7 ± 34.13	61.29 ± 35.15	0.072	
Acute effect score	-	2.24 ± 0.42	2.49 ± 0.52	0.119	
Positive effect score		1.51 ± 0.38	2.05 ± 0.69	0.006	P > E
Negative effect score		1.39 ± 0.37	2.41 ± 0.58	0.000	P > E
Other lifetime drug use:					
Amphetamine	2.10 ± 6.94	84.05 ± 104.72	258.36 ± 566.75	0.000	C < P & E
Cocaine	0.85 ± 1.79	88.35 ± 127.61	208.71 ± 529.17	0.000	C < P & E
Crack	-	1.10 ± 4.47	1.50 ± 3.16	0.109	
Opiates	-	182.85 ± 816.08	1.14 ± 2.25	0.055	
Cannabis	59.3 ±165.19	1733 ± 1636.13	2658.93 ± 5156.27	0.000	C < P & E
Benzodiazepines		3.70 ± 11.20	354.07 ± 1196.34	0.008	C < P & E
LSD	0.05 ± 0.22	23.55 ± 46.10	86.21 ± 263.71	0.000	C < P & E
Magic Mushrooms	0.05 ± 0.22	9.20 ± 13.36	8.14 ± 26.47	0.000	C < P & E
Solvents	0.05 ± 0.22	4.10 ± 10.93	3.00 ± 5.74	0.072	
Poppers	0.30 ± 1.13	62.25 ± 221.29	78.93 ± 195.20	0.000	C < P & E
Ketamine		3.70 ± 7.26	40.50 ± 132.80	0.008	C < P & E
Prozac	0.10 ± 0.45		86.57 ± 189.21	0.002	P > C & E
GHB	-	0.35 ±1.09	0.14 ± 0.36	0.269	
Tobacco (per day)	3.85 ± 7.71	9.40 ± 6.67	8.50 ± 11.45	0.102	
Alcohol (units per week)	10.45 ± 7.52	17.35 ± 13.22	10.50 ± 12.92	0.109	
Cannabis (per month)	0.20 ± 0.52	14.95 ± 12.85	19.36 ± 54.39	0.000	C < E < P

Table 7: Percentages of non-problematic and problematic ecstasy users reporting changes in ecstasy use consumption and perceptions of their patterns of use

% of participants in each group	**Non-problematic Ecstasy Users (n=20)**	**Problematic Ecstasy users (n=14)**	**Chi-square group effect**
Increase number of tablets	30	43	0.440
Effects of ecstasy changed	75	71	0.816
Not Suffer without usage	100	93	0.225
Did not need to take ecstasy	100	93	0.225
Felt dependent/addicted to ecstasy	5	7	0.794
Considered stable user	80	50	0.066
Continue to use	70	24	0.005
Use drugs to alleviate ecstasy side effects	10	29	0.162

Table 8: Number of psychiatric disorders reported in polydrug, non-problematic and problematic ecstasy users of those who reported individual psychiatric and family psychiatric histories

	Participants			**Immediate family**		
Disorder	**Polydrug Controls n = 5**	**Ecstasy users n = 6**	**Problem users n = 11**	**Polydrug Controls n = 10**	**Ecstasy users n = 10**	**Problem users n = 7**
Anxiety	3	0	7	3	1	4
Depression	3	4	9	9	5	7
Schizophrenia	0	0	5	0	2	1
Phobia	0	0	1	0	0	0
Panic Attacks	2	0	5	3	0	2
Eating Disorder	1	2	0	0	1	0
Alcohol and/or drug dependency	0	1	3	2	2	1

Table 9 : Modified BSI subscale scores for polydrug controls, non-problematic and problematic ecstasy users. (Means and standard deviations)

Symptom	Polydrug Controls (C)	Non-problematic Ecstasy Users (E)	Problem Ecstasy users (P)	Group effect	Post Hoc Comparisons ($p<0.05$)
Negative Symptoms					
Somatisation	0.41 ± 0.37	0.52 ± 0.38	1.11 ± 0.78	0.004	P > C & E
Obsessive-compulsive	1.10 ± 0.66	1.31 ± 0.99	1.64 ± 0.88	0.396	
Interpersonal sensitivity	0.81 ± 0.68	0.59 ± 0.54	1.75 ± 1.07	0.002	P > C & E
Depression	0.58 ± 0.64	0.44 ± 0.51	1.63 ± 1.30	0.002	P > C & E
Anxiety	0.68 ± 0.66	0.44 ± 0.36	1.67 ± 1.23	0.001	P > C & E
Anger/hostility	0.46 ± 0.33	0.65 ± 0.65	1.13 ± 1.02	0.118	
Phobic anxiety	0.29 ± 0.33	0.14 ± 0.39	1.00 ± 1.07	0.000	P > C & E
Paranoid ideation	0.67 ± 0.45	0.68 ± 0.57	1.73 ± 0.97	0.000	P > C & E
Psychoticism	0.45 ± 0.54	0.40 ± 0.41	1.29 ± 0.82	0.001	P > C & E
Negative psychobiology	0.55 ± 0.39	0.64 ± 0.51	0.77 ± 0.39	0.308	
MDMA side effects	1.05 + 0.62	1.04 + 0.72	1.56 + 0.80	0.087	
Sexual functioning	0.39 ± 0.36	0.38 ± 0.34	0.81 ± 0.74	0.226	
Cognitive failures	1.22 ± 0.70	1.69 ± 0.94	2.01 ± 1.20	0.135	
Positive Symptoms					
Feeling content with life	2.28 ± 0.82	2.38 ± 0.76	1.99 ± 0.99	0.322	
Mood state	2.21 ± 0.74	2.24 ± 0.69	1.71 ± 0.87	0.056	
Sociability	2.28 ± 0.52	2.44 ± 0.77	2.07 ± 0.94	0.297	
Positive psychobiology	2.06 ± 0.62	2.23 ± 0.63	1.92 ± 1.13	0.316	

Figure 1. BSI: mean somatisation scores
(Bars indicate 1 standard error of mean)

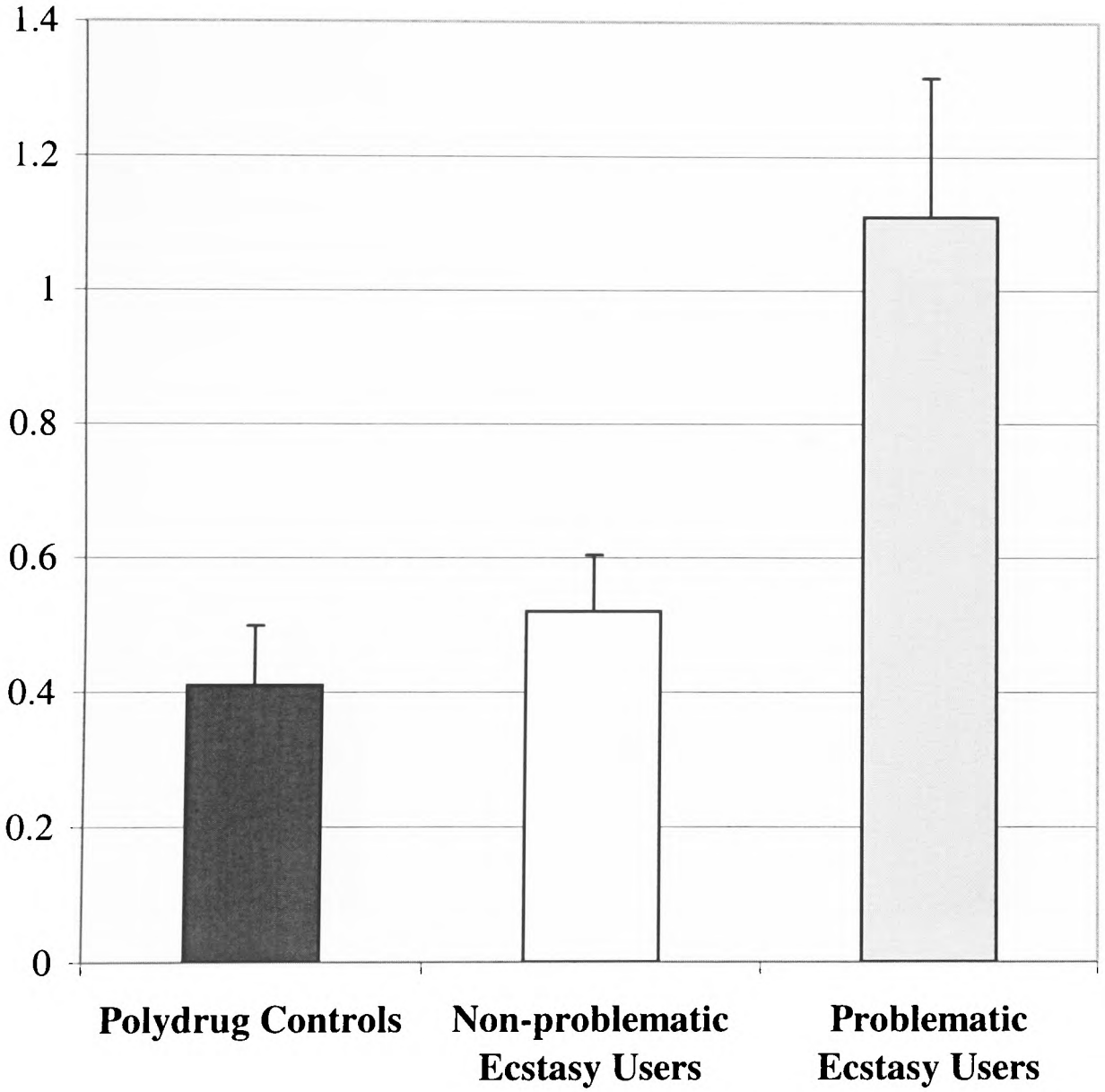


Figure 2. BSI: mean interpersonal sensitivity scores
(Bars indicate 1 standard error of mean)

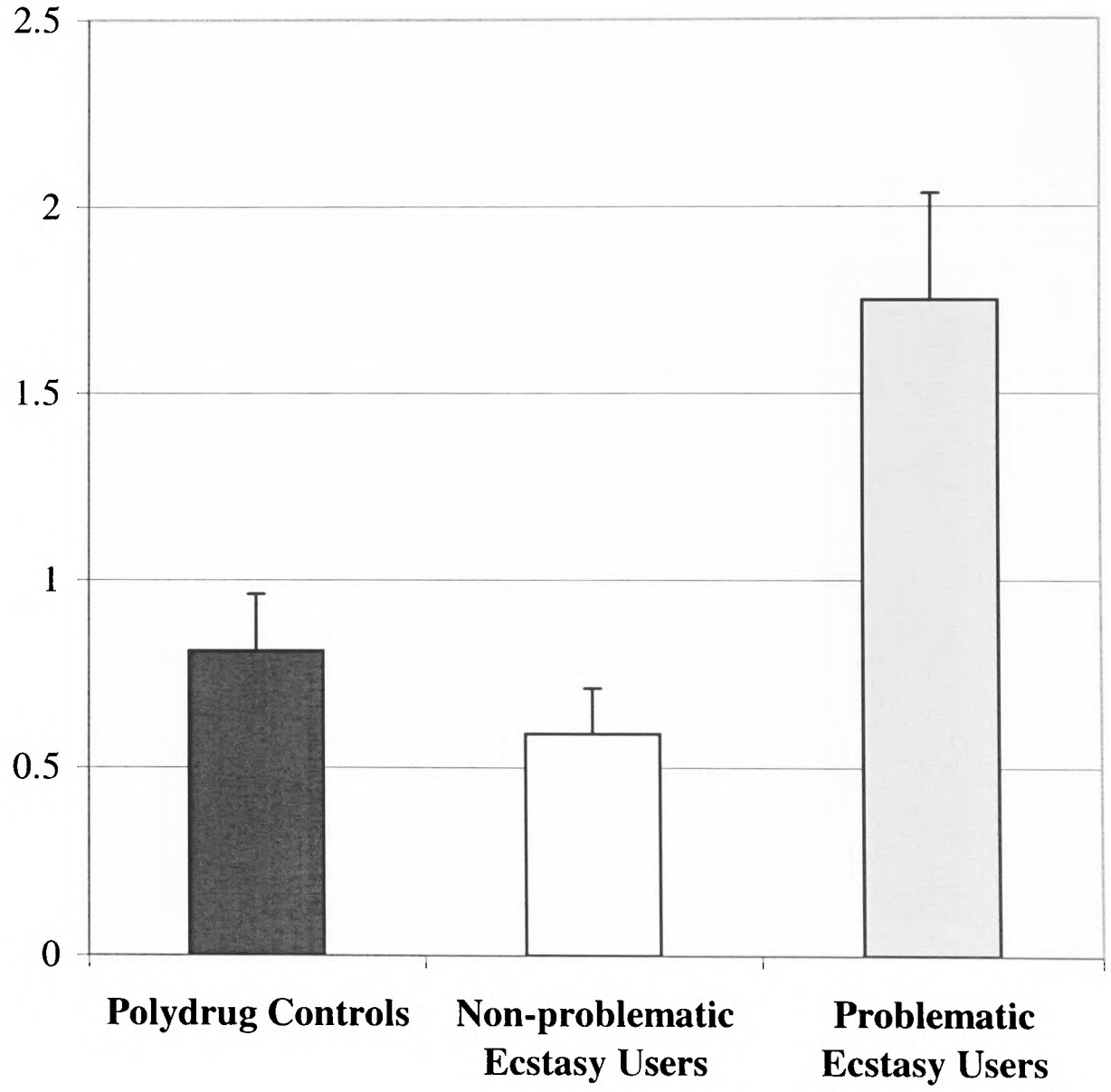


Figure 3. BSI: mean depression scores
(Bars indicate 1 stanard error of mean)

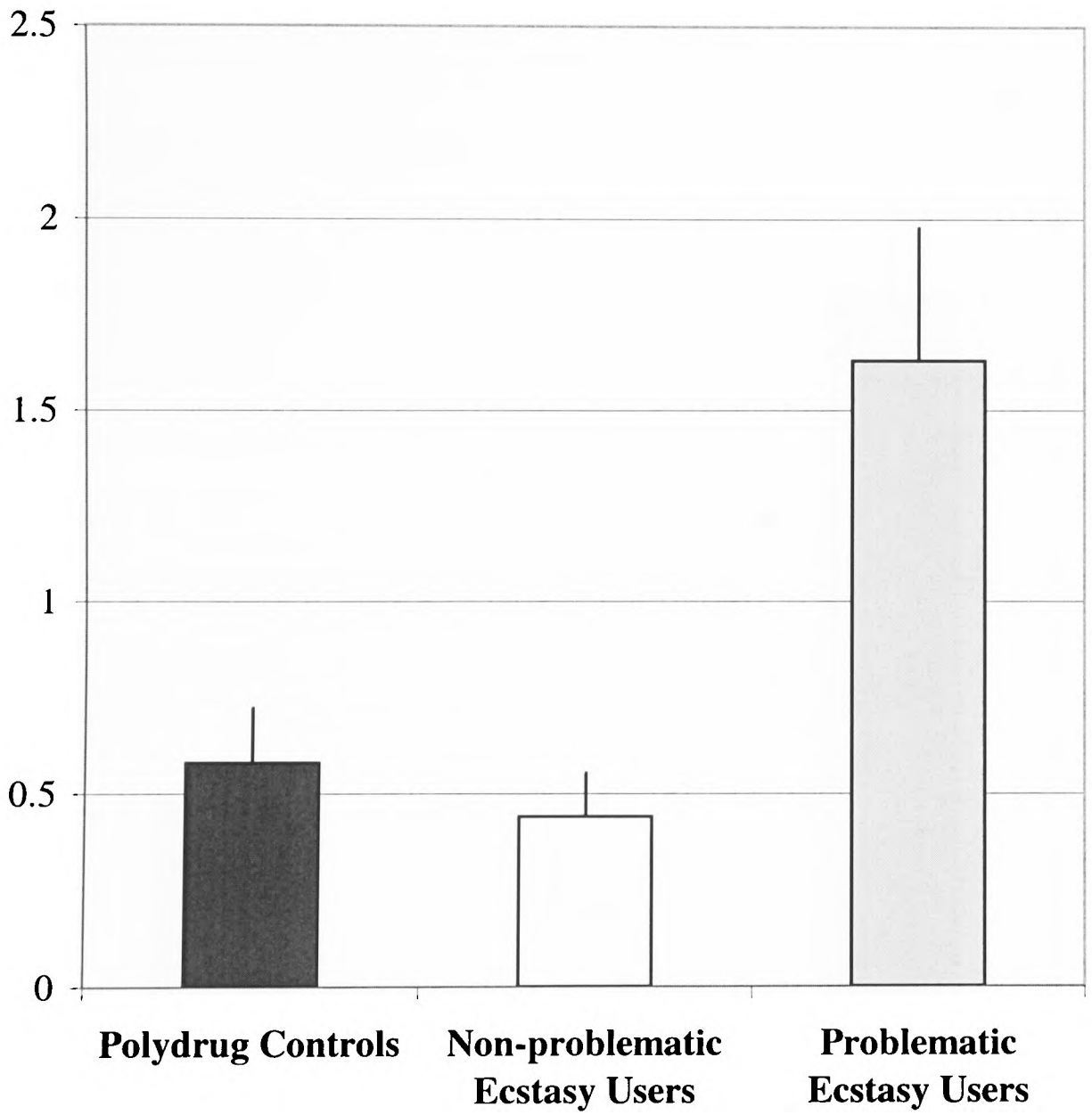


Figure 4. BSI: mean anxiety scores
(Bars indicate 1 standard error of mean)

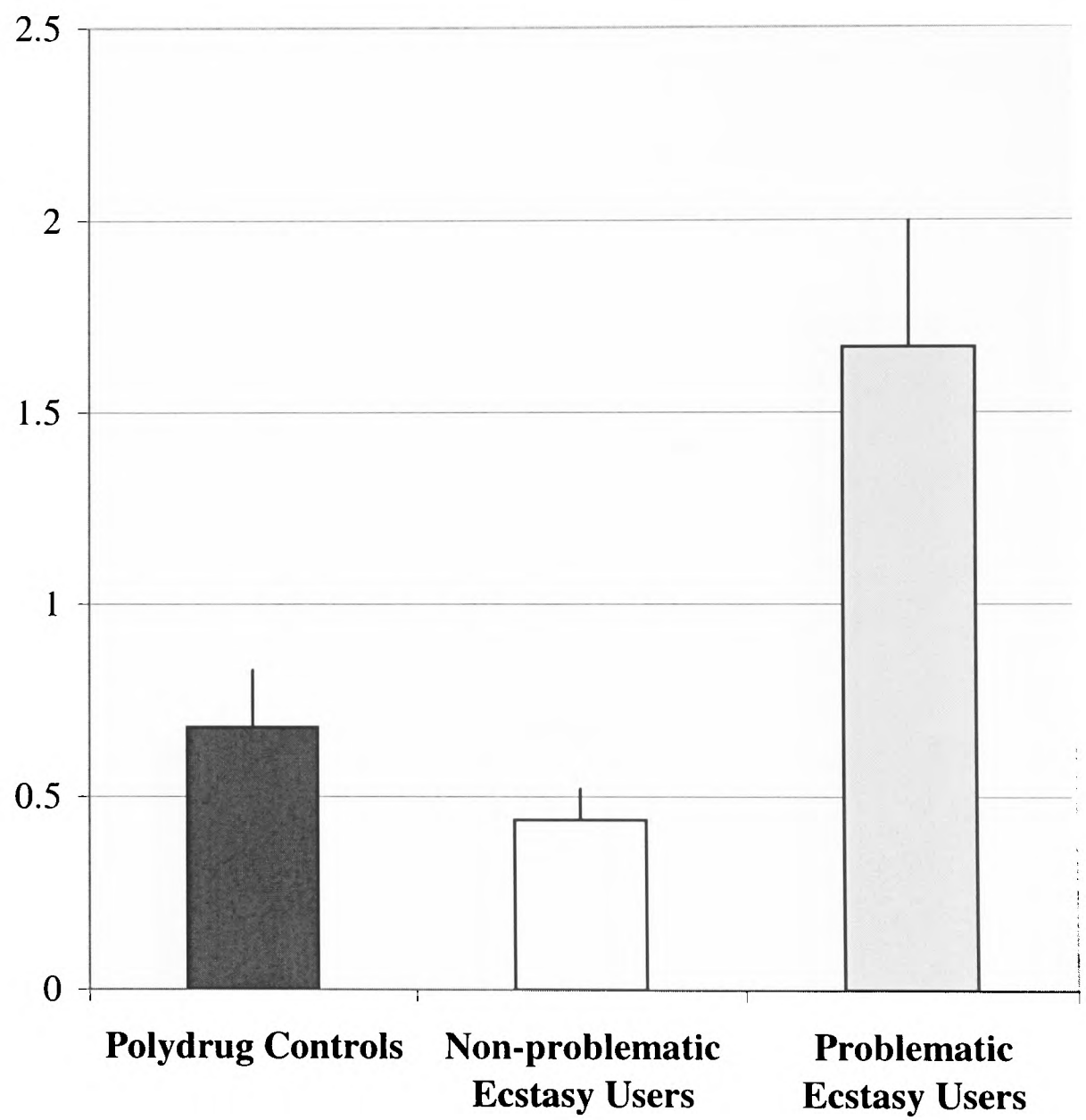


Figure 5. BSI: mean phobic anxiety scores
(Bars indicate 1 standard error of mean)

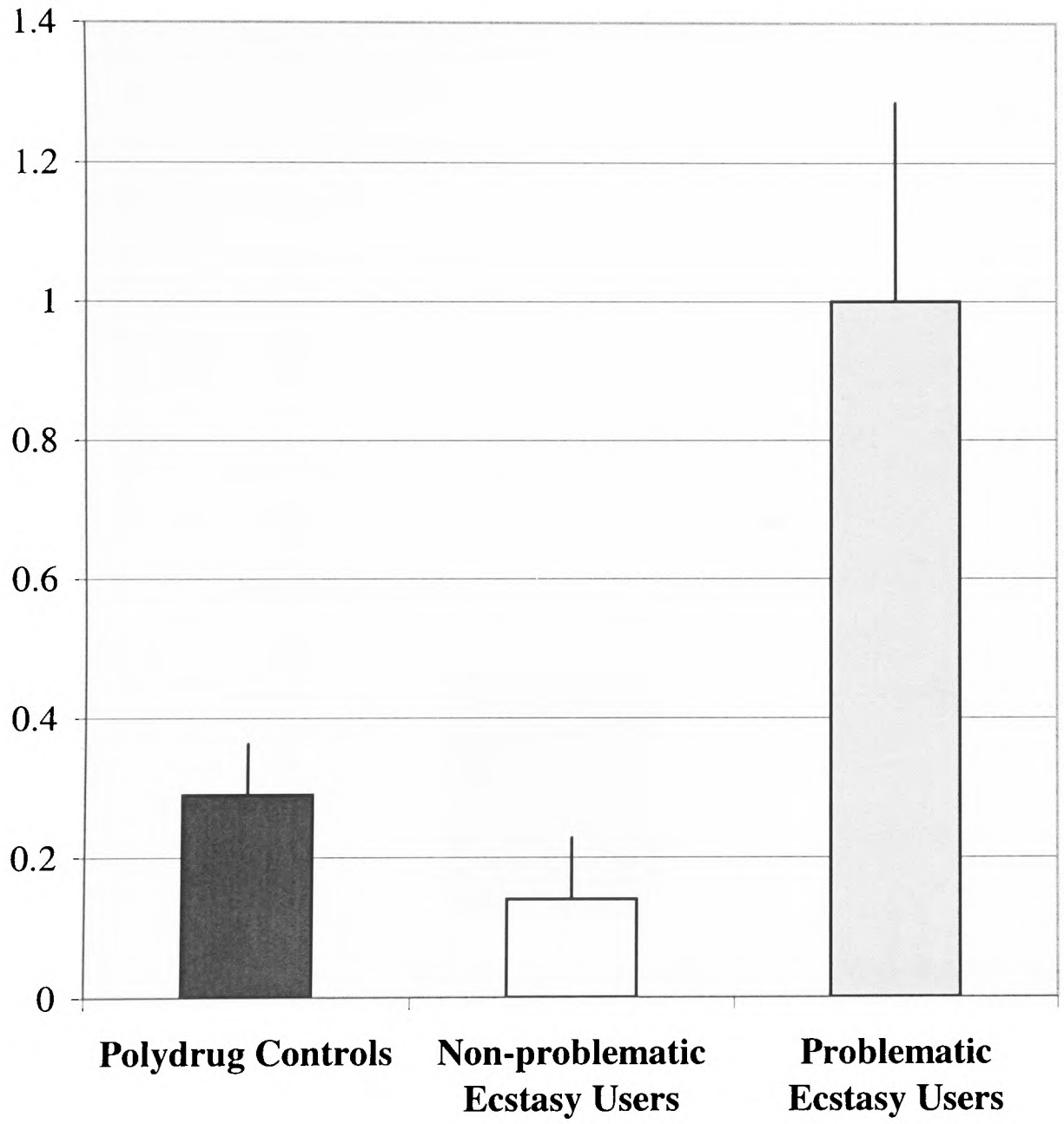


Figure 6. BSI: mean paranoid ideation scores
(Bars indicate 1 standard error of mean)

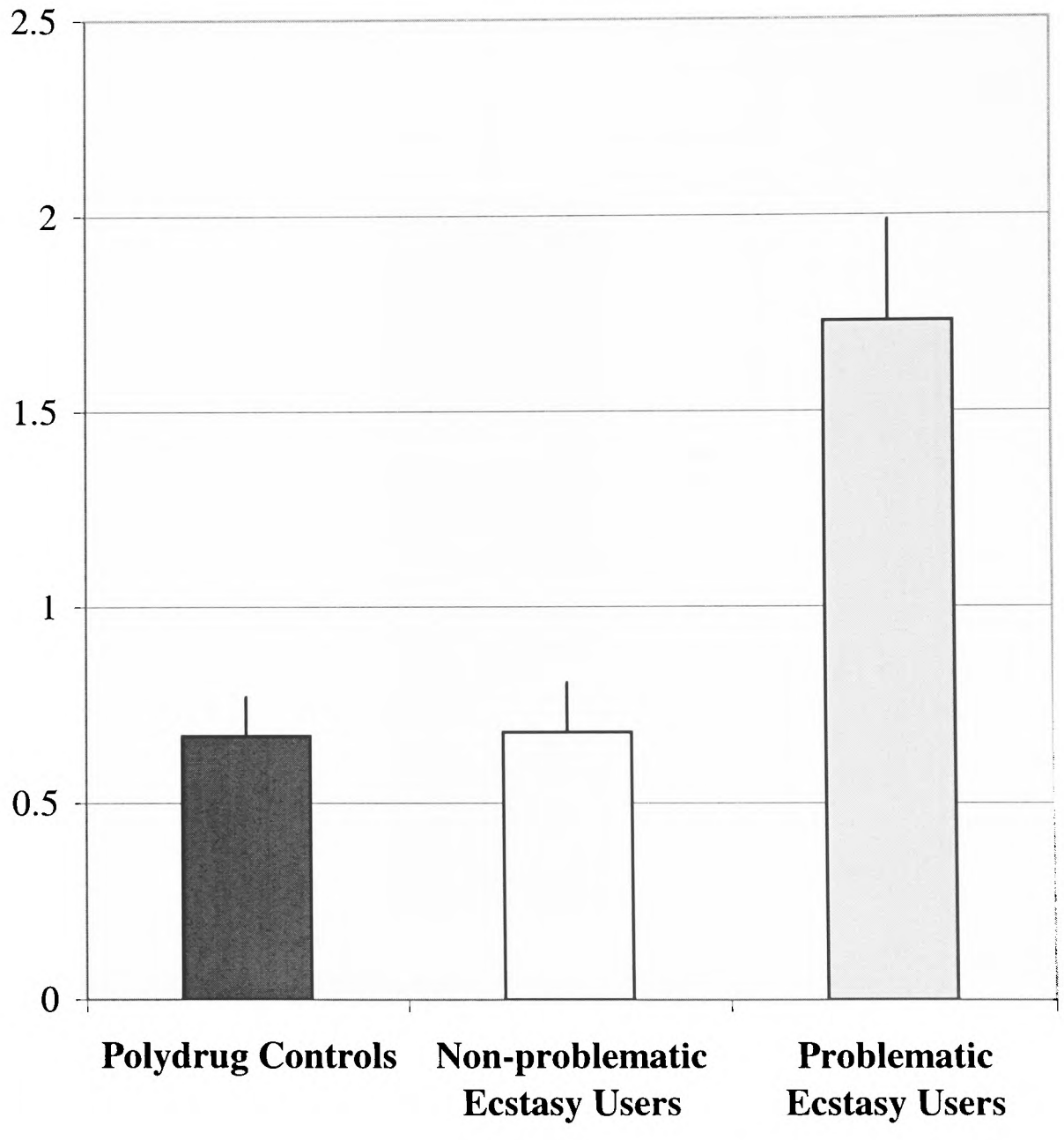
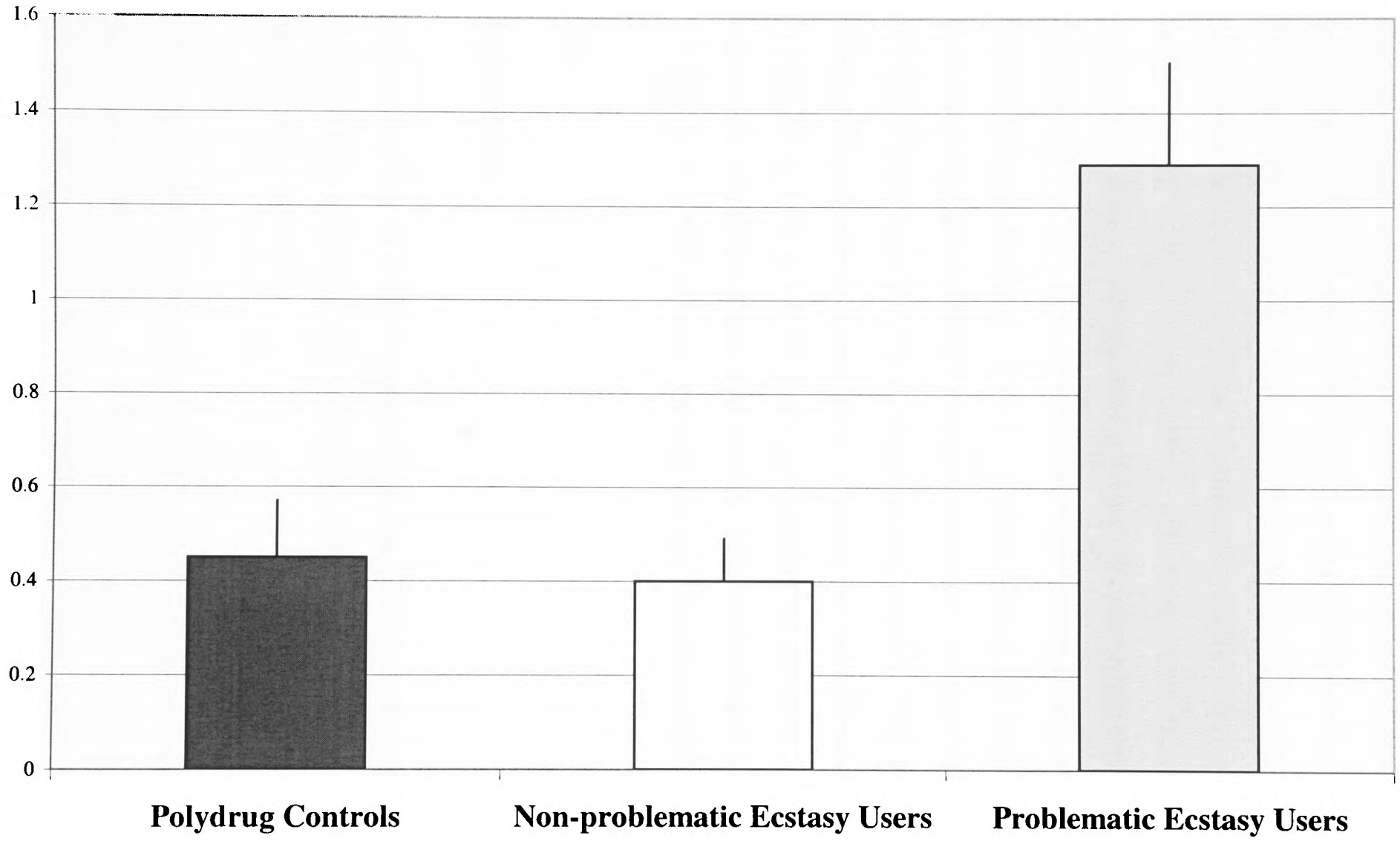


Figure 7. BSI: mean psychoticism scores

(Bars indicate 1 standard error of mean)



Measures of cognitive assessment All cognitive task data are displayed in table 10.

There were no significant group differences on the reaction time task, AVLT recall across all trials or the number of word repetitions for this task. There were no significant differences between the three groups for planning and solution times across all trials on the Tower of London, nor where there any significant differences between the numbers of errors made and the number of incomplete trails. There were no significant group differences on the screening and standardised profile scores for the RBMT. However, when analysing the data of individual RBMT components, there were significant group differences in 'remembering to deliver a message (immediate)' [$\chi^2(2) = 13.85$, $p = 0.001$], with problematic ecstasy users scoring significantly worse than ecstasy users, $p<0.001$ (figure 8); and in the 'remembering a name' component [$\chi^2(2) = 8.62$, $p = 0.013$], with the problematic ecstasy users scoring significantly worse than polydrug controls ($p = 0.012$: figure 9). An adjusted ANCOVA model was conducted on these significant RBMT component scores, with age entered as a covariate, as there was a significant age difference in groups (see earlier). This adjusted model revealed no change in the significant main effect of group on 'remembering to deliver a message' (immediate) [$F(2,52) = 7.62$, $p = 0.001$] after co-varying for age [$F(1,54) = 0.010$, $p = 0.923$]; and no change in the significant main effect in the 'remembering a name' component [$F(2,52) = 3.298$, $p = 0.045$], after co-varying for age [$F(1,54) = 0.081$, $p = 0.777$].

Correlational analyses

Dose-response effects of ecstasy

The estimated lifetime consumption of ecstasy negatively correlated with delayed recall on the AVLT ($r = -0.393$, $p = 0.022$), and positively correlated with the positive subscale 'content' on the BSI ($r = 0.517$, $p = 0.002$).

The reported average dose consumed negatively correlated with trial 6 (post-interference recall trial) and delayed recall on the AVLT ($r = -0.0388$, $p = 0.023$; $r = -0.361$, $p = 0.036$ respectively) The reported average dose consumed negatively correlated with, 'remembering a name' from the RBMT ($r = -0.860$, $p = 0<0.001$), but only in the problematic ecstasy users. Whilst interpersonal sensitivity significantly correlated with the average dose consumed ($r = 0.481$, $p = 0.032$), but only in the non-problematic ecstasy users. Additionally the average

dose consumed also positively correlated with scores on the acute effects of ecstasy questionnaire (r = 0.443, p= 0.009).

The largest dose of ecstasy on any one occasion negatively correlated with RBMT immediate story recall (r = -0.352, p = 0.041) and with trials one (r = -0.368, p = 0.032), two (r = -0.381, p = 0.026), four (r = -0.359, p = 0.037), post-interference trial six (r = -0.364, p = 0.034) and the total words recalled from the first 5 trials (r = -0.375, p = 0.029) on the AVLT. The largest dose of ecstasy on any one occasion positively correlated with the 'remembering a name' component of the RBMT in problematic ecstasy users (r = -0.810, p = 0.001), but not in non-problematic ecstasy users (r = -0.029, p = 0.903). Additionally, the largest dose consumed in one occasion positively correlated with the scores on the acute effects of ecstasy questionnaire (r = 0.551, p = 0.001) and with the scores on the questions regarding the negative effects of ecstasy,; although this latter finding was only in problematic ecstasy users (r = 0.538, p = 0.047), and not non-problematic ecstasy users (r = 0.075, p = 0.755).

Measures of acute effects and long-term effects

Scores on the questionnaire scale regarding the acute effects of ecstasy positively correlated with the scores on the long-term negative effect questions (r = 0.461, p = 0.006) and the somatisation (r = 0.397, p = 0.020) and phobic anxiety (r = 0.358, p = 0.038) subscales of the BSI.

Scores to the 7 positive questions on the long-term experiences from ecstasy questionnaire positively correlated with the negative effect score on the same questionnaire (r = 0.514, p = 0.002) and the following scales of the BSI: somatisation (r = 0.340, p = 0.049), paranoid ideation (r = 0.369, p = 0.032), psychoticism (r = 0.358, p = 0.037), negative psychobiology (r = 0.356, p = 0.039) and sexual dysfunction (r = 0.422, p = 0.013). Scores to the 21 negative questions on the long-term experiences from ecstasy questionnaire positively correlated with somatisation (r=0.584, p<0.001), obsessive-compulsive disorder (r = 0.367, p = 0.033), interpersonal sensitivity (r = 0.641, p<0.001), depression (r = 0.549, p = 0.001), anxiety (r = 0.592, p<0.001), anger/hostility (r = 0.485, p = 0.004), phobic anxiety (r = 0.536, p = 0.001), paranoid ideation (r = 0.543, p = 0.001), psychoticism (r = 0.512, p = 0.002), MDMA side effects (r = 0.490, p = 0.003) and sexual dysfunction (r = 0.567, p<0.001).

Table 10: RBMT component and test scores, reaction times, TOL times and AVLT scores by trial for polydrug controls, non-problematic and problematic ecstasy users.
(Means and standard deviations)

	Polydrug Controls (C)	Non-problematic Ecstasy Users (E)	Problem Ecstasy users (P)	Group effect	Post Hoc Comparisons (p<0.05)
RBMT					
SCREENING SCORE	9.45 ± 1.05	9.15 ± 1.35	8.71 ± 1.49	0.269	
PROFILE SCORE	20.85 ± 1.57	20.50 ± 1.88	20.07 ± 2.17	0.486	
Story recall					
Immediate	7.65 ± 2.44	9.18± 2.75	7.64 ± 1.99	0.098	
Delayed	6.73 ± 2.70	7.83 ± 3.14	6.86 ± 1.86	0.391	
Pictures	9.95 ± 0.22	9.90 ± 0.31	10.00 ± 0.00	0.459	
Faces	3.80 ± 0.41	3.75 ± 0.55	3.64 ± 0.63	0.692	
Route					
Immediate	5.00 ± 0.00	4.95 ± 0.22	5.00 ± 0.00	0.427	
Delayed	5.00 ± 0.00	4.90 ± 0.31	5.00 ± 0.00	0.177	
Message					
Immediate	2.85 ± 0.37	3.00 ± 0.00	2.43 ± 0.65	0.001	E > P
Delayed	2.75 ± 0.44	2.90 ± 0.31	2.64 ± 0.63	0.324	
Orientation & date	9.45 ± 0.89	9.40 ± 0.88	9.71 ± 0.47	0.502	
Remembering an appointment	1.80 ± 0.41	1.65 ± 0.49	1.86 ± 0.36	0.336	
First & second name	4.00 ± 0.00	3.95 ± 0.22	3.57 ± 0.85	0.013	C > P
Remembering a belonging	3.70 ± 0.47	3.45 ± 0.76	3.29 ± 0.61	0.147	
REACTION TIME					
Reaction time	471.79 ± 51.55	488.09 ± 85.76	530.92 ± 77.94	0.070	
Reaction time errors	18.45 ± 1.64	18.20 ± 1.28	17.50 ± 2.71	0.340	
TOWER OF LONDON					
Total Planning times	6.95 ± 2.17	6.07 ± 2.59	8.08 ± 3.72	0.129	
Total Solution times	4.07 ± 0.89	3.91 ± 0.73	4.27 ± 1.30	0.551	
No. of errors	2.80 ± 3.21	5.15 ± 3.79	4.43 ± 2.14	0.072	
No. of incomplete trials	0.20 ± 0.41	0.20 ± 0.70	0.64 ± 0.74	0.081	
AVLT					
Immediate Recall					
Trial 1	6.30 ± 1.79	6.75 ± 1.48	5.93 ± 1.77	0.368	
Trial 2	8.80 ± 2.24	9.50 ± 1.88	8.57 ± 2.41	0.414	
Trial 3	10.80 ± 2.67	10.35 ± 2.32	9.43 ± 2.95	0.329	
Trial 4	10.80 ± 2.46	11.70 ± 1.95	11.00 ± 2.08	0.406	
Trial 5	11.55 ± 2.26	11.60 ± 1.73	11.00 ± 2.72	0.705	
Total Recall	48.25 ± 9.95	49.95 ± 7.36	45.21 ± 10.60	0.347	
Interference Trial	5.70 ± 2.64	4.80 ± 1.58	4.86 ± 2.25	0.372	
Trial 6	9.10 ± 2.81	10.50 ± 2.95	9.79 ± 2.69	0.303	
Delayed Recall	6.05 ± 5.60	9.15 ± 3.45	8.29 ± 3.32	0.079	
Number of repeats	5.00 ± 5.48	6.55 ± 4.98	6.29 ± 15.59	0.851	
Intrusion from list A	0.05 ± 0.22	0	0.43 ± 0.76	-[1]	
Intrusion from list B	0.10 ± 0.31	0.10 ± 0.45	0	[1]	

[1] No analyses were conducted due to floor effects

Figure 8. RBMT: mean scores for 'immediately remembering to deliver a message'
(Bars indicate 1 standard error of mean)

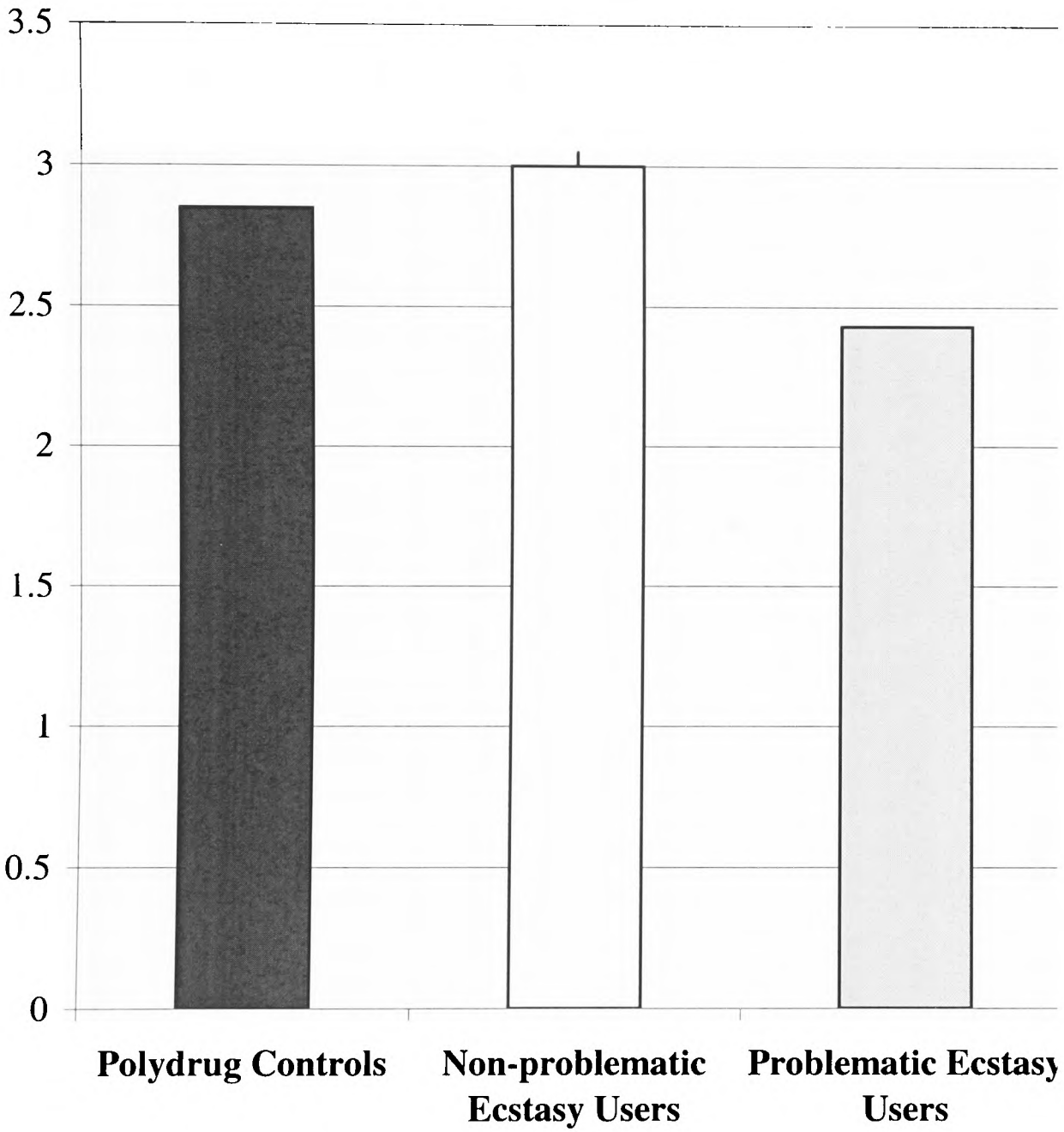
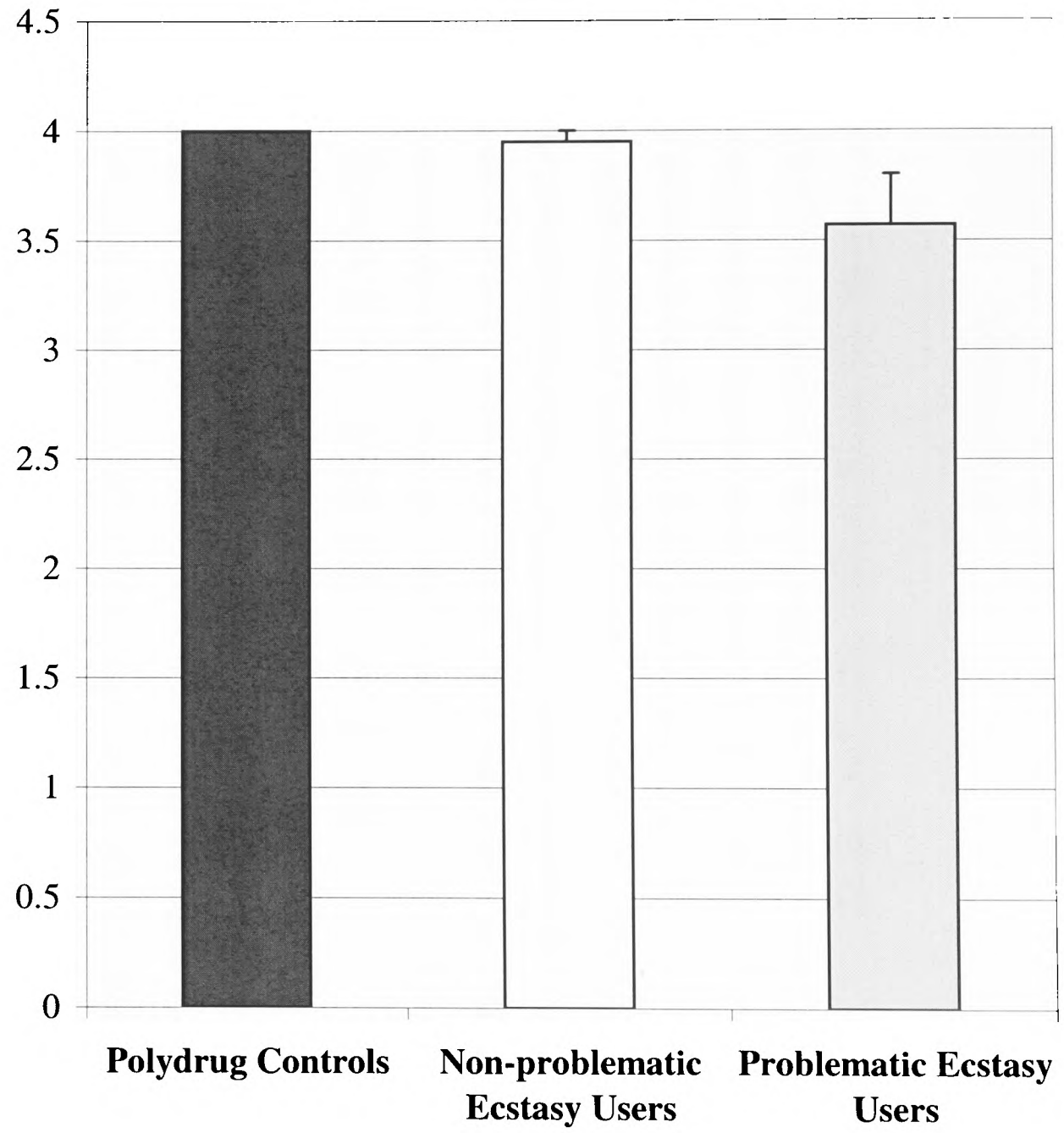


Figure 9. RBMT: mean recall scores of first and second name
(Bars indicate 1 standard error or mean)



DISCUSSION

The results of the present study indicate that non-problematic ecstasy users are not demonstrating any profound deficits in cognitive abilities compared to polydrug controls, despite polydrug controls having used significantly lower amounts of most other drugs (table 6). This is inconsistent with previous empirical research where ecstasy users were shown to have selective deficits on the same cognitive assessment measures compared to non-ecstasy using controls. This previous research showed that ecstasy users recalled significantly fewer words on the initial three recall trials and delayed recall trial on the AVLT (Fox et al, 2001a); displayed longer planning times on the TOL (Fox et al, 2001b and Schifano et al, 1998); and showed significant memory impairment on the RBMT (Schifano et al, 1998).

Problematic ecstasy users did show some cognitive deficits, but only in one subtest of the RBMT (remembering a first and second name); compared to polydrug controls (figure 9). This lends only tentative evidence to support the cognitive findings found in the sub-sample of problematic ecstasy users assessed by Schifano et al (1998). The only cognitive difference between problematic and non-problematic ecstasy users was poorer performance in the remembering to deliver a message component of the RBMT (immediate; figure 8). The fact that problematic and non-problematic ecstasy users displayed similar cognitive performance on most of the tasks supports the findings of Fox et al (2001), who demonstrated similarities in cognitive performance between problematic and non-problematic ecstasy users despite differences in perceived problems attributable to their ecstasy use.

In the current study the psychopathological status of non-problematic ecstasy users does not appear to differ from polydrug controls (table 9). However, as expected problematic ecstasy users do appear to report higher psychopathological scores on a number of subscales compared to polydrug controls and non-problematic ecstasy users; namely somatisation (figure 1), interpersonal sensitivity (figure 2), depression (figure 3), anxiety (figure 4), phobic anxiety (figure 5), paranoid ideation (figure 6) and psychoticism (figure 7). These differences in psychopathology appear to be independent of ecstasy dosage and other patterns of ecstasy use since both ecstasy-using groups showed similar drug consumption profiles, (Soar & Parrott, 2002). This confirms the finding from Fox et al (2001) who concluded that perceived problematic ecstasy use was not dose-related and also independent from other patterns of ecstasy use. Both these findings are in contrast to that of Parrott, Sisk and Turner

(2000), who demonstrated that heavy ecstasy users reported significantly higher scores than controls on paranoid ideation, psychoticism somatisation, obsessionality, anxiety, hostility, phobic anxiety, altered appetite and restless sleep. However, this study only addressed dosage and psychopathology, not whether users perceived themselves to be problematic or not. This later point is also true of other studies that have demonstrated psychopathology in ecstasy users (Parrott et al, 2001; Dugherio et al, 2001; Morgan et al, 2002).

The lack of cognitive differences between groups may be due to the performance of the polydrug control group. Evidence to suggest this comes when comparing the AVLT scores from this study with normative data. Normative data indicates that immediate recall appears to run within the range of 6.3 to 7.8 (Lezak, 1995). Even though the control group is performing within these limits, scores are at the very bottom end of the range. Delayed recall is also poor in this group compared to normative data. There should be little loss between recall on trial 6 and the delayed recall trial, yet the control group demonstrate a dramatic drop in recall score between these two trials (9.1 on trial 6 and 6.05 on the delayed recall trial). It appears that the polydrug controls themselves may show signs of memory dysfunction, such that any existent cognitive deficits exhibited by the ecstasy using groups would not necessarily be visible because of this poor cognitive performance by the control group masking the effect.

When looking at the ecstasy user's performance for immediate recall, the non-problematic ecstasy users are actually performing slightly better than polydrug controls on the story recall of the RBMT and on most trials of the AVLT, though such differences did not reach statistical significance. However, ecstasy users performance on the AVLT are at the lower end of the score range for normative data, whereas problematic ecstasy users are performing worse than normative scores thus indicating memory dysfunction. Recall for trial 5 in non-problematic and problematic ecstasy users (11.60 and 11.00 respectively) is also lower than normative data, which typically indicates a range of 12 to 14 (Lezak, 1995). Additionally, delayed recall scores on story recall of the RBMT and AVLT, are slightly better in non-problematic ecstasy users compared to polydrug controls and problematic ecstasy users; though once again delayed recall is lower in both ecstasy using groups compared to normative data. It appears therefore that both ecstasy-using groups are showing poorer cognitive performance on the AVLT compared to normative data.

On the TOL test, non-problematic ecstasy users were seen to perform better than polydrug controls, exhibiting quicker planning and solution times; though this effect failed to reach statistical significance. The validity of the control group could again be questioned; however there is no normative data available for the manual version of the TOL to make valid comparisons. However, direct comparisons can be made, with TOL performances, with similar groups from the study by Fox et al (2001b). Planning times demonstrated by the control group in the current study do not appear to differ greatly from the performance of Fox et al's (2001b) control group (6.95 seconds and 6.5 seconds, respectively); however the planning and solution times for ecstasy users seem to differ markedly between the two studies. Fox et al (2001b) demonstrated planning and solution times twice that of the non-problematic ecstasy users in this current study (13.3 seconds and 6.07 seconds, respectively for planning times and 6.4 and 3.91 seconds respectively for solution times). This could suggest that non-problematic ecstasy users are not demonstrating impairments relative to other ecstasy using sub-groups. This is only speculative since comparisons can only be made with the one study; ideally comparisons need to be made with standardised normative data.

It may appear that non-problematic ecstasy users are performing better than polydrug controls on the TOL, by exhibiting decreased planning and solution times; however this could be at the expense of making more errors. The number of errors made in the non-problematic ecstasy users were higher than polydrug controls (table 10), though this effect did not reach statistical significance. These results would support similar findings by Morgan et al (2002) who demonstrated significantly quicker first responses in the MFF20 in ecstasy users compared to controls and polydrug controls. These ecstasy users committed more errors however, suggesting a trade-off between greater speed and accuracy (Morgan et al, 2002).

Further support for the issue of a poorly performing control group arises from the dose-related cognitive findings in ecstasy users. It appears that the greater the amount of ecstasy consumed in a lifetime and the larger the dose consumed on any one occasion, were associated with an impaired ability to remember a name (RBMT) and also poorer delayed recall (AVLT). This latter finding supports the dose-response effects on delayed recall found by Morgan (2002) and Fox et al (2001c). However, it is important to note that any dose-related findings within this study should be treated with extreme caution, since no statistical corrections were made to the correlational analyses to control for type 1 errors.

Another reason for lack of group differences in cognitive abilities may be due to the lack of sensitivity to ecstasy-induced effects in the test procedures used. This applies specifically to the RBMT, since previous research using the AVLT and the manual version of the TOL have been shown to indicate deficits in ecstasy users (Fox et al, 2001b; Fox et al, 2001c; Schifano et al, 1998; Milani & Schifano, 2000; Reneman et al, 2000; Reneman et al, 2001). A potential problem with the RBMT is that when used on individuals with intact cognitive abilities it can demonstrate ceiling effects. It has been argued that ecstasy-induced cognitive effects are selective and thus any mild cognitive deficits exhibited by these individuals may not be detected with such a test, since it is not thought to be suitable for detecting subtle memory deficits; whether due to brain damage or the introduction of a drug (Wall et al, 1994; Wills et al, 2000). Based on the standardised profile score of the RBMT there was a hypothesised trend for problematic ecstasy users to score lower than ecstasy users, who in turn scored lower than polydrug controls, however these differences did not reach statistical significance.

It has been suggested that the ecstasy users may experience a mild form of the serotonin syndrome whilst under the influence of the drug (Parrott, 2002). Tentative support for this notion has been shown, with higher levels of ecstasy consumption being associated with an increased chance of experiencing those acute effects of ecstasy that are representative of the serotonin syndrome (Gillman, 1997). Additionally, this study suggests a link between experiences of these acute effects of ecstasy and the long term effects. Those ecstasy users who reported higher symptoms whilst 'on drug', also reported higher psychopathological scores and higher ratings of long term effects attributed to ecstasy use. However, problematic and non-problematic ecstasy users did not differ on their subjective ratings on these negative acute effects, as such; the extent of acute effects of ecstasy does not appear to be a defining feature of problematic ecstasy use.

Assessing the reported long-term positive and negative effects attributed to the consumption of ecstasy, it appears that whilst ecstasy users reported experiencing negative effects from ecstasy, these are probably outweighed by the greater reported positive effects also experienced. However, problematic ecstasy users report both significantly higher positive and negative life experiences compared to non-problematic ecstasy users (table 6). Thus, the negative effects reported by the problematic ecstasy users may be exacerbated, but their perceptions of the positive effects are also much stronger than non-problematic users. It may be that certain problematic ecstasy users are just more emotionally reactive than other ecstasy

(non-problematic) users, which may account for both of these findings. Enhanced sensitivity to both the positive and negative long term effects of MDMA, in some of these problematic ecstasy users, could also be accounted for by certain genetic and neurochemical differences. There is evidence from both animal and human research, to suggest that there may be a critical threshold of serotonergic activity below which functional sequalae develop. It is possible that problematic ecstasy users may be more vulnerable to the MDMA neurotoxicity by virtue of a lower serotonergic 'injury' threshold. Individual 5-HT neurons may be more robust in non-problematic ecstasy users and thus this injury threshold is not reached and functional problems do not develop. Alternatively, and perhaps more likely, some individuals may have lower levels of 5-HT to begin with and less severe serotonergic injury is needed to reach a critical threshold, and thus develop the functional psychological and cognitive problems demonstrated in these problematic ecstasy users. Additionally, this vulnerability to the long-term effects of MDMA- induced serotonergic neurotoxicity could also be due to differences in individual's abilities to metabolise MDMA. Kreth et al (2000) and Ramamoorthy et al (2002) have shown that individuals who lack fully functioning cytochrome P450 2D (CYP2D6 - the polymorphic enzyme involved in the metabolism of MDMA) have a reduced ability to metabolise MDMA. Since unexpected adverse effects of drugs are often related to their metabolism, it is possible that the differences in the capacity to metabolise ecstasy, specifically MDMA, may determine or modulate inter-individual acute toxic reactions (Schifano, 2004) and, potentially, long-term ecstasy-related neurotoxicity, and this could modulate the development of ecstasy-related problems in particular individuals. Thus it could be speculated that the problematic ecstasy users demonstrating psychological difficulties in the current study, had a predisposing genetic risk to the long term effects of MDMA exposure.

In addition to the methodological issues discussed in the literature review (chapter 2), there are also a number of related points that need to be addressed which are specific to this study. Firstly, any significant cognitive and psychopathological differences found between polydrug controls and the ecstasy using groups cannot be solely attributed to ecstasy use, since the polydrug control group used significantly less illicit drugs than both ecstasy groups (table 6). Previous research has attempted to control for other drug use using statistical techniques such as regression models or analysis of covariance for other drug use. Daumann et al (2001) and Morgan et al (2002) found that concomitant use of other drugs, specifically cannabis, influenced the levels of psychopathology in ecstasy users. Rodgers et al (2001) assessed the

influence of cannabis use further using a regression design to try to isolate the contribution of individual drugs to the variance in prospective memory performance scores in groups of ecstasy and cannabis users. They found a double dissociation between the impact of cannabis and ecstasy. Cannabis, but not ecstasy, was found to be associated with short-term and internally cued prospective memory, whilst ecstasy use, but not cannabis, was associated with long-term memory deficits. However, they also reported that cannabis and ecstasy use were significantly correlated. This is a problem that is consistently found when trying to control for other drug use via statistical techniques: the extent and duration of ecstasy use tends to be highly correlated with other drug use and this multicolinearity poses statistical limitations in producing any meaningful analysis on its own. Additionally, co-varying for drug use does not account the for possible drug-drug interactions that occur. Since ecstasy users predominantly use other drugs in combination with Ecstasy (Strote et al, 2002; Riley et al, 2001; Winstock et al, 2001) it is likely that administering such drugs together produce different effects compared to using ecstasy alone (Hernandez-Lopez et al, 2002). A recent study has also suggested an additive effect nicotine has on neurocognitive functioning in ecstasy users (Friend et al, 2004). Thus, co-varying for different drug use does not address these additive and/or drug interaction effects, and it is for this reason that such analyses were deemed inappropriate in this research.

What is more important in respect of the cognitive and psychopathological findings here is that the amounts of illicit drug use was matched between ecstasy using groups, with the exception of monthly cannabis use and Prozac. There is the possibility that the psychopathological status of the problematic ecstasy users could be confounded by their monthly cannabis use, which was higher in this group compared to both polydrug controls and non-problematic ecstasy users. This confounding effect would be consistent with that of Morgan et al (2002) who concluded that cannabis use predicted most measures of the SCL-90-R, whereas ecstasy consumption did not. Whilst other drug use was matched between the two ecstasy using groups, this match is a rather crude measure, since reported lifetime drug use did not take into account potential differences between groups in the period of time and subsequently the intensity of drug use.

The explicit selection process for this study allowed ecstasy users to allocate themselves into one of three groups, depending upon their past ecstasy experiences. This selection process of overtly advertising for problematic and non-problematic ecstasy users may have influenced

demand characteristics and thus affected the outcome of the study. Non-problematic ecstasy users may have a vested interest in defying the negative opinion surrounding the long-term effects of ecstasy and therefore be more motivated to perform to the best of their ability. This may have contributed to a paucity of statistical cognitive effects found and also the performance on the TOL, as discussed earlier. In addition, self-selecting problematic ecstasy users may have been influenced by the pessimistic attention surrounding ecstasy portrayed by the public and media and also be more likely to volunteer to participate in order to 'find out what's wrong with them' (Turner & Parrott, 2000). For such reasons caution should be made in extrapolating results to other ecstasy users. Ideally future studies should perhaps be refined to use post hoc methods of group allocation to avoid such confounds.

No formal psychiatric assessment was conducted to assess whether self-perceived problematic users actually demonstrated /exhibited psychological problems. However, the fact that they had sought some help, mostly from a GP, clinical psychologist and psychiatrist (table 5), strongly suggests that their problems may have been clinically defined at some point. The significantly high scores on the BSI also provided some data to indicate that they were experiencing problems. However, labelling users 'problematic' or 'non-problematic' on the basis of a single question relating to the experience of 'problems' which users attribute to ecstasy is a somewhat crude classification system. This effectively replicates the method used in Fox et al (2001), although this study did also ask participants to give some qualitative information regarding the nature of problems. The problems most commonly reported were related to low mood, depression and anxiety, and to experiences of cognitive difficulties (Fox, 2002). However, limiting assessment to a single question may have missed some important information as the word 'problem' is of course open to wide interpretation. Additionally, asking users to self-identify themselves as problematic could be argued to be an approach that may produce some response bias. As participants were defining themselves by their 'help-seeking' behaviour, it is perhaps not surprising that they will have differed on self-reports of psychological distress. However it could be argued that this would be demonstrated by evidence of systematic responding on a questionnaire, in this case the BSI. The current data, however, show a selective pattern of decrements on this scale; i.e. the problematic ecstasy users did not score higher than non-problematic ecstasy users in all the subscales (table 9).

An additional problem is that distinguishing between the two groups just on the basis of labelling them as 'problematic' or 'non-problematic', does not address the potential confound

of whether the ecstasy users continued to use or not. From table 7, it is clear that a considerably higher number of the problematic ecstasy users, were in fact ex-users (only 24% continued to use the drug), compared to the non-problematic group (70% reported continued ecstasy use). Therefore, conceptually, these problematic ecstasy users not only differ on their self-reported problems, but also whether they are current or ex-ecstasy users. Verheyden et al (2003) reported that there were two different types of ex-ecstasy users: those who stopped using for mental health reasons and those who stopped for circumstantial reasons (e.g. changes in circumstances, boredom, a fall in the quality of ecstasy). Of those ecstasy users that stopped using because of mental health reasons, 62% reported having received professional help for these problems, which was significantly higher that those who had stopped in the circumstantial group (27%). These two groups, 'circumstantial' and 'mental health', did not differ on any measure of ecstasy use or other drug use, which is consistent with the findings from this study. This suggests, as with the current study, that some users may be more vulnerable to the long-term effects of ecstasy.

The issue of causality is also complex to address within this study. Whether ecstasy use actually caused the problems reported by the problematic ecstasy users is difficult to ascertain. There is the suggestion that the basis of these problems could have already existed prior to ecstasy use, since poor premorbid adjustment is associated with increased drug use (Fox et al, 2001a). In a prospective-longitudinal study in a non-clinical sample, Lieb et al (2002) found that in a majority of cases, ecstasy and other polydrug use was actually secondary to the onset of mental disorders and psychological problems. However, there was only a difference in individual, but not family psychiatric between the two ecstasy using groups, which could argue against a vulnerability to a predisposition to psychopathological problems.

To conclude, this study has shown that contrary to previous research, ecstasy users do not exhibit the selective cognitive deficits relative to polydrug controls. Problematic ecstasy users did display a few significant deficits in cognitive performance compared to polydrug controls, but compared to non-problematic ecstasy users, problematic ecstasy users generally displayed similar cognitive performance, despite differences in perceived problems. The findings suggest that cognitive problems are dose-related rather than due to accurate self-attribution of ecstasy-adverse effects. Problematic ecstasy users were found to exhibit higher psychopathological symptoms across a number of dimensions compared to non-problematic

and polydrug controls, which objectively verifies their subjective awareness of clinical problems. These reported problems do not appear to be related to patterns of ecstasy use or polydrug use. It could be that this sub-sample of problematic users is simply more vulnerable to ecstasy-induced psychological effects, both positive and negative, than non-problematic ecstasy users, and/or that they are predisposed to psychiatric disturbances. Another issue that needs to be explored concerns the length of abstinence from ecstasy consumption, this was not addressed in the current study and may have important implications concerning the presentation of problems related to ecstasy use.

CHAPTER 4

Case Study of Persistent Psychobiological Problems Attributed to Ecstasy After Seven Years Abstinence[1]

[1] A brief summary paper of this case study can be seen in Soar et al (2004), a copy of which is included in the appendix

INTRODUCTION

The current chapter focuses on a case study concerning a problematic ecstasy user who approached the researcher during the previous study into the cognitive and psychological status of ecstasy and problematic ecstasy users (chapter 3). This individual (RW) was unique in his profile compared to other problematic ecstasy users, in that he had developed an extensive number of psychiatric and psychological problems which he attributed to having taken high amounts of ecstasy and that remained troublesome despite remaining abstinent from ecstasy for seven years. Because of this unique profile and length of abstinence from ecstasy use he was deemed inappropriate to include in the previous study and instead was assessed separately in order to document his current cognitive and psychological status after seven years of abstinence from ecstasy, using the same battery of cognitive assessment measures used in the previous study, with documented sensitivity to ecstasy-induced effects (Fox et al, 2001b & c; Parrott et al, 2000).

There are numerous case studies and empirical research data suggesting that recreational ecstasy users demonstrate psychopathological problems (see Soar et al (2001) and chapter 2 for a review). Despite the large body of empirical evidence demonstrating cognitive deficits in recreational ecstasy users, only two case studies have reported severe cognitive problems. The first case was by Spatt et al (1997); this involved a 26-year-old woman who developed a pure amnestic syndrome after ecstasy use, with ongoing memory problems up to nine months after presentation. Secondly, Kopelman et al (2001) presented a 26 year old woman who was left with severe anterograde memory problems and evidence of executive/frontal lobe impairments and although there were cognitive improvements eight years after ecstasy consumption, severe deficits remained. In both cases MRI or PET scans indicated brain abnormalities in regions rich in serotonin releasing neurons.

These two case studies also demonstrated that cognitive problems are persistent in nature. Other case studies suggesting that psychiatric symptomatology is persistent have also been reported (Cohen, 1996; McCann & Ricaurte, 1992, Windhaber et al, 1998). In one particular case a 24-year old male who had been taking ecstasy for 4 years and reported use on about 150 occasions was diagnosed with chronic atypical psychosis. However, symptoms in this individual, such as hallucinations, loss of appetite, weight loss, reduced sexual activity, mood swings, paranoia and aggressive outbursts, were reported to have begun 4 years prior to

diagnosis (Schifano, 1991). Schifano and Magni (1994) also presented a number of case studies where psychological problems were strongly associated with ecstasy use, and still evident on presentation to a clinic from 6 months to 30 months after discontinued ecstasy consumption.

However, there is relatively little empirical research to show whether psychological or cognitive deficits remain after abstinence from ecstasy, or show signs of recovery. Tentative empirical evidence for the persistence of cognitive deficits has been shown by Wareing et al (2000). In this study, current and previous ecstasy users were tested on measures of central executive functioning and on self-reported levels of anxiety. Both groups were found to have deficits on some aspects of central executive functioning and measures of anxiety compared to a control group of non-ecstasy users, suggesting that the neuropsychological effects persisted after the cessation of ecstasy use. Morgan et al (2002) found evidence for selective cognitive impairments remaining after an average of two years of abstinence. Ex-ecstasy users showed significant impairments on the RBMT recall measure and committed significantly more errors on the MFF20 relative to polydrug users (who did not use ecstasy). Evidence of the persistence of psychiatric symptoms after abstinence of ecstasy use has also been shown by MacInnes et al (2001). They reported higher levels of depression in former ecstasy users compared to matched controls. However, the 'drug free status' in these former ecstasy users was somewhat ambiguous, since abstinence was reported for an average of 6 months, but some ecstasy users reported use as little as 2 weeks before testing.

In light of the discussed case studies and limited empirical research documenting persistent effects of cognitive or psychological problems associated with past ecstasy use, the main objective in this study was to assess the cognitive abilities and current psychopathological status, of RW in light of his reported psychiatric and psychological problems, seven years after abstaining from ecstasy use. Cognitive performance and current psychopathological states were measured using the same assessment employed in the previous study (chapter 3). This was to compare RW's cognitive and psychopathological status with non-problematic ecstasy users, problematic ecstasy users and polydrug controls from the previous study (chapter 3), to establish the extent of his problems in relation to a group of non-clinical recreational drug users. The study also aimed to assess RW's current status with available normative data (Geffen et al, 1990 and Derogatis & Melisaratos, 1983, respectively).

METHOD

Participant Characteristics and drug use

RW contacted the researcher at the University of East London by telephone. He described himself as having severe problems, which he attributed to past ecstasy use. We arranged for a semi-structured interview at the University of East London along with the completion of standard drug use questionnaires, which included specific questions on experiences and patterns of ecstasy usage (the same questionnaires given to ecstasy using groups in the previous empirical study (appendix A-D)).

RW was a 26-year-old Caucasian male, who reported no history of psychiatric illness prior to his ecstasy use, but a history of anxiety and depression amongst first-degree relatives. After 3 years of heavy ecstasy use (1991-1994) he started to develop problems, which he attributed solely to ecstasy consumption. These problems consisted of depression, suicidal thoughts, visual disturbances, panic attacks, social phobia, sexual impotence and severe sleeping difficulties. The severity of these problems increased to such an extent that by 1994 he decided to cease taking the drug. However, with no alleviation of these symptoms on cessation, he approached the local health services. At various times he was seen by his local GP (general medical practitioner), a clinical psychologist and a psychiatrist, in addition to gaining some help and advice from a local drug clinic. He was diagnosed has having a constellation of psychiatric disorders including anxiety, depression, phobia and panic attack disorders, which were related to drug dependency. RW was prescribed various medications including fluoxetine, all of which proved ineffective. However he was eventually placed on 15mg of oral trifluoperazine, which reduced the severity of some symptoms. However, the remaining symptoms were and still are distressing enough that this individual often consumes illicit diazepam, which he claims reduces the symptoms further.

Between 1991 and 1994, RW took approximately 750 ecstasy tablets, initially taking 1-2 tablets on each occasion, but this increased to an average of 10 per night. On some evenings he would take 25 tablets, stating *"...they were like sweeties, I just kept popping them in my mouth one after the other..."*. The most he claimed to have taken in one overnight session was 25 tablets. He claimed that during the course of this 3-year period, he needed to take ecstasy

and felt psychologically dependent and addicted to the drug, despite not suffering if he sometimes went without it. In addition, he also reported using amphetamine (10 occasions), cocaine (25 occasions), crack cocaine (6 occasions), LSD (35 occasions), solvents (20 occasions) and nitrates or poppers (20 occasions), during the same 3 year period of ecstasy. use. During this period he smoked cannabis on a daily basis, and continued using it for a year after the onset of these psychological symptoms. Since 1994, he reported using benzodiazepines (BZs) on approximately 300 occasions, with the sole purpose of self-medication to relieve the psychiatric symptoms mentioned above. Currently he reported consuming an average 18 units of alcohol/week, and smoked an average of 30 cigarettes/day. Current daily medication consists of 15mg of trifluoperazine. He stated that he was currently not using BZs on the day he attended the University of East London for testing.

After RW gave written informed consent to take part in the study, which was approved by the University of East London Ethics Committee (appendix S), he was given a battery of assessment measures to empirically determine his cognitive and psychopathological status after seven years of abstinence from ecstasy (MDMA). Other than his daily medication of 15mg of trifluoperazine, RW reported being drug free on the day of testing.

Assessment Measures

Current psychopathological status was assessed using the same modified version of the Brief Symptom Inventory (BSI) as in the previous study. Cognitive performance was also assessed using the same battery of tasks as in the former study, in the following order: Auditory Verbal Learning Task (AVLT; Rey 1964), Tower of London (TOL; Shallice 1982) and the Version A of the Rivermead Behavioural Memory Test (RBMT; Wilson, Cockburn, Baddley & Hiorns, 1991), hence the methodology for each task being identical to that used in the previous study (see methodology section, chapter 3)

Statistical Analysis

The individual score for each cognitive test was converted to a 'z' score, and compared with group values for polydrug controls (n = 20), non-problematic ecstasy users (20) and problematic ecstasy users (14) from the previous study. Also, AVLT comparisons were made

with normative data taken from Geffen et al (1990). Individual RBMT scores were assessed using the standardised profile scoring criteria depending on the degree of deficit, with '0' indicating abnormal performance; '1' indicating borderline; and '2' indicating normal performance. The total standardised profile score was assessed against the cut-off points established by Wilson et al (1991). RW's scores on the BSI were also compared to 3 published norms: a sample of heterogeneous outpatients (n = 1002), psychiatric inpatients (n = 3130) and a sample of non-patient normal subjects (n = 685) (Derogatis and Melisaratos, 1983).

RESULTS

Task Data

Brief Symptom Inventory [Modified Version]

Table 11 shows RW scores on all dimensions of the BSI compared to the drug using groups from the previous study. Compared to polydrug controls RW scored higher on all negative subscales and lower on all positive subscales. Scores were significantly higher on somatisation ($z = 5.84$, $p<0.001$), interpersonal sensitivity ($z = 3.96$, $p = 0.001$), depression ($z = 4.83$, $p<0.001$), anxiety ($z = 4.53$, $p<0.001$), anger/hostility ($z = 9.73$, $p<0.001$), phobic-anxiety ($z = 9.72$, $p<0.001$), paranoid ideation ($z = 4.76$, $p<0.001$), MDMA side effects ($z = 2.50$, $p = 0.006$), sexual function ($z = 5.58$, $p<0.001$) and cognitive failures ($z = 3.11$, $p = 0.001$) subscales. Scores were, significantly lower on positive mood ($z = -2.54$, $p = 0.006$), sociability ($z = -2.13$, $p = 0.017$) and psychobiology ($z = -2.40$, $p = 0.008$) sub-scales.

Compared to non-problematic ecstasy users, RW also scored higher on all negative subscales and lower on all positive subscales. Scores were significantly higher on somatisation ($z = 5.39$, $p<0.001$), interpersonal sensitivity ($z = 5.39$, $p<0.001$), depression ($z = 6.33$, $p<0.001$), anxiety ($z = 8.97$, $p<0.001$), anger/hostility ($z = 4.65$, $p<0.001$), phobic-anxiety ($z = 8.62$, $p<0.001$), paranoid ideation ($z = 3.72$, $p<0.002$), psychoticism ($z = 1.95$, $p = 0.026$), negative psychobiology ($z = 2.02$, $p = 0.022$), sexual functioning ($z = 5.94$, $p<0.001$) and cognitive failures ($z = 1.82$, $p = 0.034$) subscales. Scores were also significantly lower on positive mood state ($z = 2.77$, $p = 0.003$), sociability ($z = 1.65$, $p = 0.05$) and positive psychobiology ($z = -2.63$, $p = 0.004$) subscales.

Compared to problematic ecstasy users, RW scored higher on nearly all negative subscales (the exception being on the psychoticism scale) and lower on all positive subscales. However, scores were only significantly higher on somatisation ($z = 1.87$, $p = 0.031$), interpersonal sensitivity ($z = 1.64$, $p = 0.05$), anxiety ($z = 1.63$, $p = 0.05$), anger/hostility ($z = 2.49$, $p = 0.006$), phobic anxiety ($z = 2.34$, $p = 0.01$) and sexual functioning ($z = 2.15$, $p = 0.016$) subscales and none of the scores reached significance on the positive scales.

Table 12 illustrates RW's scores on 9 dimensions of the BSI in comparison to normative data taken from non-patient subjects, psychiatric in-patients and psychiatric out-patients (Derogatis and Melisaratos, 1983). Compared to non-patient normals RW scored significantly higher on all of the nine subscales: somatisation ($z = 5.7$, $p<0.001$), obsessive-compulsive ($z = 3.27$, $p<0.002$), interpersonal sensitivity ($z = 6.63$, $p<0.001$), depression ($z = 7.37$, $p<0.001$), anxiety ($z = 7.38$, $p<0.001$), anger/hostility ($z = 7.90$, $p<0.001$), phobic anxiety ($z = 9.25$, $p<0.001$), paranoid ideation ($z = 5.47$, $p<0.001$) and psychoticism ($z = 3.39$, $p<0.006$). In comparison to psychiatric in-patients RW scored higher on all of the nine subscales, reaching significance on the somatisation ($z = 1.71$, $p = 0.044$), interpersonal sensitivity ($z = 1.82$, $p = 0.03$), anxiety ($z = 1.71$, $p = 0.04$), anger/hostility ($z = 2.75$, $p = 0.003$) and phobic anxiety ($z = 2.19$, $p = 0.014$) subscales. Compared to psychiatric out-patients RW scored higher in all nine dimensions and in nearly all reaching significance: somatisation ($z = 2.18$, $p=0.01$), interpersonal sensitivity ($z = 1.83$, $p = 0.03$), depression ($z = 1.73$, $p = 0.04$), anxiety ($z = 1.97$ $p = 0.02$), anger/hostility ($z = 2.70$, $p = 0.004$), phobic anxiety ($z = 3.00$, $p = 0.001$) and paranoid ideation ($z = 1.75$, $p = 0.04$).

Auditory Verbal Learning Task

Table 13 shows RW's AVLT scores for each trial compared to drug using groups and normative data. Despite the fact that RW recalled fewer words than the three drug using groups on most of the AVLT trials, none of them were significantly lower. However, compared to normative data, RW scored significantly lower for retention of newly learned information on trial 1 of immediate recall ($z = -2.83$, $p = 0.002$) and its loss due to retroactive interference, shown by trial six ($z = -2.41$, $p = 0.008$), see figure 10.

Tower of London

Table 13 shows RW's planning and solution times compared to polydrug controls and ecstasy using groups. RW exhibited longer planning (figure 11) and solution times (figure 12), compared to all drug using groups. Planning times were significantly longer compared to polydrug controls ($z = 3.03$, $p<0.001$), non-problematic ecstasy users ($z = 3.56$, $p<0.002$), and problematic ecstasy users ($z = 1.94$, $p = 0.026$). Solution times were significantly longer

compared to polydrug controls ($z = 2.84$, $p = 0.002$), non-problematic ecstasy users ($z = 3.68$, $p<0.002$) and problematic ecstasy users ($z = 1.79$, $p = 0.04$).

Rivermead Behavioural Memory Test

RW demonstrated normal functioning (scores of 2) on the following items: delayed article recall, remembering a belonging, remembering an appointment, immediate route recall, delayed route recall, orientation for time & place and picture recognition. Borderline performances (scores of 1) were found on immediate article recall and message delivery. A poor performance (score of 0) was found in aspects of face recognition. According to cut-off points established by Wilson et al, (1991), the total memory score of this individual (=16) indicates moderately impaired memory function, but normal expressive language ability and perceptual functioning. Compared to the drug using groups from the previous study RW's memory profile score (table 13) was significantly lower than all the experimental groups.

Table 11: Group mean scores (SD) for the BSI, for polydrug controls, non-problematic and problematic ecstasy users and the individual case study scores.

	Polydrug controls (C)	Non-problematic ecstasy users (E)	Problematic ecstasy users (P)	Case study (RW)	RW v C	RW v E	RW v P
Negative symptoms							
Somatisation	0.41 ± 0.37	0.52 ± 0.38	1.11 ± 0.78	2.57	**	**	*
Obsessive-compulsive	1.10 ± 0.66	1.31 ± 0.99	1.64 ± 0.88	2.00			
Interpersonal sensitivity	0.81 ± 0.68	0.59 ± 0.54	1.75 ± 1.07	3.50	**	**	*
Depression	0.58 ± 0.64	0.44 ± 0.51	1.63 ± 1.30	3.67	**	**	
Anxiety	0.68 ± 0.66	0.44 ± 0.36	1.67 ± 1.23	3.67	**	**	*
Anger/hostility	0.46 ± 0.33	0.65 ± 0.65	1.13 ± 1.02	3.67	**	**	*
Phobic anxiety	0.29 ± 0.33	0.14 ± 0.39	1.00 ± 1.07	3.50	**	**	*
Paranoid ideation	0.67 + 0.45	0.68 + 0.57	1.73 + 0.97	2.80	**	*	*
Psychoticism	0.45 ± 0.54	0.40 ± 0.41	1.29 ± 0.82	1.20		*	
Negative psychobiology	0.55 ± 0.39	0.64 ± 0.51	0.77 ± 0.39	1.67		*	*
MDMA side effects	1.05 ± 0.62	1.04 ± 0.72	1.56 ± 0.80	2.60	*	*	
Sexual functioning	0.39 ± 0.36	0.38 ± 0.34	0.81 ± 0.74	2.40	**	**	*
Cognitive failures	1.22 ± 0.70	1.69 ± 0.94	2.01 ± 1.20	3.40	**	*	
Positive Symptoms							
Feeling content with life	2.28 ± 0.82	2.38 ± 0.76	1.99 ± 0.99	1.50			
Mood state	2.21 ± 0.74	2.24 ± 0.69	1.71 ± 0.87	0.33	*	*	
Sociability	2.28 ± 0.52	2.44 ± 0.77	2.07 ± 0.94	1.17	*	*	
Positive psychobiology	2.06 ± 0.62	2.23 ± 0.63	1.92 ± 1.13	0.57	*	*	

*P≤ 0.05, **P≤ 0.001

Table 12: Group mean scores (SD) for the 9 primary symptom dimensions of the BSI for normative data (psychiatric outpatients, psychiatric in-patients, non-patient normals) and the individual case study scores.

	Non-patients (N)	Psychiatric Inpatients (I)	Psychiatric Outpatients (O)	Case study (RW)	RW v N	RW v I	RW v O
Somatisation	0.29 ± 0.40	1.01 ± 0.91	0.83 ± 0.80	2.57	**	*	*
Obsessive-compulsive	0.43 ± 0.48	1.51 ± 1.07	1.57 ± 1.00	2.00	**		
Interpersonal sensitivity	0.32 ± 0.48	1.48 ± 1.11	1.58 ± 1.05	3.50	**	*	*
Depression	0.28 ± 0.46	1.77 ± 1.21	1.80 ± 1.08	3.67	**		*
Anxiety	0.35 ± 0.45	1.70 ± 1.15	1.70 ± 1.00	3.67	**	*	*
Anger/hostility	0.35 ± 0.42	1.00 ± 0.97	1.16 ± 0.93	3.67	**	*	*
Phobic anxiety	0.17 ± 0.36	1.07 ± 1.11	0.86 ± 0.88	3.50	**	*	*
Paranoid ideation	0.34 ± 0.45	1.26 ± 1.02	1.14 ± 0.95	2.80	**		*
Psychoticism	0.15 ± 0.31	1.26 ± 0.98	1.19 ± 0.87	1.20	**		

* $P \leq 0.05$, ** $P \leq 0.001$

Table 13: Group mean scores (SD) for the battery of cognitive tests, for polydrug controls, non-problematic and problematic ecstasy users, normative data and the individual case study scores.

	Polydrug controls (C)	Non-problematic ecstasy users (E)	Problematic ecstasy users (P)	Normative Data (N)	Case study (RW)	RW v C	RW v E	RW v P	RW v N
RBMT									
Profile Score	20.85 ± 1.57	20.50 ± 1.88	20.07 ± 2.17	-	16	**	*	*	-
Tower of London									
Planning times	6.95 ± 2.17	6.07 ± 2.59	8.08 ± 3.72	-	15.28	**	*	*	-
Solution times	4.07 ± 0.89	3.91± 0.73	4.27 ± 1.30	-	6.60	*	*	*	-
AVLT									
Immediate Recall									
Trial 1	6.30 ± 1.79	6.75 ± 1.48	5.93 ± 1.77	8.4 ± 1.2	5				*
Trial 2	8.80 ± 2.24	9.50 ± 1.88	8.57 ± 2.41	10.8 ± 1.9	8				
Trial 3	10.80 ± 2.67	10.35 ± 2.32	9.43 ± 2.95	11.3 ± 1.6	11				
Trial 4	10.80 ± 2.46	11.70 ± 1.95	11.00 ± 2.08	12.2 ± 1.8	11				
Trial 5	11.55 ± 2.26	11.60 ± 1.73	11.00 ± 2.72	12.2 ± 2.2	12				
Total Recall	48.25 ± 9.95	49.95 ± 7.36	45.21 ± 10.60	54.9 ± 7.0	47				
Interference Trial	5.70 ± 2.64	4.80 ± 1.58	4.86 ± 2.25	6.5 ± 1.8	5				
Trial 6	9.10 ± 2.81	10.50 ± 2.95	9.79 ± 2.69	11.1 ± 1.7	7				*
Delayed Recall	6.05 ± 5.60	9.15 ± 3.45	8.29 ± 3.32	10.6 ± 2.4	7				

* $P \leq 0.05$, ** $P \leq 0.001$

Figure 10. Mean recall scores on the AVLT across all trails for RW and experimental groups

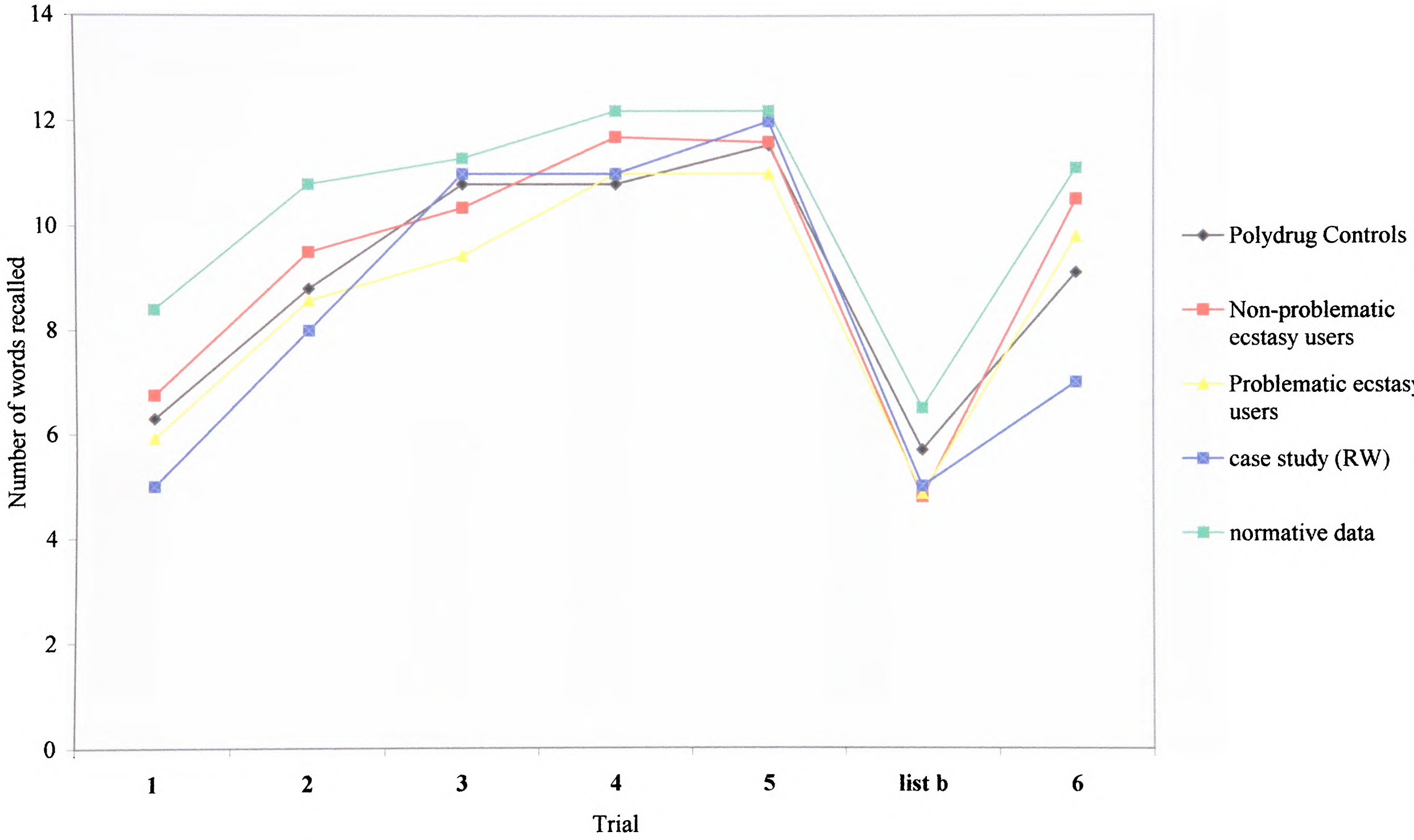


Figure 11. Mean planning times on the TOL for RW and experimental groups

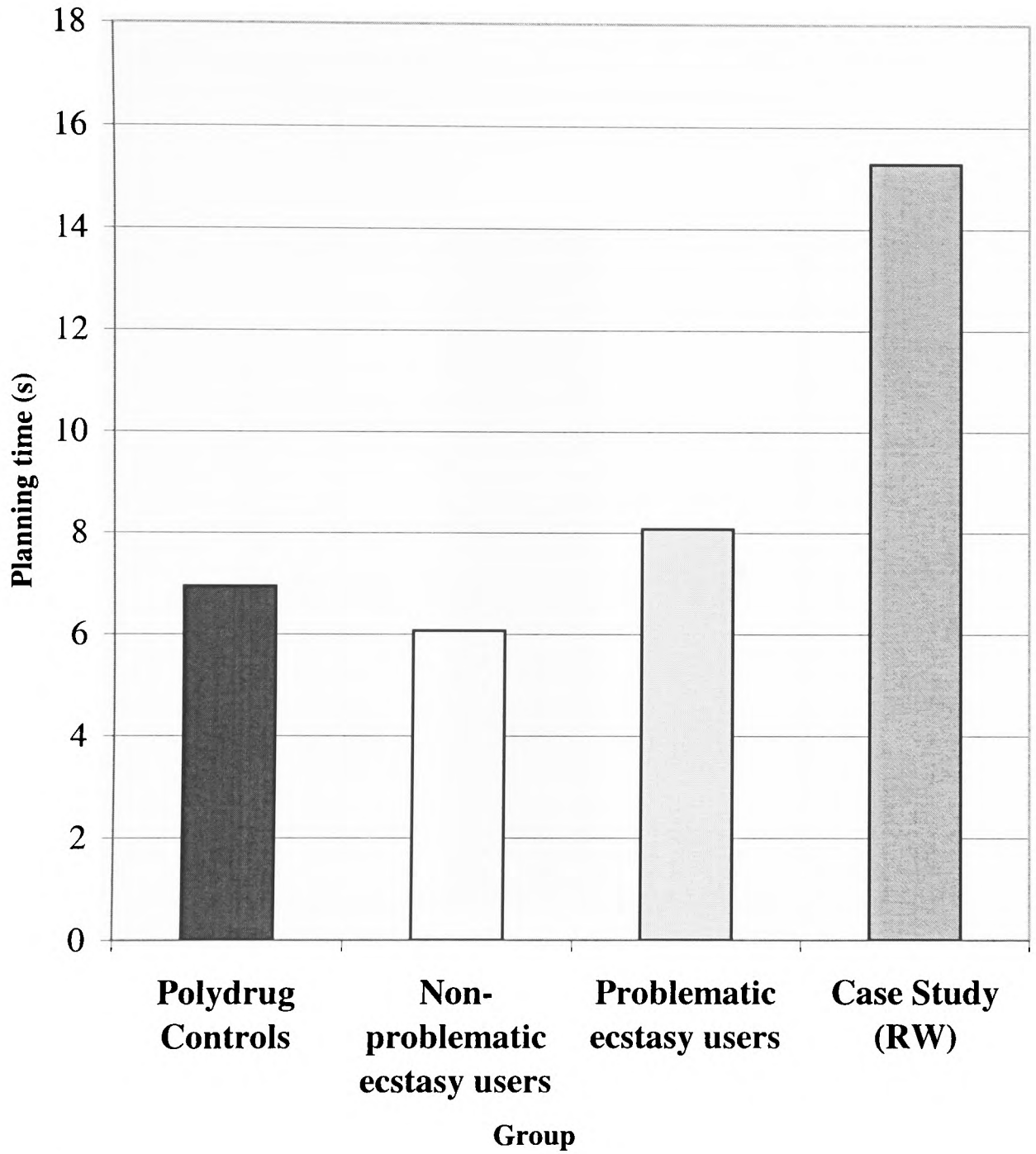


Figure 12. Mean solution times in seconds on the TOL for RW and experimental groups

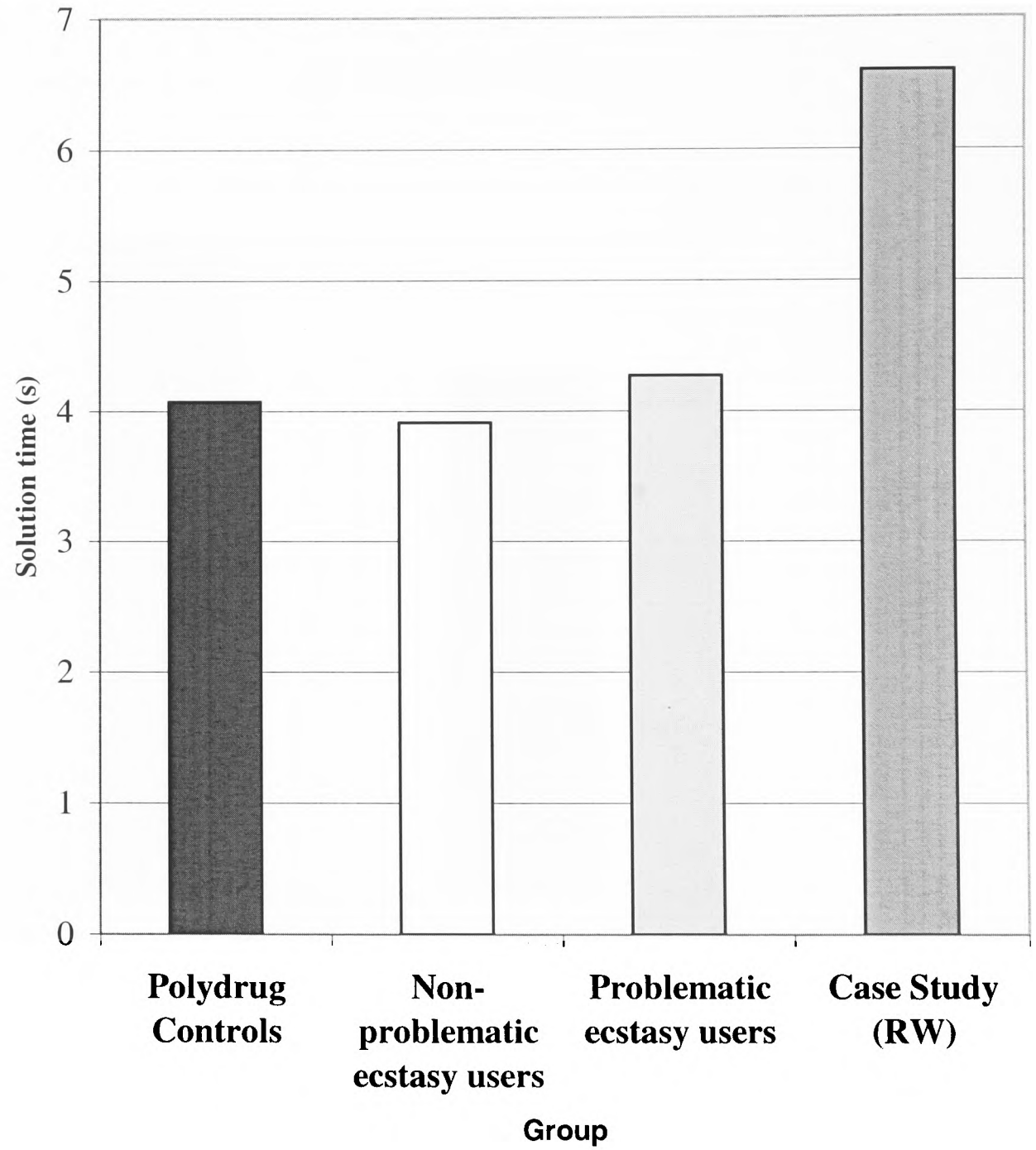
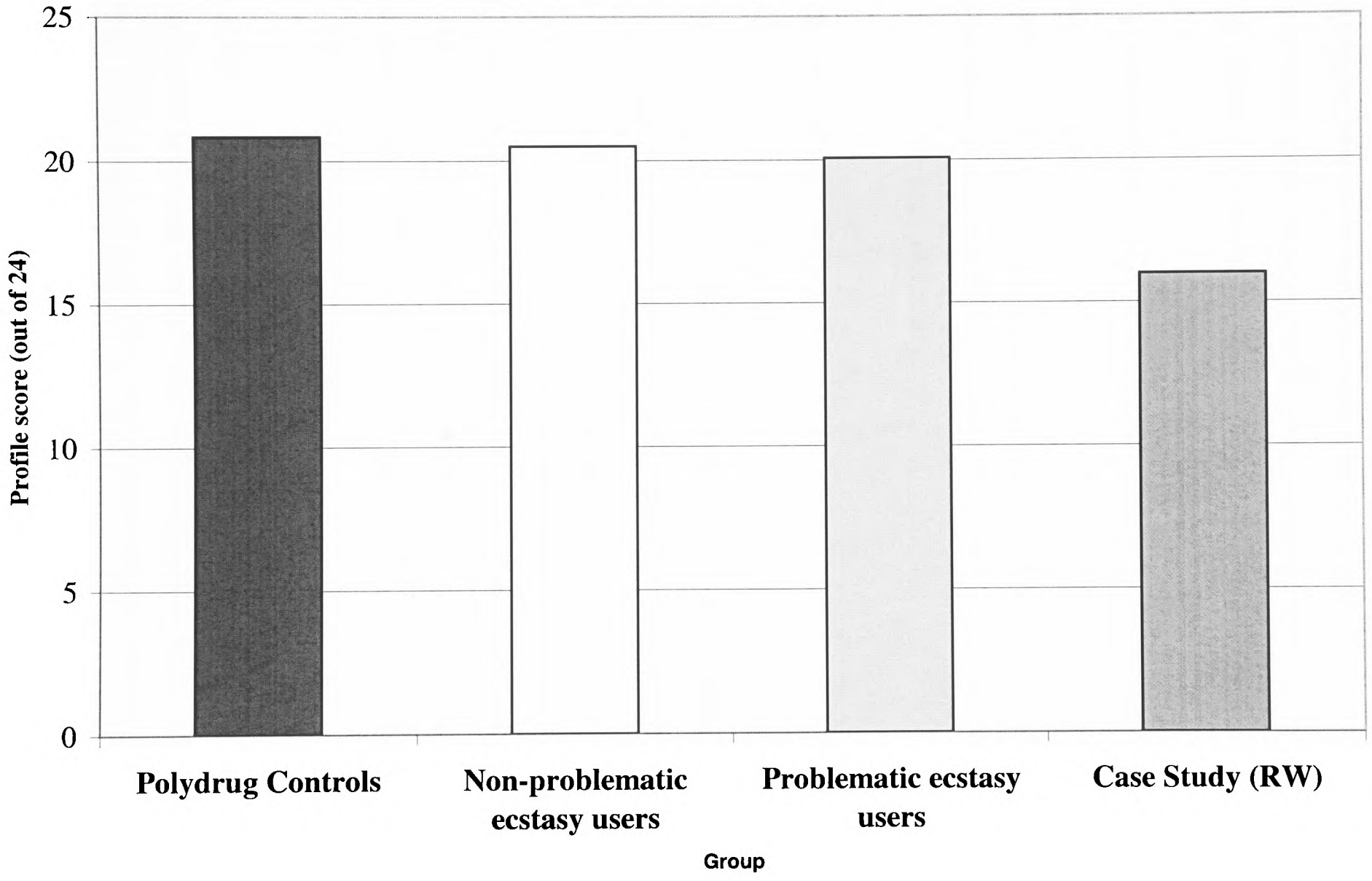


Figure 13. RBMT: mean profile scores for RW and experimental groups



DISCUSSION

Like many ecstasy users RW reported that with continued ecstasy use he reported the need to increase his self-dosing, but this dosage escalation is typical of regular users (Parrott, 2002). However the maximum number of tablets taken on one occasion, twenty-five, is considered to be very high, although high rates of ten tablets/occasion or more have been described previously (McGurie & Fahy, 1991; Winstock et al, 2001; Janssen, 1999). RW stated that it was during this period of heavy usage that he started to develop psychological problems, including poor sleep, depression, phobic anxiety, memory/concentration difficulties, and sexual impotence. He attributed this constellation of problems to his increasing use of ecstasy, and therefore decided to stop taking it. Nevertheless cessation did not lead to a resolution of the problems, but instead they have continued unabated for the past seven years. It was against this biographic profile that RW was assessed on the cognitive and psychiatric symptom test battery, used in the previous study.

The cognitive test results confirmed that RW had various deficits, with a significant impairment in immediate memory compared to normative data in addition to everyday memory and executive functioning (as measured by the TOL), compared with polydrug controls, current non-problematic ecstasy users and problematic ecstasy users (see table 13). This was consistent with previous reports of selective cognitive problems in heavy ecstasy polydrug users, on similar and in some cases the same cognitive tests (Fox et al, 2001b; 2001c; Morgan et al, 2002). RW's subjective complaints of memory/cognitive problems were also consistent with the verbal reports of other recreational users. For example, Parrott et al (2002) found in their sample that 73% of heavy ecstasy polydrug users complained of memory difficulties which they attributed to ecstasy.

The adverse scores on the BSI were also indicative of severe problems and difficulties (table 11). On some subscales RW indicated scores in the clinical range for psychiatric patients (table 12); somatisation, interpersonal sensitivity, depression, anxiety, anger/hostility, phobic anxiety and paranoid ideation. This profile was unsurprisingly consistent with RW's reports of depression, suicidal thoughts, panic attacks, social phobia, sexual impotence and sleeping problems, which he had been reporting for seven years. Surveys have revealed that recreational ecstasy polydrug users often report raised psychiatric symptom profiles (Schifano et al, 1998; Parrott et al, 2000; 2001). Interestingly though, the extreme BSI scores reported

by RW were much higher than the raised group means apparent in the above surveys (table 11) but were consistent with many of the published case studies of severe clinical problems in ecstasy users: e.g. paranoia (McGurie and Fahy, 1991), panic attacks (Windhaber et al, 1998), delirium (Alciati et al, 1999) and psychosis (Bone et al, (2000). For a comprehensive review of this extensive literature of individual case studies, see Soar et al (2001).

The importance of this current case study was that RW had been abstinent from ecstasy for seven years, yet was still suffering severe psychobiological problems. It is well documented that ecstasy use can be associated with cognitive and psychiatric deficits. However, there is little empirical evidence on whether these effects endure over time. Wareing et al (2001) found deficits on executive functioning and measures of anxiety in previous ecstasy users, and MacInnes et al (2001) found higher levels of depression in former ecstasy users up to 6 months after drug cessation. Morgan et al (2002) found ex-ecstasy users exhibited significantly impaired RBMT recall performance and committed significantly more errors in the MFF20 test than polydrug users, despite being tested at least 6 months after their last ecstasy experience. They also showed that ex-ecstasy users exhibited elevated psychopathology scores on the SCL-90-R relative to polydrug users on a subset of measures: positive symptom distress index, inter-personal sensitivity and altered appetite/restless sleep. The above studies demonstrate that anxiety, depression, altered sleep patterns and impairments in executive functioning and verbal recall can persist for up to 6 months to 2 years after the cessation of ecstasy. The present case study suggests that such effects may persist for considerably longer and that spontaneous recovery might never occur. Deficits of this magnitude, seen here after seven years of abstinence are consistent with the case presented by Kopelman et al (2001).

However, as with any retrospective case study, there are always numerous interpretative difficulties and limitations (Schifano & Magni, 1994; Pallanti & Mazzi, 1992). Firstly, there was no psychiatric data prior to the onset of ecstasy use. Poor premorbid adjustment has been associated with increased drug use and since there were no formal psychiatric assessments performed prior to the onset of his problems, it is difficult to rule out psychiatric disturbance of some degree existing prior to ecstasy use. Also RW may have had a genetic predisposition towards neuropsychiatric illness. This possibility is supported by the history of anxiety and depression in his first-degree relatives. The latter point cannot be ruled out but it is important

to note the RW did not report to his GP with any previous psychological disturbances prior to ecstasy use. In addition, RW stated that his symptoms gradually developed over a period of time during which his ecstasy use was escalating.

A second, similar problem is that there is no objective measure of pre-morbid cognitive capacity, and so it is possible that RW exhibited this cognitive profile prior to ecstasy use. Previous studies have found cognitive deficits in ecstasy users screened to exclude those with clinical-psychiatric distress (Fox et al, 2001b; Fox et al, 2001c; Morgan et al, 2002). However in the present case study it might be that the psychiatric symptoms exacerbated the cognitive difficulties, or that these impairments could have been entirely secondary to the psychiatric problems. However, as with the psychological problems, RW did not report cognitive problems prior to taking ecstasy and his symptoms were described as developing over the period when ecstasy was being used at markedly escalating levels. Thus the high doses of ecstasy seem to be the crucial releasing factor, whether or not there was any premorbid predisposition. Of course, this interpretation of the development of both psychopathological symptomatology and cognitive impairments is solely based on the assessment from RW himself.

The use of other psychoactive drugs was another important potential confounding factor, since cannabis, amphetamine, LSD, or other polydrug use, may have contributed to these psychobiological problems (Parrott et al, 2001; Morgan et al, 2002) and cognitive deficits (Rogers and Robbins, 2001). However, McGuire et al (1994), Series et al (1994), Creighton et al. (1991) and Schifano (1991) all concluded there was an association with ecstasy and adverse symptomatology, despite occasional and sporadic use of other drugs (LSD, heroin, amphetamines, and cannabis). Also similar adverse symptomatology (paranoia, anxiety, aggression, depersonalisation, panic attacks, melancholia, suicidal ideation and repetitive thought patterns) was reported in an individual who had taken ecstasy over the course of 6 years with no other drug use except ecstasy and cannabis (Cohen, 1996). These case studies all show similar sporadic polydrug use profiles comparable to that of RW.

It is possible that cannabis could have contributed to the development of RW's problems, since it was regularly taken during the time of ecstasy use and this would also be consistent

with the idea that cannabis is an important contributor to elevated psychopathological profiles (Morgan et al, 2002). However, as with other case studies that report adverse reactions to ecstasy with concurrent cannabis use (Williams et al, 1993, McCann & Ricaurte, 1992; Creighton et al, 1991; McGuire et al, 1994; Cassidy & Ballard, 1994), no reported adverse reactions were attributed by the individual to cannabis. Regarding the possible confounding effects of previous use of cannabis on RW's cognitive profile, it is difficult to dissociate the contributions of ecstasy and cannabis in any empirical research to date.

BZ use may also have contributed to RW's cognitive deficits, since BZs can impair memory, particularly on complex tasks and/or those involving episodic aspects. However, tasks which involve remembering a few verbal items for a period of seconds, e.g. cued-recall and recognition, are not generally affected by BZs (Curran, 2002). However, the use of BZs may have contributed to the poor performance of AVLT recall and story recall in the RBMT. However, it would not necessarily account for the poor performance of face recognition within the RBMT or Tower of London planning times since benzodiazepines do not seem to affect performance on traditional tests of frontal functioning (Curran, 2002). Rather this profile is more akin to that suggested by current literature to be characteristic of that induced by ecstasy use.

It could be argued that RW's cognitive profile may be accounted for by his current use of trifluoperazine. Typical antipsychotic drugs, such as trifluoperazine, have been found to impair memory (Goldstone et al, 1979; Tune et al, 1982; Medalia et al, 1988; Cassens et al, 1990; Cleghorn et al, 1990) however, this is possibly attributable to the conjunctive use of other anticholinergic medication (Mishara & Goldberg, 2004). On the contrary Eitan et al (1992) showed that whilst there was no impairment on immediate memory, long-term memory and visual short-term memory, trifluoperazine was shown to improve short-term verbal memory. Wickert et al (2003) has also shown significant cognitive performance improvements with the administration of atypical agents compared to placebo controls. A more recent meta-analysis (Mishara & Goldberg, 2004) of typical antipsychotic medication suggests that modest-to moderate gains are seen in multiple cognitive functions: attention, language function, intellectual and perceptual function, memory, and executive function.

Therefore, RWs cognitive impairments are very unlikely to be a result of his current medication.

There are a number of methodological limitations, which need to be addressed. The first is the reliance on subjective reports of drug use. Objective assessment of past ecstasy and other drug consumption is difficult, since in this case as in most case studies the individual stops taking the ecstasy before presentation. It would be useful in future cases such as this to use the hair analysis technique (Kikura et al, 1997; Allen & Oliver, 2000) to have an objective measure of drug use. However, this could only really assess relatively recent drug use, not drug use seven years previously. Additionally, it is difficult to infer that these cognitive and psychobiological problems are the result of serotonin neurotoxicity incurred from past ecstasy use without support from neurological evidence: for example from brain MRI scans. The two case studies concerning severe cognitive deficits related to ecstasy use, as discussed in the introduction to this chapter (Kopelman et al, 2001 and Spatt et al, 1997), were supported by MRI and PET scans indicating brain abnormalities in regions rich in serotonin releasing neurons, indicating that ecstasy possibly contributed to such abnormalities and subsequent functional consequences. Despite the absence of scan data for RW it is nonetheless significant that his behavioural profile is akin to those in the latter two studies.

In summary, RW displayed clear cognitive deficits and extensive psychological problems which he attributes to his former heavy use of ecstasy, which are consistent in nature and magnitude to data in many empirical studies of current and former ecstasy users (Parrott et al, 2001; Morgan et al, 2002; Wareing et al, 2001; MacInnes et al, 2001). There was some evidence of psychiatric predisposition (family history), which did not appear to be producing symptoms prior to ecstasy use, that may explain to some degree in combination with ecstasy use, the problems experienced by RW. That these problems are still evident seven years after cessation of the drug suggests that heavy ecstasy consumption may be associated with irreversible long-term psychological and cognitive problems. It may be that having a psychiatric predisposition, it may be more likely that one suffers from the long term effects and/or have reduced ability to recover following cessation of ecstasy. Thus, further studies are needed to assess the persistence of ecstasy-induced psychopathological and cognitive effects and the role of premorbid factors.

CHAPTER 5

Persistency of cognitive and psychological effects of recreational ecstasy use

INTRODUCTION

Several studies have indicated the persistence of what are thought to be ecstasy-induced effects. These include case study reports where psychiatric symptomatology has been associated with ecstasy long after discontinued use (Cohen, 1996; McCann & Ricaurte, 1992, Windhaber et al, 1998; Schifano, 1991). Schifano and Magni (1994) presented a number of individual case studies with psychiatric symptomatology, present for 6 months to over 2 years after ecstasy cessation. The case study in the previous chapter (4) showed cognitive deficits in immediate memory, everyday memory and executive functioning and psychological problems thought to be attributable to ecstasy consumption 7 years previously. As discussed in the previous chapter there are a number of methodological limitations with such case studies, which restricts interpretation concerning the persistency of ecstasy-induced effects. This study aims to investigate the persistence of these psychological deficits using the same battery of tasks used in the previous two studies, by assessing ecstasy users who have abstained from using the drug for at least a year.

Recently, neuroimaging studies have demonstrated possible recovery from ecstasy induced 5-HT neurotoxicity (Reneman et al, 2001; Reneman et al, 2001) which have considerable implications regarding whether or not the behavioural and cognitive effects associated with recreational ecstasy use are reversible or persistent in nature. Empirical studies involving non-clinical samples have specifically addressed the issue of persistency of psychological effects associated with ecstasy; with varying results. MacInnes et al (2001) reported higher levels of depression in former ecstasy users compared to matched controls, though the 'drug free' status in these former ecstasy users was somewhat ambiguous, since abstinence was reported for an average of 6 months, but some ecstasy users reported use as little as 2 weeks before testing. Gerra et al (2000) actually found an improvement in hostility scores on the Buss Durkee Hostility Inventory, in ecstasy users 12 months after ecstasy discontinuation. However, these findings are limited since there were no control group comparisons. In contrast, Morgan et al (2002) failed to find any differences on the SCL-90-R or IVE, between current and ex-ecstasy users.

Persistency of cognitive deficits has been explored in a few studies, again with varying results. Tentative evidence for the persistence of neurocognitive deficits has been shown by Wareing et al (2000). Current and previous ecstasy users were tested on measures of central

executive functioning in addition to self-reported levels of anxiety. Both groups were found to have deficits on some aspects of central executive functioning and raised levels of anxiety compared to a control group of non-ecstasy users, suggesting that the neuropsychological effects persisted after the cessation of ecstasy use. Morgan et al (2002) found selective cognitive impairments to remain after an average of two years of abstinence, with ex-ecstasy users showing significant impairments in recall on the RBMT and committing significantly more errors on the MFF20 relative to 'non-ecstasy' polydrug user controls. Zakzanis and Young (2001) demonstrated impairments in abstinent ecstasy users on aspects of the Behavioural Assessment of Dysexecutive Syndrome (BADS) compared to controls. However, these findings are questionable since the length of abstinence varied in the ecstasy user group from 2 to 156 weeks, with no current ecstasy user group comparison. Additionally, Reneman et al (2001) showed that whilst ecstasy and ex-ecstasy users demonstrated impairment on the AVLT compared to controls, ex-users still showed impairment. Together these studies indicate that whilst it is difficult to ascertain empirically whether psychological symptoms associated with ecstasy are persistent in nature, the effects on some aspects of memory function certainly appear to be prolonged.

The present study sought to extend understanding of which psychological and cognitive impairments associated with ecstasy use might be persistent in nature, by assessing the cognitive and psychopathological profiles of ex-ecstasy users who had not used ecstasy for a period of at least a year. There scores were compared with current ecstasy users and also with a polydrug control group. 'Ex-ecstasy' use was defined by a one year period of abstinence. This one year cut off point for ex-ecstasy users was chosen based on the criteria used in Reneman et al's study (2001) as discussed above.

All three groups were assessed and compared on the same TOL and AVLT tasks used in the previous two studies, but not the complete RBMT. Instead of using the complete version of the RBMT, only the story recall and prospective memory components were used. This methodological alteration was made since the complete RBMT is not thought to be suitable for detecting subtle memory deficits (Wall et al, 1994; Wills et al, 2000) and also because any cognitive effects in ex-ecstasy users are likely to be more even more subtle than current ecstasy users because of hypothesised cognitive recovery. The prose recall component was used since numerous studies employing this component have demonstrated impaired performance in ecstasy users (Morgan, 1999; Morgan et al, 2002; see chapter 2). The two

prospective memory components from the RBMT (remembering to ask for a belonging and remembering to ask a particular question relating on future cues), were used since recent research has shown that prospective memory is impaired in ecstasy users (Heffernan et al, 2001; Rodgers et al, 2001) and also to validate the self-reported cognitive failure questions included in the BSI. Based on previous research and the employment of more sensitive tests, it is hypothesised that current ecstasy users will display cognitive deficits compared to polydrug controls. Whether or not ex-ecstasy users will display cognitive deficits to the extent of current ecstasy users or whether they indicate similar cognitive profiles compared to polydrug controls will be addressed.

As in the previous studies, psychopathological status was assessed in all three groups using the same modified version of the BSI. Again this was used to establish whether ecstasy users displayed higher self-reported psychopathological profiles than polydrug controls, as has been repeatedly shown (Parrott et al, 2000; Parrott et al, 2001; Daumann et al, 2001; Dugherio et al, 2001), and also to indicate whether these psychopathological symptoms were persistent or if they recovered to the level of polydrug controls after a period of abstinence from ecstasy. Based on the findings of this previous research it is hypothesised that current ecstasy users will display different psychopathological profiles to ex-ecstasy users. A further objective of this study is to explore whether the potential problems and deficits in ex-ecstasy users are simply weaker versions of the same problems reported in the problematic ecstasy users in the first study (chapter 3) and the individual case study or different problems altogether.

The usage of other drugs, patterns of ecstasy consumption and self-reported positive and negative effects associated with ecstasy, were also assessed using a similar questionnaire as in the previous two studies, to try and establish any possible differences between the two ecstasy using groups. The drug use questionnaire differed slightly from that used in the previous studies, with the omission of questions focusing on the acute effects of ecstasy. This was to shorten the questionnaire, but at the same time to focus more on the main objective of the thesis (i.e. the 'long-term' effects associated with ecstasy), rather than the acute effects.

Another objective of the study was to replicate the cognitive and psychological dose-related findings from the initial study (chapter 3) and to confirm previous findings (e.g. Schifano et al, 1998; Parrott, Sisk & Turner, 2000; MacInnes et al, 2001; Fox et al, 2001b; Reneman et al, 2001). In order to achieve this, the psychopathological and cognitive test

scores in all ecstasy users (both current and ex-ecstasy users) will be correlated with ecstasy use; factors include:- lifetime consumption, average dose consumed on any one occasions and largest dose consumed on a single occasion. Correlation analyses involving the psychopathological and cognitive test scores and 'duration since last used ecstasy' should help validate any significant group effects between current and ex-ecstasy users.

The fact that the methodology used in this present study is nearly identical to that used previously, may also allow for confirmation of the results found for ecstasy users and polydrug users in the first study. This partial replication will help determine whether ecstasy users demonstrate cognitive and psychological deficits compared to polydrug controls, and thus establish whether the lack of findings in the first study were partly due to a poorly performing polydrug control group, as discussed previously (chapter 3).

METHOD

Participants

Subjects were recruited via the 'snowball' technique' (28%) (Solowij et al, 1992), word of mouth (44%) and posters around the University of East London (28%). First year undergraduate psychology students, who volunteered for the study, did so as part of a course requirement (n=20). All participants were assessed for ratings of health, age, number of years in education and premorbid verbal IQ, as measured by the NART (Nelson, 1982). Participants were excluded from the study if they reported any of the following conditions: head injury, current or previous asthma, depression, anxiety, obsessive compulsive disorder, schizophrenia or paranoia, panic attacks, eating disorders, alcohol or drug dependency.

Sixty-one subjects participated in this study: 21 (13 male, 8 female) current recreational ecstasy users who had used ecstasy at least 20 occasions in their lifetime, but had not used within the last 2 weeks; 20 (14 male, 6 female) recreational ecstasy users who had used ecstasy on at least 20 occasions in their lifetime, but had been abstinent for at least 1 year; and 20 (6 male, 14 female) polydrug controls who had no history of ecstasy exposure but otherwise used other illicit drugs. Those participants that did not meet the exclusion criteria were then formally assessed with a questionnaire. This comprised of questions concerning their own and immediate family psychiatric history and details of past illicit drug use. The University of East London ethics committee approved the study (see appendix U for the application for ethical approval and confirmation of approval. All participants gave written informed consent (see appendix Y) and were paid £10 each for participating.

Assessment Measures

Participant's drug usage patterns were assessed using the same drug use questionnaire as the previous study for assessing their history of drug use (Appendix A). Individuals in the ecstasy group were asked to complete the additional questionnaire used in the previous study regarding patterns of ecstasy use (Appendix B). In addition they were asked to indicate when they last consumed ecstasy and also whether they used other drugs in conjunction with ecstasy and to indicate what these were. They were also asked to complete the same 4-point

self-report Likert scale on the long-term positive and negative effects of ecstasy on life experiences (Appendix B).

Psychopathological status was assessed using the same modified version of the Brief Symptom Inventory (BSI) as in the first study. Cognitive performance was assessed using the following tasks in the order presented below:

Prospective Memory tasks: The two prospective memory test components were taken from the RBMT (Wilson et al, 1991). The first of these was 'Remembering an appointment'. Participants were required to ask a particular question relating to the near future when an alarm sounds during the experiment. The second was 'Remembering a belonging', where participants were requested to ask for a belonging, which had previously been hidden by the experimenter, on the cue of the experimenter saying *"that is the end of the test"* and to remember where it has been hidden. These two test items were scored using the standardised profile scoring system for the RBMT (see methodology, chapter 3): 2 points awarded for each task if completed successfully, 1 point awarded for each task if they completed the tasks after a prompt and 0 points if they failed to remember to complete the task, even after prompting.

Prose recall (immediate and delayed). After listening to a short passage read aloud by the experimenter, each participant was required to recall as much as possible immediately after the reading and again after a period of delay. The story was taken from the prose recall component of the RBMT (Wilson et al, 1991) and comprised five sentences containing 65 words and 21 'ideas'. Recall was scored with one point given to each of the 21 ideas recalled perfectly or a close synonym and half a point for partial recall or partial synonym.

Auditory Verbal Learning Test (AVLT; Rey, 1964). The methodology for this task is identical to that in the first study (see methodology section, chapter 3).

Tower of London (TOL): The methodology for this task is identical to that in the first study (see methodology section, chapter 3).

Statistical Analysis

Data analysis was conducted using SPSS 10 for windows. ANOVA tests were performed for all cognitive tasks (AVLT, TOL, prose recall and prospective memory) and the BSI data to assess whether there were any group differences between polydrug controls, ecstasy users and ex-ecstasy users. Post Hoc analyses comprised of paired comparisons between groups using the Tukey's range statistic.

As drug use violated parametric assumptions, Kruskall Wallis was employed to assess differences in drug use between the three experimental groups. Post hoc analysis comprised of paired comparisons between groups using the Mann Whitney test. Bonferroni corrections were employed by dividing the standard error rate ($\alpha = 0.05$) by the number of groups in the analysis, in this case $\alpha/3 = 0.017$, to minimise the risk of type 1 errors.

There was no need to conduct further separate analyses of covariance, since age did not differ between experimental groups. Again co-variation for other drug use was not carried out for the reasons given in the discussion of chapter 3.

The independent samples t-test was used to assess differences between current and ex-users, in the patterns of ecstasy use as well as reported positive and negative effects of ecstasy. Chi-squared tests were used to establish any significant differences between these groups in response to questions regarding both the positive and negative effects of ecstasy on life experiences and gender.

After collapsing the two ecstasy groups, Pearson Product Moment Correlational Analyses were conducted to assess whether there were any associations between patterns of ecstasy use and BSI data, negative and positive effects of ecstasy and cognitive performance; and whether data from the positive and negative effects of ecstasy were associated with data from the BSI. There were no statistical corrections made to the correlational analyses to control for type 1 errors, thus it is important to note that significant findings should be treated with extreme caution due to the large number of correlations and potential chance occurrences.

RESULTS

Personal characteristics and drug data

Tables 14 to16 show the demographic and drug use data. There were no significant group differences for age, rating of health and verbal IQ. However, there was a significant group difference of gender ratios [χ^2 (2) = 7.23, p = 0.027] with significantly more males than females in the control group than in the current and ex-ecstasy using groups.

With regard to drug consumption (see table 14), polydrug controls reported significant less drug use than the ecstasy groups for a number of compounds: amphetamine [χ^2 = 24.46, p<0.001], cocaine [χ^2 = 20.56, p<0.001], crack cocaine [χ^2 = -6.48, p=0.039, opiates [χ^2 = 10.01, p=0.004], cannabis [χ^2 = 19.29, p<0.001], LSD [χ^2 = 20.04, p<0.001], magic mushrooms [χ^2 = 15.14, p<0.001], poppers [χ^2 = 23.10, p<0.001], ketamine [χ^2 = 8.10, p = 0.017], tobacco [χ^2 = 9.74, p = 0.008] and monthly cannabis [χ^2 = 22.05, p<0.001].

As expected, current ecstasy users reported a significantly shorter duration since they last consumed ecstasy [t(38) = -4.54, p<0.001]. They also reported a significantly higher maximum dosage compared with ex-ecstasy users [t(39) = 2.54, p = 0.016] (table 14). There were no differences on the reported long-term positive and negative effects scale that ecstasy had had on life experiences between the two ecstasy using groups (table 14).

Regarding use of other drugs specifically on occasions when using ecstasy (see table 16), a greater percentage of current ecstasy users reported use of cannabis (65% vs. 43%), cocaine (65% vs. 24%), alcohol (25% vs. 14%) and poppers (15% vs. 10%) in conjunction with ecstasy compared to ex-ecstasy users; who reported greater use of amphetamine (43% vs. 30%) and LSD (10% vs. 5%) in conjunction with ecstasy.

Table 14: Participant demographics, levels of illicit drug use and patterns of ecstasy use consumption in polydrug controls, current and ex-ecstasy users (means and SDs).

	Polydrug Controls (C)	**Current Ecstasy Users (E)**	Ex-Ecstasy Users (Ex)	Group Effect *p*	Post Hoc Comparisons
Age	27.95 + 6.12	24.48 + 3.4	27.1 + 3.78	0.063	-
Verbal IQ	112.05 ± 7.48	111.57 ± 5.16	113.15 ± 4.36	0.675	-
Current rating of health	3.5 ± 0.69	3.29 ± 0.46	3.45 ± 0.69	0.286	
Patterns of ecstasy use:					
Average dose		2.14 ± 0.91	1.73 ± 0.57	0.088	
Maximum dose		5.83 ± 3.13	3.75 ± 2.03	0.016	
Total consumption		238.95 ± 286.92	185.25 ± 148.86	0.460	
Duration of ecstasy use (months)		87.42 ± 41.86	75.40 ± 37.01	0.348	
Weeks since last used		11.55 ± 14.79	146.45 ± 132	<0.001	
Positive effect score		12.10 ± 4.53	14.10 ± 4.56	0.166	
Negative Effect Score		31.90 ± 7.91	30.30 ± 8.46	0.535	
Other drug use:					
Amphetamine	11.55 ± 44.62	56.86 ± 70.84	75.25 ± 83.42	<0.001	C < E & Ex
Cocaine	12.25 ± 44.70	130.86 ± 233.56	40.95 ± 58.10	<0.001	C < E & Ex
Crack	-	1.43 ± 4.42	0.55 ± 1.05	0.039	C < E & Ex
Opiates	0.05 ± 0.224	0.90 ± 1.92	4.05 ± 11.07	0.004	C < Ex
Cannabis	175.90 ± 338.90	1436.52 ± 1753.93	1590.25 ± 1453.34	<0.001	C < E & Ex
Benzodiazepines	0.10 ± 0.45	3.67 ± 10.93	3.40 ± 11.32	0.067	
LSD	10.60 ± 44.64	21.57 ± 48.99	35.00 ± 49.44	<0.001	C < E & Ex
Magic Mushrooms	1.60 ± 6.69	4.19 ± 7.55	14.00 ± 17.89	0.001	C < E & Ex
Solvents		1.43 ± 3.17	3.65 ± 10.8	0.088	
Poppers	0.30 ± 1.18	59.90 ± 216.00	12.39 ± 23.31	<0.001	C < E & Ex
Ketamine	-	3.19 ± 7.79	4.40 ± 8.57	0.017	C < E & Ex
Prozac	0.10 ± 0.45	-		0.359	-
GHB	-	0.48 ± 1.12	0.25 ± 0.91	0.128	-
Tobacco (Per day)	3.30 ± 6.91	8.00 ± 6.46	12.25 ± 11.88	0.008	C < E & Ex
Alcohol (Units per week)	9.60 ± 10.15	14.43 ± 14.48	11.30 ± 11.62	0.660	
Cannabis (Per month)	0.3 ± 0.57	12.43 ± 11.96	11.65 ± 12.77	<0.001	C < E & Ex

Table 15: Percentage of group participants who answered yes to questions concerning patterns of ecstasy use; current and ex-ecstasy users

% of participants in each group	Current Ecstasy Users (n=21)	Ex-Ecstasy Users (n=20)	Chi square
Have you increased the number of tablets you have taken on each occasion?	15	35	0.144
Has the effects of ecstasy changed, the more you have taken it?	80	60	0.168
Do you suffer if you for sometime without taking ecstasy?	0	0	1.000
Do you need to take ecstasy?	0	0	1.000
Do you feel dependent or addicted to ecstasy in any way?	5	5	1.000
Do you considered yourself to be a stable user, using approximately the same amount of tablets on each occasion with regular intervals between each occasion?	55	50	0.752
Do you take drugs that are supposed to prevent ecstasy side effects?	10	10	1.000
Do you usually take other drugs together with ecstasy?	85	65	0.144

Table 16: Reported drug use whilst using ecstasy, for current and ex-ecstasy using groups

% of participants in each group	**Current Ecstasy Users (n=21)**	**Ex-Ecstasy Users (n=20)**
Cannabis	65%	43%
Amphetamine	30%	43%
Cocaine	65%	24%
Alcohol	25%	14%
Nicotine	5%	10%
Caffeine	0%	5%
Poppers	15%	10%
LSD	5%	10%
Magic Mushrooms	0%	5%
Opiates	0%	0%

Table 17: Modified BSI subscale scores for polydrug controls, current ecstasy and ex-ecstasy users (means and SDs).

	Polydrug Controls	**Current Ecstasy Users**	**Ex-Ecstasy Users**	**ANOVA Group Effect *p***
Negative symptoms				
Somatisation	0.37 ± 0.34	0.63 ± 0.56	0.57 ± 0.50	0.200
Obsessive-compulsive	1.05 ± 0.75	1.09 ± 0.73	1.28 ± 0.72	0.567
Interpersonal sensitivity	0.71 ± 0.70	0.69 ± 0.59	0.79 ± 0.60	0.876
Depression	0.53 ± 0.64	0.45 ± 0.63	0.65 ± 0.68	0.619
Anxiety	0.55 ± 0.68	0.56 ± 0.45	0.62 ± 0.56	0.927
Anger/hostility	0.49 ± 0.47	0.60 ± 0.49	0.67 ± 0.71`	0.600
Phobic anxiety	0.25 ± 0.30	0.13 ± 0.22	0.11 ± 0.21	0.167
Paranoid ideation	0.51 ± 0.38	0.58 ± 0.52	0.68 ± 0.73	0.632
Psychoticism	0.39 ± 0.56	0.41 ± 0.53	0.46 ± 0.46	0.907
Negative psychobiology	0.51 ± 0.38	0.49 ± 0.33	0.46 ± 0.42	0.915
MDMA side effects	0.99 ± 0.71	0.98 ± 0.68	1.04 ± 0.53	0.952
Sexual functioning	0.38 ± 0.34	0.59± 0.55	0.52 ± 0.48	0.313
Cognitive failures	1.14 ± 0.79	1.30 ± 0.76	1.51 ± 0.82	0.336
Positive Symptoms				
Feeling content with life	2.40 ± 0.95	2.41 ± 0.94	2.49 ± 0.86	0.943
Mood state	2.30 ± 0.87	2.32 ± 0.87	2.37 ± 0.63	0.963
Sociability	2.22 ± 0.64	2.45 ± 0.77	2.43 ± 0.67	0.493
Positive psychobiology	2.22 ± 0.72	2.28 ± 0.88	2.36 ± 0.81	0.853

Table 18: Cognitive assessment data for polydrug controls, current and ex-ecstasy users (means and SD's)

	Polydrug Controls	Current Ecstasy Users	Ex-Ecstasy Users	Group Effect *p*
Story recall				
Immediate	7.87 ± 2.95	8.33 ± 2.46	7.38 ± 2.50	0.514
Delayed	7.15 ± 3.23	7.88 ± 2.91	6.33 ± 2.12	0.213
Prospective memory				
Remembering an appointment	1.95 ± 0.22	2.00 ± 0.32	1.80 ± 0.52	0.281
Remembering a belonging	3.35 ± 0.67	2.90 ± 0.89	3.25 ± 0.72	0.157
Tower of London				
Planning times	7.48 ± 3.57	8.20 ± 4.23	9.31 ± 4.42	0.370
Solution times	4.11 ± 0.96	3.78 ± 0.68	4.13 ± 1.81	0.600
Number of errors	3.60 ± 3.71	3.90 ± 3.77	3.75 ± 2.97	0.962
Number of incomplete trials	0.15 ± 0.37	0.05 ± 0.22	0.15 ± 0.37	0.505
AVLT				
Immediate Recall				
Trial 1	6.40 ± 1.79	6.19 ± 1.72	6.10 ± 2.00	0.869
Trial 2	8.65 ± 2.62	9.48 ± 2.14	8.30 ± 1.92	0.233
Trial 3	10.95 ± 2.58	10.33 ± 2.27	9.55 ± 2.16	0.176
Trial 4	11.10 ± 2.65	11.43 ± 2.29	11.10 ± 1.65	0.863
Trial 5	11.60 ± 2.44	11.62 ± 1.91	11.15 ± 1.98	0.730
Total Recall				
Interference Trial	5.45 ± 2.67	4.14 ± 1.28	4.40 ± 1.47	0.075
Trial 6	9.70 ± 2.94	10.43 ± 2.62	10.1 ± 2.07	0.664
Delayed Recall	10.30 ± 2.75	9.90 ± 2.13	9.25 ± 3.35	0.490
Number of Errors	2.25 ± 2.59	1.57 ± 1.89	2.75 ± 3.26	0.360
Number of Repeats	5.25 ± 4.39	4.43 ± 4.09	4.2 ± 3.76	0.695
Intrusion from list A	0	0.0476 ± 0.22	0.10 ± 0.31	
Intrusion from list B	0.10 ± 0.31	0.19 ± 0.60	0.15 ± 0.37	0.811

Group differences

Measures of psychopathology

Table 17 shows the group scores for all the subscales of the modified version of the BSI. Despite the ex-ecstasy users scoring higher on most of the negative scales (obsessive-compulsive, interpersonal sensitivity, depression, anxiety, anger/hostility, paranoid ideation, psychoticism, MDMA side effects, and cognitive failures) compared to polydrug controls and current ecstasy users, these differences did not reach statistical significance.

Measures of cognitive performance

Table 18 shows the group scores for all task data. There were no significant group differences on the prose recall task or prospective memory components of the RBMT. Ex-ecstasy users performed lower on all trials of the AVLT compared to current ecstasy users and polydrug controls; and polydrug controls demonstrated greater delayed recall compared to current and ex-ecstasy users (illustrated in figure 14). However, none of these differences approached significance. On the TOL, polydrug controls also showed quicker planning times (figure 15) and fewer errors (figure 16) compared to current and ex-ecstasy users. Again, these did not approach significance, nor were there any significant group differences in solution times or the number of incomplete trials.

Correlational analyses

Dose-response relationships

There were no significant correlations between total ecstasy consumption, average and maximum number of ecstasy tablets consumed on one occasion and any subscale of the BSI and TOL. Lifetime ecstasy consumption positively correlated with delayed story recall ($r = 0.337$, $p = 0.031$) and recall on trial three of the AVLT ($r = 0.346$, $p = 0.027$) and negatively correlated with recall on trial six of the AVLT ($r = -0.343$, $p = 0.028$).

Duration of use

Duration of ecstasy use negatively correlated with interpersonal sensitivity ($r = -0.318$, $p = 0.05$) and depression ($r = -0.401$, $p = 0.011$) and positively correlated with positive psychobiology ($r = 0.42$, $p = 0.008$). In addition, there were significant positive correlations between the number of weeks since ecstasy use and obsessive-compulsive ($r = 0.328$, $p = 0.039$) and depression scores ($r = 0.383$, $p = 0.015$), as well as scores on the positive effects attributable to ecstasy scale ($r=0.530$, $p = 0.001$).

Measure of drug use

Estimated lifetime consumption positively correlated with the average ($r = 0.340$, $p = 0.029$) and maximum ($r = 0.370$, $p = 0.017$) number of tablets consumed in one occasion, and the duration of ecstasy use ($r = 0.347$, $p = 0.030$). Regarding other drug use, total lifetime consumption positively correlated with lifetime cannabis consumption ($r = 0.355$, $p = 0.023$), cocaine ($r = 0.423$, $p = 0.006$), benzodiazepines ($r = 0.621$, $p<0.001$) and monthly cannabis consumption ($r = 0.384$, $p = 0.013$). Duration of ecstasy use positively correlated with lifetime consumption of cannabis ($r = 0.385$, $p = 0.015$), cocaine ($r = 0.355$, $p = 0.027$) and GHB ($r = 0.328$, $p = 0.041$).

Measure of long-term psychological effects

The total score for the long-term negative effects attributable to ecstasy positively correlated with most of the negative subscales of the BSI: somatisation ($r = 0.420$, $p = 0.006$), obsessive-compulsive ($r = 0.485$, $p = 0.001$), depression ($r = 0.385$, $p = 0.013$), anxiety ($r = 0.590$, $p < 0.001$), anger/hostility ($r = 0.472$, $p = 0.002$), phobic anxiety ($r = 0.416$, $p = 0.007$), paranoid ideation ($r = 0.337$, $p = 0.031$), psychoticism ($r = 0.516$, $p = 0.001$), negative psychophysiology ($r = 0.414$, $p = 0.007$), MDMA side effects ($r = 0.438$, $p = 0.004$), sexual functioning ($r = 0.494$, $p = 0.001$) and cognitive failures ($r = 0.312$, $p = 0.050$). Scores on the long-term positive effects attributable to ecstasy positively correlated two of the positive subscales of the BSI: feeling content with life ($r = 0.336$, $p = 0.032$) and sociability ($r = 0.331$, $p = 0.035$) and also sexual functioning ($r = 0.379$, $p = 0.015$).

Figure 14: Mean AVLT recall scores, across all trials, for polydrug controls, current ecstasy users and ex-ecstasy users.

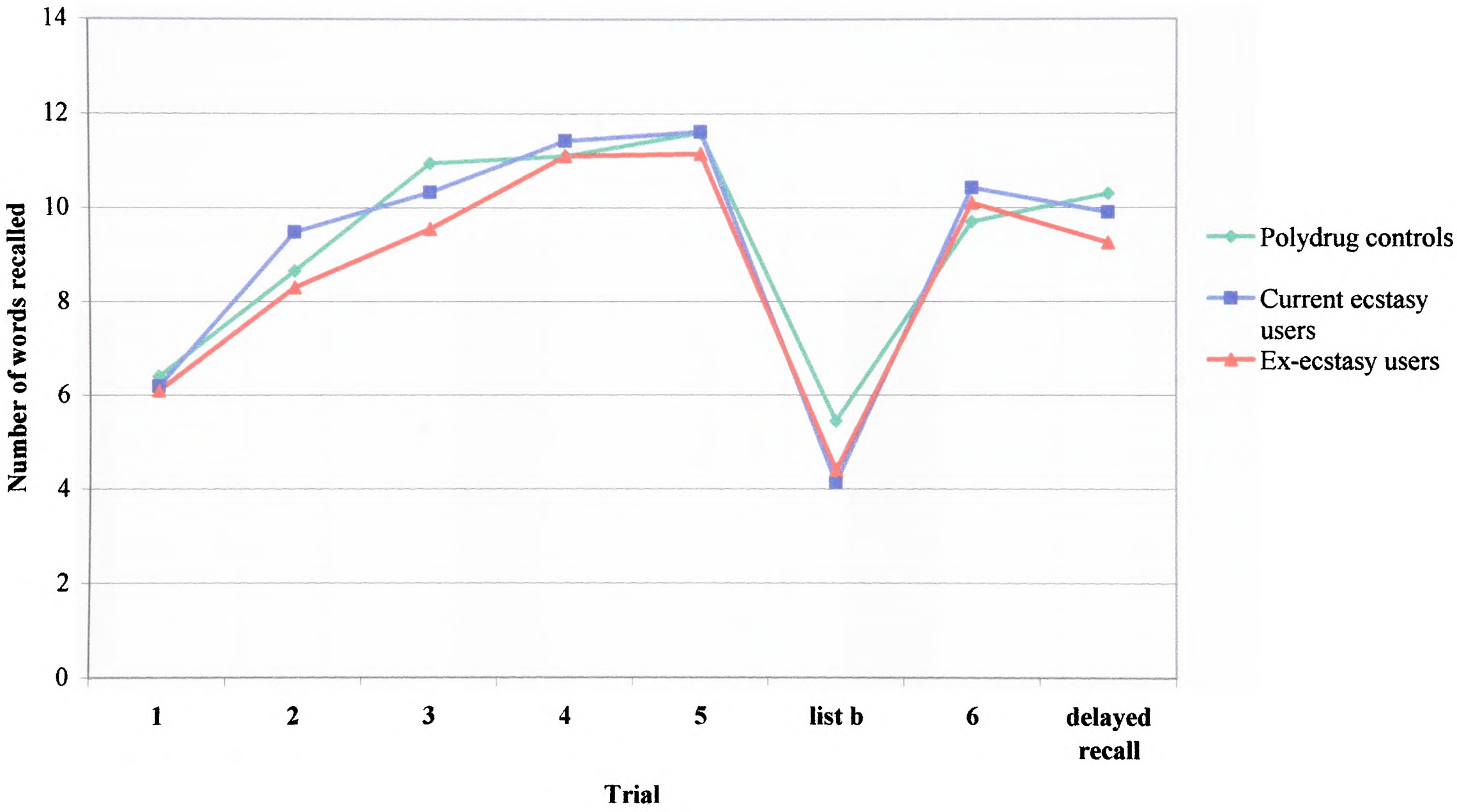


Figure 15: Group mean planning times (in seconds) on the TOL
(Bars indicate 1 standard error of mean)

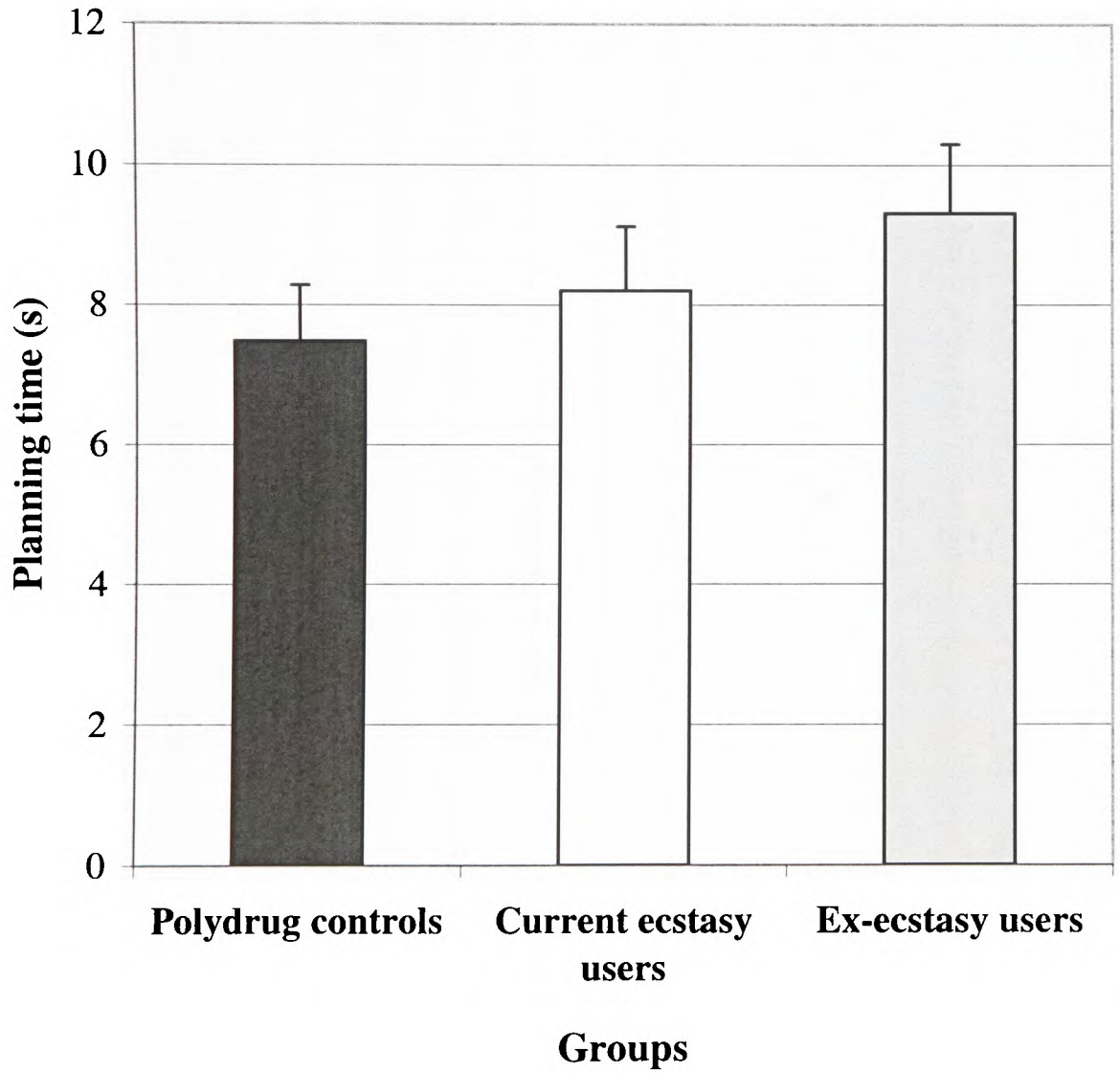
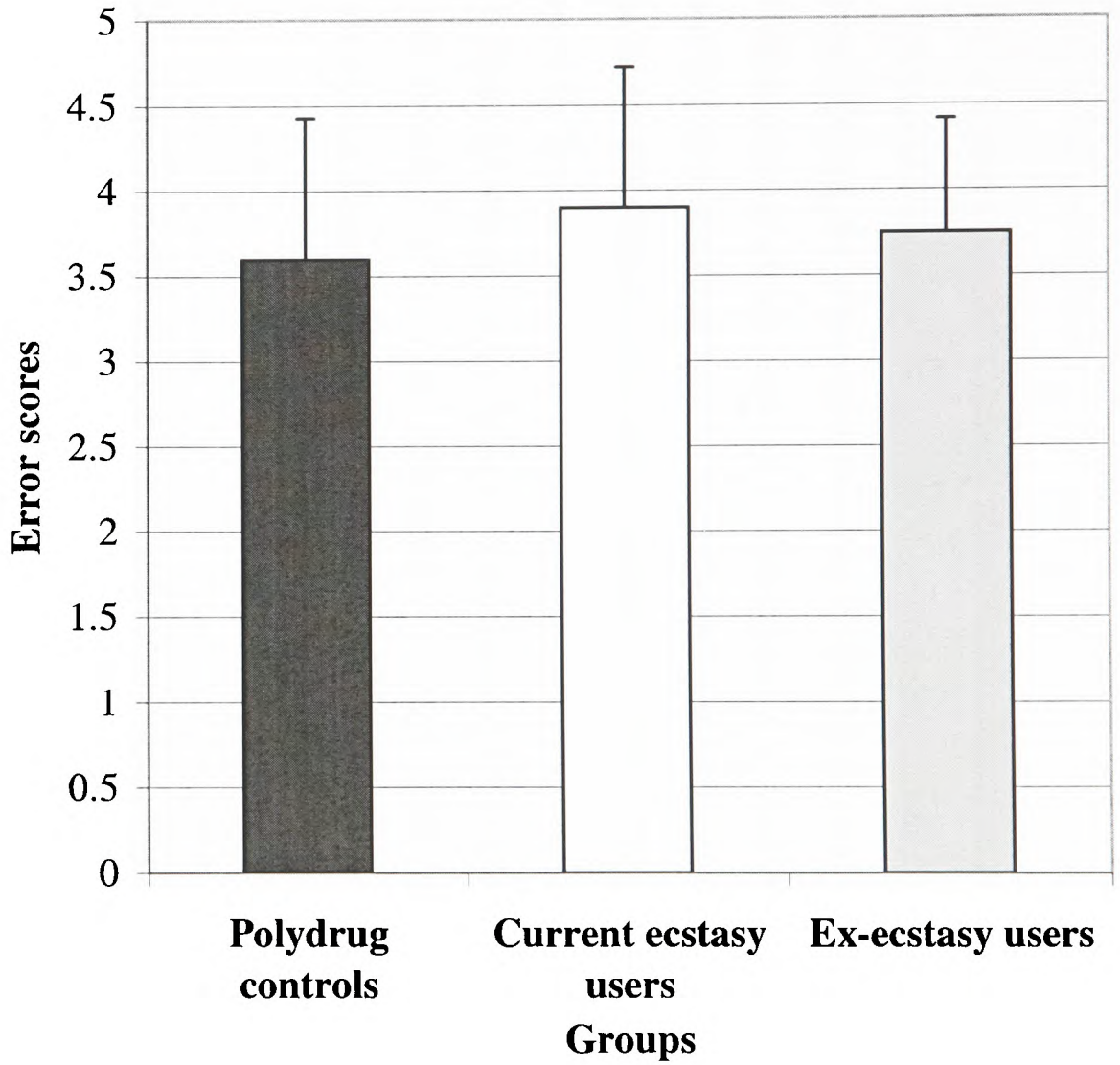


Figure 16. Group mean errors on the TOL
(Bars indicate 1 standard error of mean)



DISCUSSION

The current study indicates that current ecstasy users do not differ in cognitive abilities and psychopathological status compared to ecstasy users that have abstained from ecstasy use for over a year (ex-users). These findings are inconsistent to that of MacInnes et al (2001) and Gerra et al (2000) who demonstrated recovery from psychopathology e.g. depression and hostility. However, both studies have methodological limitations, in the ambiguity of abstinence in the ex-ecstasy users (MacInnes et al, 2001) and due to a lack of appropriate control comparisons (Gerra et al, 2000). The current findings are however, also consistent with the previous empirical research which avoid these methodological limitations (Morgan et al, 2002; Wareing et al, 2000; Reneman et al, 2001: Zakzanis & Young, 2001), indicating further evidence that ex-ecstasy users do not differ from current ecstasy users in cognitive and psychological abilities.

However, the current ecstasy and ex-ecstasy users do not seem to be displaying cognitive deficits or psychological impairments compared to the polydrug controls employed within this study; despite the fact that the polydrug controls had used significantly lower amounts of most other illicit drugs (table 14). These results replicate those found in the first study (chapter 3), which demonstrated that ecstasy users had similar cognitive abilities and psychopathological profiles to polydrug controls. However, they are inconsistent with previous research studies, which have demonstrated that current ecstasy users display cognitive deficits and psychopathology compared to non-ecstasy using controls (Parrott et al, 2000; Morgan et al, 2002; Fox et al, 2001b; Fox et al, 2001c).

There were a number of possible dose-related effects in relation to cognitive and psychopathological status. Recall scores on trial 6 of the AVLT, were shown to worsen with higher lifetime consumption, suggesting that it is the cumulative amount of ecstasy that affects some aspects of cognitive function, an idea which is supported in some previous literature (Morgan et al, 2001; Reneman et al, 2001; Thomasius et al, 2003). However, in surprising contrast to previous research, the current study demonstrated a significant positive correlation with lifetime consumption of ecstasy and delayed story recall on the RBMT. The results also suggested that interpersonal sensitivity and depression scores are higher in individuals who have be using ecstasy for a much shorter time period, this may be accounted for by individuals becoming tolerant to these negative symptoms the longer they use ecstasy.

However, a degree of caution needs to be exerted in drawing conclusions from these correlational analyses due to the high chance that such significant findings occurred by chance, since there was no control for type 1 errors and also because of the collapsed data for what are arguably two distinct ecstasy using groups into one. Apart from the expected difference in the time each of the two groups last consumed ecstasy, evidence to suggests that these two groups are different in relation to their ecstasy use is shown by current ecstasy user's using significantly higher amounts on one occasion than ex-ecstasy users (table 14) and also their reports of using other drugs in combination with ecstasy. Another difference highlighted in the correlational analyses, is that it appears that the longer you abstain from using ecstasy, the more likely you are to report obsessive-compulsive and depressive symptoms. This may constitute as tentative evidence that ecstasy use may be a form of self-medication for psychological problems in some individuals. This self-medication hypothesis postulates that "drug users seek to self-administer substances that correct or compensate for discomforting features of their biology and usual emotional state" (Gunnarsdottir et al, 2000). This has been shown in certain cocaine users with dysphoric moods (Gunnarsdottir et al, 2000) and drug using schizophrenics (Batel, 2000). Therefore ecstasy users may be using the drug to alleviate obsessive-compulsive and depressive symptomatology, as evidenced from a case study of one ecstasy using individual, who met the diagnostic criteria for Post-traumatic Stress disorder (PTSD; Jansen, 1999).

In summary, it appears there were no group differences in cognitive and psychopathological performances, and specifically no evidence of any persistent effects of ecstasy. However, on closer inspection of the results there may be differences between the two ecstasy using groups, as indicated to by the correlational analyses involving the 'time since last consumed ecstasy', but these differences are being masked by poor performance of the control group.

As with the first study, the lack of statistically significant cognitive differences between polydrug controls and ecstasy using groups brings into question the validity of the polydrug control group. The polydrug controls performed within the levels of normative data for immediate recall on the AVLT (6.3 to 7.8, Lezak, 1995) but, again, they performed at the lower end of the scale (6.4). When examining the ecstasy users performance for immediate recall compared with normative data, both current and ex-ecstasy users scored lower than normative data (6.19 and 6.10 respectively); indicating signs of memory dysfunction. Delayed recall performance was much better in the polydrug controls than the previous study

and there is an expected trend of polydrug controls showing better delayed recall than both ecstasy using groups. However, once again, polydrug controls performed lower than normative data, so any memory deficits in ecstasy users are not pronounced enough to produce a significant effect. Comparing AVLT scores to those of Fox et al (2001c), the ecstasy users, in this study, are displaying poorer recall across all trails, including delayed recall, compared to polydrug controls, as well as, short- and long-term ecstasy users from Fox et al's study; indicating that the control group in the present study is impaired, in addition to the current and ex-ecstasy users.

Similar comments could be made with regard to the findings from the TOL. There was a trend for ecstasy users to show increased planning times (figure 15), indicative of deficits in central executive functioning. However, these times were not significantly longer compared to polydrug controls, since the polydrug controls here demonstrated higher planning times relative to the polydrug controls in the first study and also compared to the control group used in the study by Fox et al (2001b – a study which did demonstrate significant differences in planning times between polydrug controls and ecstasy using groups). However, it is important to note that this later study only showed poorer planning abilities in heavy ecstasy users and not low ecstasy users (this will be discussed in more detail later).

The poor cognitive performance by the polydrug control group could also explain the lack of significant findings in prospective memory ability between groups. But, there were no distinct trends in this data and it is more likely that it is the task's inability to detect subtle memory deficits (Wall et al, 1994; Wills et al, 2000) which explains the lack of findings.

Concerning the group psychopathological scores, polydrug controls were actually reporting higher psychopathology across all subscales compared to normative data (Derogatis & Melisaratos, 1983). For example, depression scores for non-patient norms are 0.28 compared to the 0.55 score in polydrug controls here, and anxiety scores for norms are 0.35 compared to 0.55 in the polydrug controls. Looking at the current and ex-ecstasy users, they too demonstrate higher psychopathology scores across all BSI subscales, relative to normative data (for example; depression scores of 0.45; anxiety scores of 0.56). It is reasonable to conclude therefore, that whilst the ecstasy users show signs of psychological dysfunction, this is quite possibly being masked by a control group who are actually showing signs of psychopathology.

An alternative explanation for the lack of cognitive and psychological deficits in the ecstasy users in the current and first study (chapter 3) is that participants might not be exhibiting ecstasy-induced neurotoxicity. The fact that participants do not show any signs of cognitive and psychological dysfunction, could be evidence that they have not consumed ecstasy in the dosages required to produce neurotoxic injury to 5-HT (or other) systems. Current ecstasy users and ex-ecstasy users in this present study reported lifetime ecstasy consumption of 239 and 185 respectively. This is consistent with the number used by the low ecstasy users in the study by Fox et al (2001b). This group of ecstasy users reported using between 100 and 500 ecstasy tablets and did not differ from polydrug controls on TOL planning times. It was only in the heavy ecstasy users (500-1000 tablets) that executive problems were seen. This is demonstrated in the former case study of RW who had an estimated lifetime total use of 750 ecstasy tablets. The cognitive deficits seen in RW, as well as the increased psychopathology scores, taken together with the results from Fox et al's heavy users and the lack of effects in the ecstasy groups in this current study, could be taken to suggest that large quantities are required to induce significant, observable compromisation of 5-HT function.

However, this argument is brought into refute when considering other's research findings. Bolla et al (1998) found impairments on the AVLT in ecstasy users with a lifetime consumption of as little as 60 tablets, whilst Reneman et al (2000) and Fox et al (2001c) showed AVLT deficits in ecstasy users with similar lifetime consumption levels as the current study (218 and 224 respectively). Deficits on the prose recall of the RBMT were also found in ecstasy users with an average of 50 tablets (Morgan, 1999) and 55 tablets per lifetime (Zakzanis and Young, 2001). Evidence from these previous studies therefore would suggest that the lack of cognitive and behavioural findings in this current study is unlikely to be because of the levels of ecstasy consumption, and more likely to be due to methodological reasons (i.e. an inappropriate control group). Having a poor control group then, may suggest that there are actually problems in the ecstasy users here, with no remittance after a period of abstinence (i.e. in ex-users).

The nature of a control group is of particular importance, considering ecstasy users are notoriously polydrug users, hence the need to use a control group consisting of individuals who have also used other drugs, as in the case of this study. There were no differences in cognitive performance and psychopathological status between polydrug controls and ecstasy

groups in the current study (tables 17 & 18). Since all experimental groups displayed some level of impairment compared to normative data or previous research, it may suggest that cognitive and psychological problems could be a general profile for polydrug use rather than ecstasy per se. However, the level of polydrug use in the control group shows they used significantly less of most other drugs compared to current and ex-ecstasy users (table 14). Levels of polydrug use are also considerably lower than those reported in other polydrug control groups in previous studies, which have demonstrated differences from ecstasy user groups. For example, the polydrug control groups employed by Morgan et al (2002) actually reported smoking cannabis 590 times in the year prior to the study, where as the polydrug controls within this study only reported smoking 175.9 times in their lifetime. Similarly, other drug use here (including cocaine, LSD, magic mushrooms and amphetamine) was similar to levels reported by non-ecstasy using polydrug controls in the study by Parrott et al (2001), but they still demonstrated significant differences in psychopathology between groups. Thus, it would be expected that any effects of ecstasy over and above those produced by polydrug use, would have been detected.

The present study also allowed for the exploration of the patterns of drug use amongst ecstasy users, by collapsing the two ecstasy using groups into one group (current and ex-users combined). It appears that the greater the lifetime consumption of ecstasy the greater the consumption of cannabis, cocaine and benzodiazepines. In addition, the longer ecstasy had been used, the more likely was the use of cannabis, cocaine and GHB. This provides support for the notion that ecstasy users are more likely to be polydrug users (Strote et al, 2002; Arria et al, 2002; Webb et al, 1996; Riley et al, 2001; Winstock et al, 2001). The fact that ecstasy users also reported using high rates of cannabis, amphetamine and cocaine in conjunction with ecstasy supports the idea that stimulants and hallucinogens are the most likely drugs to be used in combination with ecstasy (Riley et al, 2001; Winstock et al, 2001).

In the same combined group of ecstasy users, there was also evidence to suggest that the reported long-term negative effects experienced from ecstasy correlated with the majority of the negative psychopathological scales of the BSI. These include somatisation, obsessive-compulsive, depression, anxiety, paranoid ideation, psychoticism, anger/hostility, MDMA side effects and sexual dysfunction. The higher the reported negative effects, the higher the psychopathological status. These findings replicate those found in the first study (chapter 3). There was also an association between the positive effects experienced from ecstasy and two

of the positive subscales of the modified BSI (feeling content with life and sociability). Together these findings validate the 'negative and positive life experiences, attributed to ecstasy questionnaire'. In addition, these results suggest that there is some association between the effects attributed to ecstasy and psychopathological profiles measured by the BSI. It appears that many individuals, who attribute more of their negative life experiences to their ecstasy use, also display higher levels of psychopathology. This could be due a cognitive bias concerning attributions of events, or a general predisposition in individuals who already have psychopathological tendencies, and/or recall the negative effects as more significant. As a result, the consumption of ecstasy is less likely to produce positive effects and more likely to produce ill-effects. Another possibility could be that some individuals may be more susceptible to the 'toxic' effects of ecstasy: both acute and chronic, as suggested from the correlation between scores on the 'MDMA side effects' subscale and negative life experiences. This could possibly suggest that short-term ill-effects of ecstasy might be a predictor of neurotoxic injury, as was found in the first study concerning higher acute symptoms which were related to higher psychopathological scores and long term effects attributable to ecstasy use (chapter 3).

To conclude, this study has shown that, contrary to some previous research, ecstasy users and ex-ecstasy users did not exhibit any selective cognitive deficits or report differential psychopathological profiles relative to polydrug controls. The ecstasy using groups may be showing cognitive deficits on tasks such as the AVLT and the TOL, (allowing for poor controls), but if so there does not appear to be performance differences between current ecstasy users and ex-ecstasy users. This is consistent with previous research, but again because of the probable methodological constraints here, it was difficult to gauge whether these potential problems were persistent. Thus there are some potentially important phenomena indicated here. However, overshadowing these notions, this study highlights the need to address the issue of a reliable control group for valid comparisons to establish the nature and persistency of the cognitive and behavioural effects of ecstasy and also the role of ecstasy in the context of polydrug use.

CHAPTER 6

Addressing the Methodological Issue of a Valid and Reliable Control Group:

Comparisons with a Drug-Naïve Control Group

INTRODUCTION

Findings from studies one and two (chapters 3 & 5) highlight some of the difficulties of using polydrug control groups in research, assessing the cognitive and psychopathological status of current and ex-ecstasy users. This has raised the question of the validity and reliability of the polydrug control group. Evidence to suggest that polydrug controls are exhibiting raised levels of psychopathology comes from comparisons in a number of subscales with normative data; polydrug controls showing elevated levels (chapter 5). Concerning cognitive performance, the polydrug control groups in both these studies (chapters 3 and 5) show subtle impairments. Evidence to suggest that polydrug controls may be showing slight cognitive impairments, comes from comparisons of memory recall scores on the AVLT with normative data, which indicate cognitive performance at the lower end of the normative performance spectrum (chapter 3 & 5). Additional evidence to suggest that the reason for the lack of statistical cognitive findings may be due to a poorly performing control group, is that, in the previous study (chapter 5), ecstasy users were actually showing signs of memory dysfunction on the delayed recall trial of the AVLT, since performances were lower than normative data (see chapter 5 for further details).

Past research assessing the cognitive effects associated with recreational ecstasy use, suggests that selective cognitive deficits occur in ecstasy users. However, many researchers highlight the possible effects of concomitant use of other drugs, especially cannabis, on cognitive performance (Gouzoulis-Mayfrank et al, 2002; Rodgers, 2000; Croft et al, 2001; Rodgers et al, 2001). For example, in a study by Morgan et al (2002) current ecstasy users were shown to have impairments in working memory and recall compared with drug-naïve controls, but not polydrug controls.

Similarly, research into the psychopathological profiles of ecstasy users also suggests that concomitant use of other drugs, specifically cannabis, may be crucial. Daumann et al (2001) found significant group differences on many subscales of the SCL-90-R (i.e. obsessive-compulsive disorder, anxiety, phobic anxiety, paranoid ideation) and its global severity index, between ecstasy users and drug-naïve controls, but not between ecstasy users and cannabis users. Also, any further differences in psychopathology between all three groups no longer remained after statistically controlling for cannabis. Morgan (1998) found differences in psychological measures between ecstasy users and non-drug users, but not polydrug controls.

Psychopathology in regular ecstasy users is even thought to be associated more with polydrug use generally. Morgan et al (2002) showed that no measure of past ecstasy use predicted psychopathological scores as measured by the SCL-90-R, whereas cannabis use did, and in some cases, so too did other drug use (e.g. poppers, amphetamine and cocaine). Whilst Parrott et al (2001) showed that psychological problems were evident in heavier ecstasy users, these users also reported the heaviest polydrug use, and psychopathological symptoms were also evident in polydrug users that had not used ecstasy.

It is apparent that polydrug use, and specifically cannabis use, is an important confound in studies concerning the cognitive impairments and psychological effects associated with recreational ecstasy use. Even though in previous studies within this thesis polydrug controls had used significantly less drugs than the ecstasy using groups, they still reported use of other drugs, specifically cannabis, amphetamine, cocaine and LSD. It is therefore possible that the use of these drugs contributed to cognitive impairment and possibly to the psychological symptoms in these polydrug controls, and as a result, any deficits in performance exhibited by the ecstasy using groups, would not have been statistically apparent compared to these control groups.

The present study sought to address this last issue by running a separate and additional control group consisting of drug naïve participants and statistically comparing their cognitive and psychological profiles, with the cognitive and psychological profiles of the ecstasy and polydrug using groups in the previous two empirical studies (i.e. data from chapters 3 and 5). The same cognitive test battery (AVLT, TOL, prose recall and prospective memory components taken from the RBMT) and BSI used in the previous study were employed for direct cognitive and psychopathological profile comparisons. Essentially this would provide two new sets of results. Firstly, this would allow exploration of any cognitive and psychological differences, between the new drug naïve controls, the polydrug controls and non-problematic and problematic ecstasy users from the first study (chapter 3; now to be referred to as comparison A). Secondly, it will be possible to make comparisons on performance between the new drug-naïve controls and the polydrug controls, current and ex-ecstasy users from the second empirical study (chapter 5; now to be referred to as comparison B). If the lack of any significant effects in the previous studies is due to impairments within polydrug controls, then it would be expected that ecstasy-using groups would exhibit higher psychopathological scores and cognitive deficits compared to the drug-naïve controls. If this

were the case, then it would support the notion that the cognitive and psychological effects associated with ecstasy are confounded by polydrug use. If significant differences are found between drug naïve and polydrug controls, this would provide evidence to suggest that polydrug use per se is problematic; contributing to cognitive deficits and elevated psychopathological symptoms.

METHOD

Participants

Subjects were recruited through an advertisement sent via e-mail around the University of East London. All participants were assessed for ratings of health, age, number of years in education and verbal IQ, as measured by the NART (Nelson, 1982). Participants were excluded from the study if they were first year undergraduate psychology students and those participants who reported any of the following: past history of any illicit drug use, head injury, depression, anxiety, obsessive compulsive disorder, schizophrenia or paranoia, panic attacks, eating disorders, alcohol or drug dependency.

Twenty subjects participated in this study (10 male, 10 female) all of whom had no current or past history of illicit drug use including cannabis.

Participants were formally assessed with a questionnaire, which consisted of personal details regarding their psychiatric history and that of their immediate family. The University of East London ethics committee approved the study. All participants gave written informed consent and were paid £10 each for participating.

Assessment Measures

Participant's alcohol and nicotine patterns were assessed using the relevant questions from the drug use questionnaire used in the previous studies.

Psychopathological status and cognitive performance were assessed using the same battery of assessment measures and in the same order of presentation as those used in chapter 5. This included the modified version of the BSI, the Prospective Memory tasks (RBMT, Wilson et al, 1991), the Auditory Verbal Learning Test (AVLT; Rey, 1964), Prose recall (immediate and delayed; RBMT, Wilson et al, 1991) and the Tower of London (TOL; Shallice, 1982), (see methodology section, chapter 5 for further detail).

Statistical Analysis

Data analysis was conducted using the Statistical SPSS 10. Data from the current drug naïve controls were combined with data from polydrug controls, problematic and non-problematic ecstasy users from chapter 3, to provide a new data set consisting of 4 experimental groups (comparison A). Data from the current drug naïve controls were also combined with the data from polydrug controls, current ecstasy and ex-ecstasy users from chapter 5, to provide another new data set, also consisting of 4 experimental groups (comparison B).

Prior to analysis the BSI data for comparison A were subjected to a square root transformation, since the data was markedly skewed with heterogeneous variances. All other data was used in is original form.

One-way ANOVAs were performed for all cognitive tasks (AVLT, TOL, prose recall and prospective memory), the BSI data, demographic and tobacco and alcohol data to assess whether there were any group differences between the four experimental groups in each study. Where there were violations of homogeneity of variance, the non-parametric Kruskall Wallis test was employed. Post Hoc analysis comprised of paired comparisons between groups using the Tukey's range statistic and the Mann-Whitney test for the non-parametric equivalent. For such pairwise tests a partial error correction was made, by dividing the standard error rate ($\alpha = 0.05$) by the number of groups in the analysis, in this case $\alpha/4 = 0.013$, to minimise the risk of type 1 errors. The Chi-squared test was used to establish any significant gender differences between groups.

Finally, to control for the significant group differences in age, data was re-analysed using analysis of covariance, to determine whether age was a statistically significant covariate, and if so, what effect this had on the statistical significance on any group differences. Again, co-variation for other drug use was not carried out for the reasons given in the discussion of chapter 3.

RESULTS

Comparison A: Drug naïve controls and data from chapter 3

Personal characteristics and drug data

Table 19 shows the demographic data and levels of tobacco and alcohol use for the current drug naïve control group as well as the data from chapter 3. Significant group differences were found with age [$F(3,70) = 3.19$, $p = 0.029$], with the drug-naive controls and polydrug controls being significantly younger than problematic ecstasy users. Differences were also evident with current rating of health [$F(3,70) = 6.04$, $p = 0.001$], with drug-naive controls reporting significantly better health than ecstasy and problematic ecstasy users. There were no significant group differences in gender and verbal IQ.

There were also significant group effects of tobacco use and alcohol consumption, [$\chi^2 = 23.17$, $p < 0.001$] and [$\chi^2 = 10.38$ $p = 0.016$] respectively. Drug-naive controls reported significantly lower levels of tobacco consumption compared to ecstasy and problematic ecstasy users. Polydrug controls also reported significantly lower levels of tobacco use compared to non-problematic ecstasy users. Drug-naïve controls also reported significantly less alcohol consumption than non-problematic ecstasy users.

Measures of psychopathology

Table 20 shows data for all the subscales of the modified version of the BSI for the current drug naïve control group and alongside the data from chapter 3. There were significant group differences on the following subscales: somatisation [$F(3,70) = 9.02$, $p = <0.001$], interpersonal sensitivity [$F(3,70) = 6.23$, $p = 0.001$], depression, [$F(3,70) = 6.90$, $p < 0.001$], anxiety [$F(3,70) = 7.92$, $p < 0.001$], phobic anxiety [$F(3,70) = 9.95$, $p = <0.001$], paranoid ideation [$F(3,70) = 6.88$, $p < 0.001$], psychoticism [$F(3,70) = 9.35$, $p < 0.001$], MDMA side effects [$F(3,70) = 4.47$, $p = 0.006$], cognitive failures [$F(3,70) = 6.56$, $p = 0.001$] and positive mood [$F(3,70) = 3.00$, $p = 0.036$].

Adjusted ANCOVA analyses were conducted on these significant BSI subscales, with age entered as a covariate, as there was a significant age difference in groups (see table 19).

These analyses revealed no change in the significant main effect of group on somatisation, interpersonal sensitivity, depression, anxiety phobic anxiety, psychoticism, MDMA side and cognitive failures (see table 44, appendix V for individual statistics). There was no change in the significant main effect of group on paranoid ideation subscale [$F(3,70) = 8.98$, $p < 0.001$], despite age showing a significant covariate [$F(1,73) = 5.34$, $p = 0.024$]. Finally, the adjusted ANOCVA model revealed that there was no longer a significant group effect on positive mood [$F(3,70) = 2.35$, $p = 0.08$), but this was change was not accounted for by age [$F(1,73) = 0.199$, $p = 0.657$].

Post hoc analyses showed that problematic ecstasy users scored significantly higher on interpersonal sensitivity, depression, anxiety, paranoid ideation and psychoticism compared to drug-naive controls, polydrug controls and problem free ecstasy users. They also scored significantly higher on MDMA side effects compared to drug-naive controls (figure 17); significantly higher than polydrug controls on somatisation (figure 19); and scored significantly higher on cognitive failures (figure 18) compared to polydrug controls and drug-naive controls. On the positive mood subscale, problematic ecstasy users scored significantly lower than drug-naive controls (figure 21).

Non-problematic ecstasy users scored significantly higher on somatisation (figure 19) and cognitive failures compared to drug-naive controls, but not polydrug controls. However, non-problematic ecstasy users scored significantly lower than drug-naïve controls and problematic ecstasy users on the phobic anxiety subscale.

Measures of cognitive performance

Table 21 shows all the cognitive assessment data for the current drug naïve control group together with the cognitive data from chapter 3. There were no significant group differences in prose recall (immediate and delayed), prospective memory, planning and solution times of the TOL. There were significant group differences with the number of errors made on the TOL [$F(2,70) = 2.89$, $p = 0.043$], with a trend showing both ecstasy using groups to have made more errors than drug naïve and polydrug controls, but these failed to reach significance on post hoc tests (figure 22).

On the AVLT there were significant group differences in the delayed recall trial [$F(3,73) = 3.22$, $p = 0.028$]. Polydrug controls were significantly impaired on delayed recall compared to drug-naïve controls (figure 23). Adjusted ANCOVA analyses were conducted on the AVLT delayed recall trial data, with age entered as a covariate, as there was a significant age difference in groups (see table 19). This adjusted model revealed no change in the significant main effect of group on the delayed recall trial [$F(3,73) = 3.169$, $p = 0.03$], after co-varying for age [$F(1,73) = 0.002$, $p = 0.964$].

Table 19. Comparison A: Group demographics and drug use data from chapter 3 and drug naïve controls (means and SDs).

	Drug-naïve Controls (C)	Polydrug Controls (P)	Non-problematic Ecstasy Users (E)	Problematic Ecstasy users (EP)	Group Effect p	Post Hoc Comparisons
Gender	10M / 10F	8M / 12F	13M / 7F	8M / 6F	0.444	
Age	24.90 ± 4.27	25.15 ± 3.87	25.70 ± 3.45	28.93 ± 4.94	0.029	C & P < EP
Verbal IQ	109.05 ± 4.26	111.65 ± 6.53	113.35 ± 4.52	113.07 ± 6.40	0.068	
Current rating of health	3.85 ± 0.37	3.45 ± 0.83	3.05 ± 0.76	2.86 ± 1.03	0.001	E & EP < C
Tobacco (Per day)	0.65 ± 2.00	3.85 ± 7.71	9.40 ± 6.67	8.50 ± 11.45	<0.001	C < E & EP; P < E
Alcohol (Units per week)	6.25 ± 7.76	10.45 ± 7.52	17.35 ± 13.22	10.50 ± 12.92	0.016	C < E

Table 20. Comparison A: Group BSI Scores from chapter 3 and drug naïve controls (means and SDs).

	Drug-naïve Controls (C)	Polydrug Controls (P)	Non-problematic Ecstasy Users (E)	Problematic Ecstasy users (EP)	Group Effect *p*	Post Hoc Comparisons
Negative symptoms						
Somatisation	0.22 ± 0.30	0.41 ± 0.37	0.52 ± 0.38	1.11 ± 0.78	<0.001	C < E & EP; P < EP
Obsessive-compulsive	0.78 ± 0.58	1.10 ± 0.66	1.31 ± 0.99	1.64 ± 0.88	0.059	
Interpersonal sensitivity	0.55 ± 0.49	0.81 ± 0.68	0.59 ± 0.54	1.75 ± 1.07	0.001	C, P & E < EP
Depression	0.34 ± 0.44	0.58 ± 0.64	0.44 ± 0.51	1.63 ± 1.30	<0.001	C, P & E < EP
Anxiety	0.37 ± 0.40	0.68 ± 0.66	0.44 ± 0.36	1.67 ± 1.23	<0.001	C, P & E < EP
Anger/hostility	0.55 ± 1.32	0.46 ± 0.33	0.65 ± 0.65	1.13 ± 1.02	0.076	
Phobic anxiety	0.48 ± 0.22	0.29 ± 0.33	0.14 ± 0.39	1.00 ± 1.07	<0.001	P < EP; E < C & EP
Paranoid ideation	0.65 ± 0.57	0.67 ± 0.45	0.68 ± 0.57	1.73 ± 0.97	<0.001	C, P & E < EP
Psychoticism	0.24 ± 0.36	0.45 ± 0.54	0.40 ± 0.41	1.29 ± 0.82	<0.001	C, P & E < EP
Negative psychobiology	0.60 ± 0.62	0.55 ± 0.39	0.64 ± 0.51	0.77 ± 0.39	0.377	
MDMA side effects	0.65 ± 0.44	1.05 ± 0.62	1.04 ± 0.72	1.56 ± 0.80	0.006	C < EP
Sexual functioning	0.40 ± 0.33	0.39 ± 0.36	0.38 ± 0.34	0.81 ± 0.74	0.335	
Cognitive failures	0.75 ± 0.56	1.22 ± 0.70	1.69 ± 0.94	2.01 ± 1.20	0.001	C < E & EP
Positive Symptoms						
Feeling content with life	2.61 ± 0.81	2.28 ± 0.82	2.38 ± 0.76	1.99 ± 0.99	0.183	
Mood state	2.38 ± 0.72	2.21 ± 0.74	2.24 ± 0.69	1.71 ± 0.87	0.036	EP < C
Sociability	2.10 ± 0.71	2.28 ± 0.52	2.44 ± 0.77	2.07 ± 0.94	0.341	
Positive psychobiology	2.58 ± 0.76	2.06 ± 0.62	2.23 ± 0.63	1.92 ± 1.13	0.063	

Table 21. Comparison A: Cognitive assessment data from chapter 3 and drug naïve controls (means and SDs).

	Drug-naïve Controls (C)	Polydrug Controls (P)	Non-problematic Ecstasy Users (E)	Problematic Ecstasy users (EP)	Group Effect *p*	Post Hoc Comparisons
Story recall						
Immediate	8.10 ± 2.99	7.65 ± 2.44	9.18± 2.75	7.64 ± 1.99	0.238	
Delayed	7.43 ± 2.69	6.73 ± 2.70	7.83 ± 3.14	6.86 ± 1.86	0.565	
Prospective memory						
Remembering an appointment	1.90 ± 0.31	1.80 ± 0.41	1.65 ± 0.49	1.86 ± 0.36	0.236	
Remembering a belonging	3.15 ± 0.75	3.70 ± 0.47	3.45 ± 0.76	3.29 ± 0.61	0.066	
Tower of London						
Planning times	6.83 ± 3.24	6.95 ± 2.17	6.07 ± 2.59	8.08 ± 3.72	0.285	
Solution times	4.52 ± 1.73	4.07 ± 0.89	3.91 ± 0.73	4.27 ± 1.30	0.422	
Errors	3.11 ± 1.71	2.80 ± 3.21	5.15 ± 3.79	4.43 ± 2.14	0.043	
Incomplete trials	0.30 ± 0.57	0.20 ± 0.41	0.20 ± 0.70	0.64 ± 0.74	0.148	
AVLT						
Immediate Recall						
Trial 1	6.10 ± 1.29	6.30 ± 1.79	6.75 ± 1.48	5.93 ± 1.77	0.443	
Trial 2	8.85 ± 1.57	8.80 ± 2.24	9.50 ± 1.88	8.57 ± 2.41	0.547	
Trial 3	10.45 ± 2.46	10.80 ± 2.67	10.35 ± 2.32	9.43 ± 2.95	0.495	
Trial 4	11.55 ± 1.70	10.80 ± 2.46	11.70 ± 1.95	11.00 ± 2.08	0.479	
Trial 5	12.10 ± 1.89	11.55 ± 2.26	11.60 ± 1.73	11.00 ± 2.72	0.531	
Interference Trial	4.70 ± 1.69	5.70 ± 2.64	4.80 ± 1.58	4.86 ± 2.25	0.405	
Trial 6	10.40 ± 2.68	9.10 ± 2.81	10.50 ± 2.95	9.79 ± 2.69	0.370	
Delayed Recall	9.55 ± 2.31	6.05 ± 5.60	9.15 ± 3.45	8.29 ± 3.32	0.028	C < P
Number of Repeats	6.35 ± 5.25	5.00 ± 5.48	6.55 ± 4.98	6.29 ± 15.59	0.932	
Intrusion from list A	0.20 ± 0.41	0.05 ± 0.22	0	0.43 ± 0.76	-[1]	
Intrusion from list B	0.25 ± 0.44	0.10 ± 0.31	0.10 ± 0.45	0	-[1]	

[1] Invalid analyses due to floor effects

Figure 17. Comparison A: Mean MDMA side effects in all four groups (Bars indicate 1 standard error of mean)

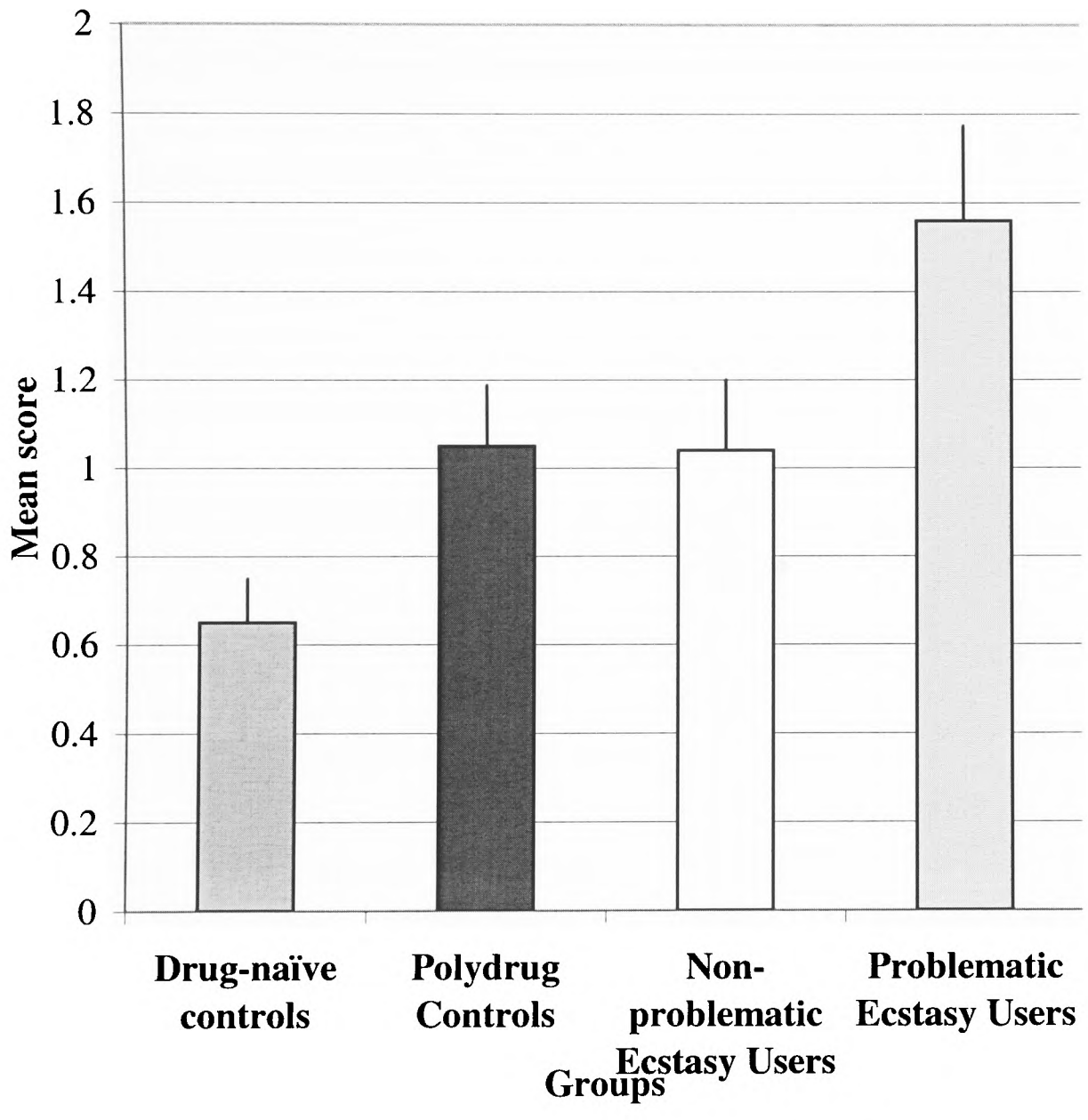


Figure 18. Comparison A: Mean cognitive failures in all groups (Bars indicate 1 standard error of mean)

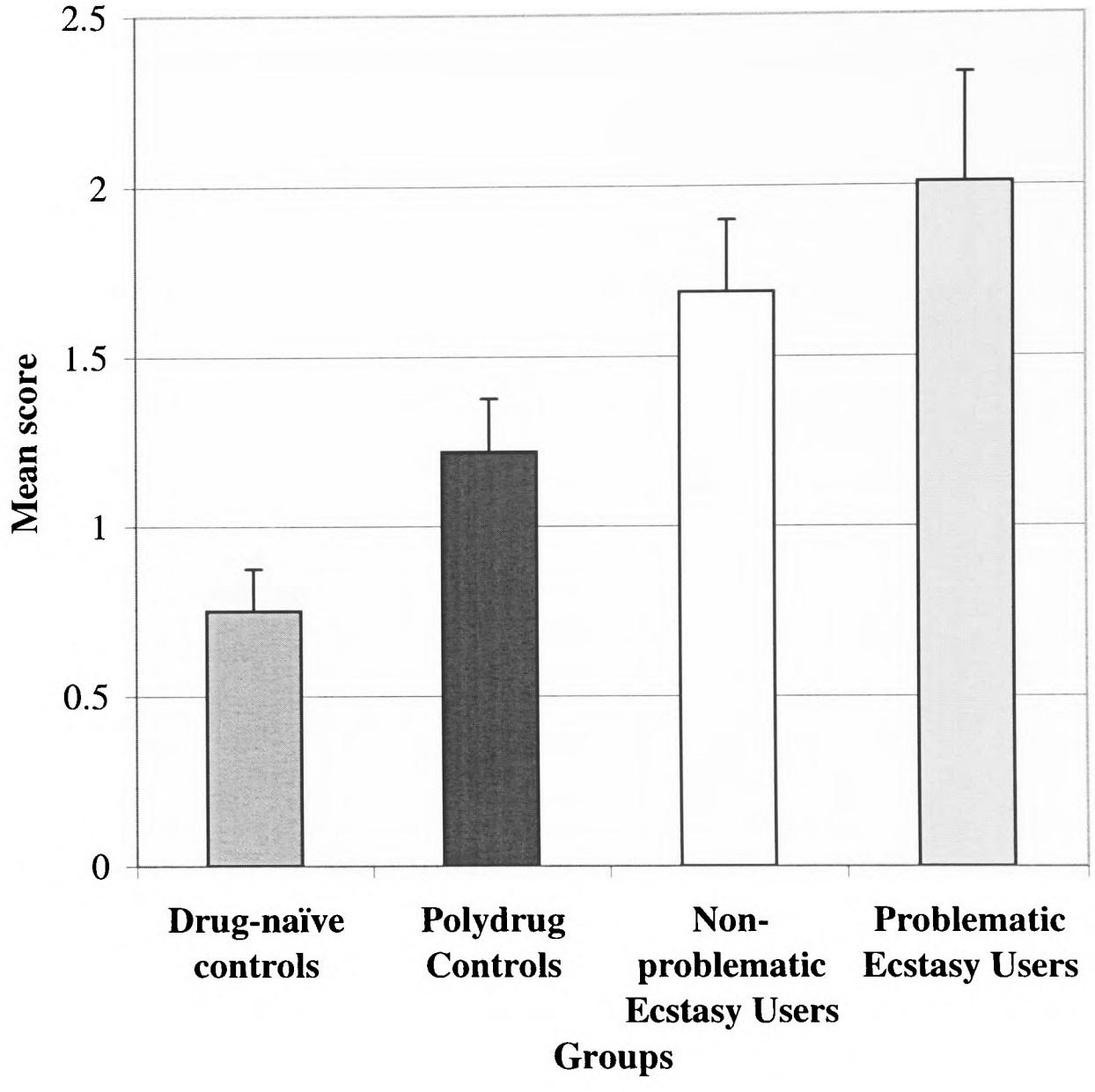


Figure 19. Comparison A: Mean BSI somatisation scores for all groups (Bars indicate 1 standard error of mean)

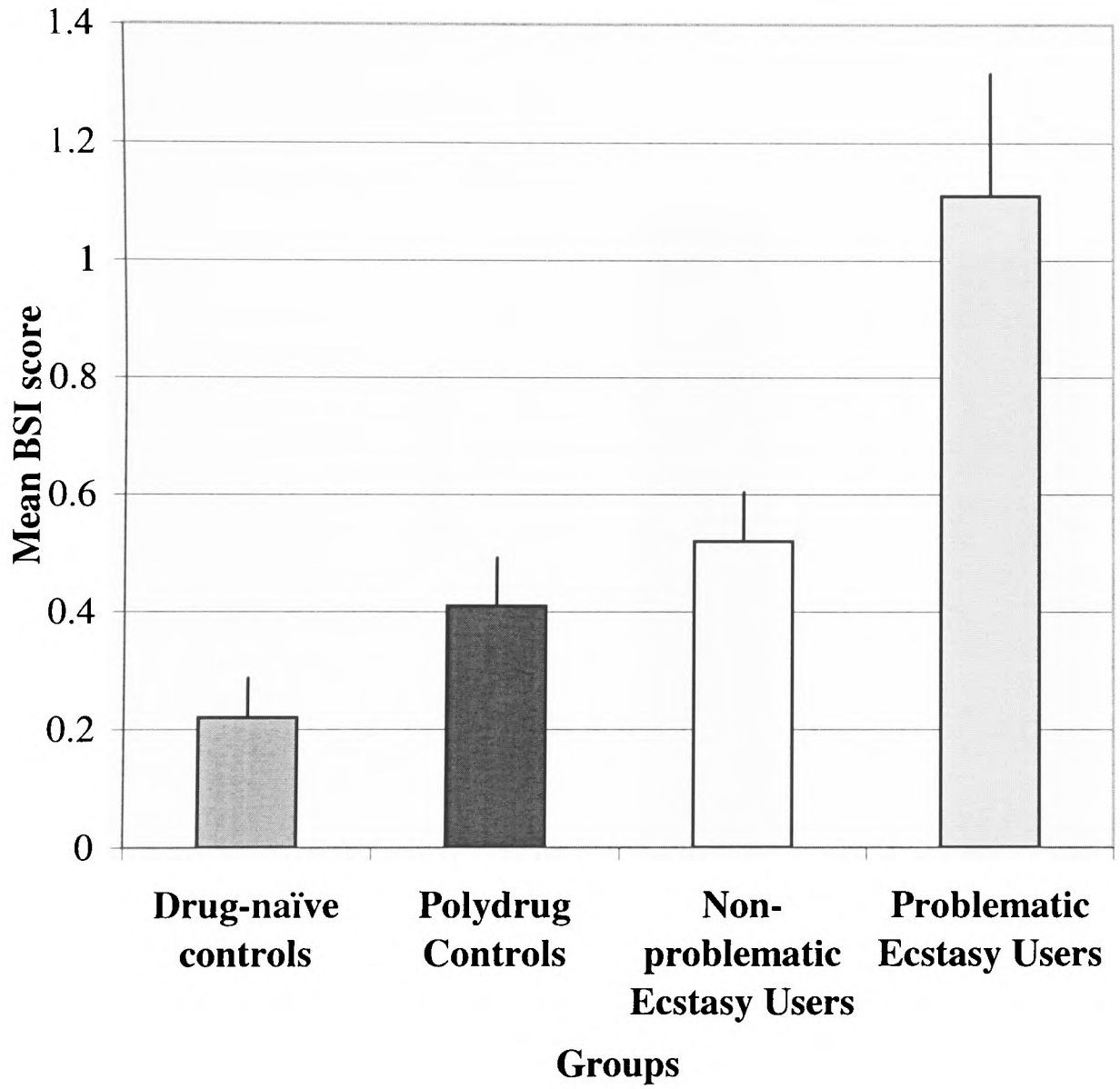


Figure 20. Comparison A: Mean BSI phobic anxiety scores for all groups (Bars indicate 1 standard error of mean)

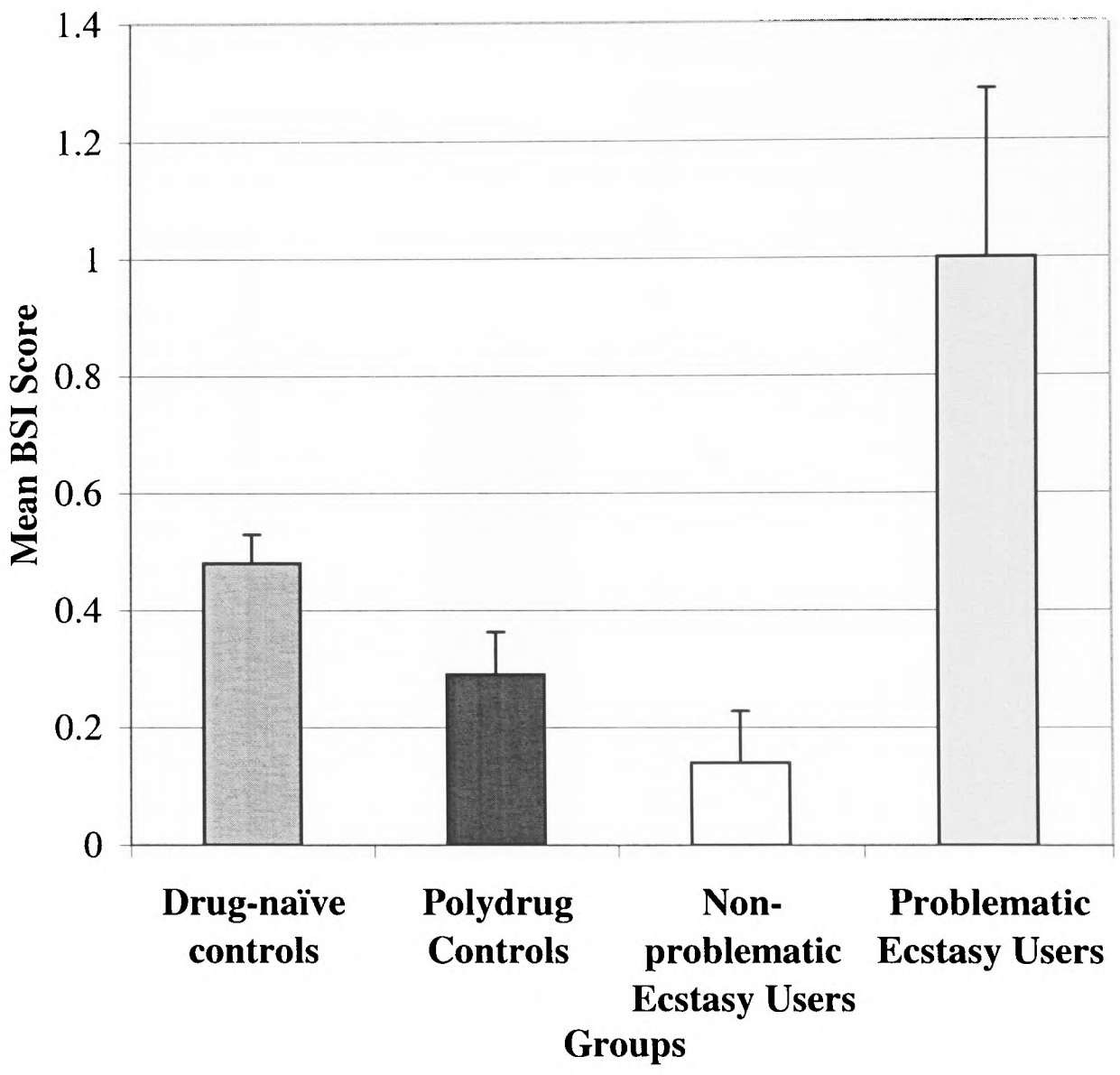


Figure 21. Comparison A: Mean BSI positive mood state scores
(Bars indicate 1 standard error of mean)

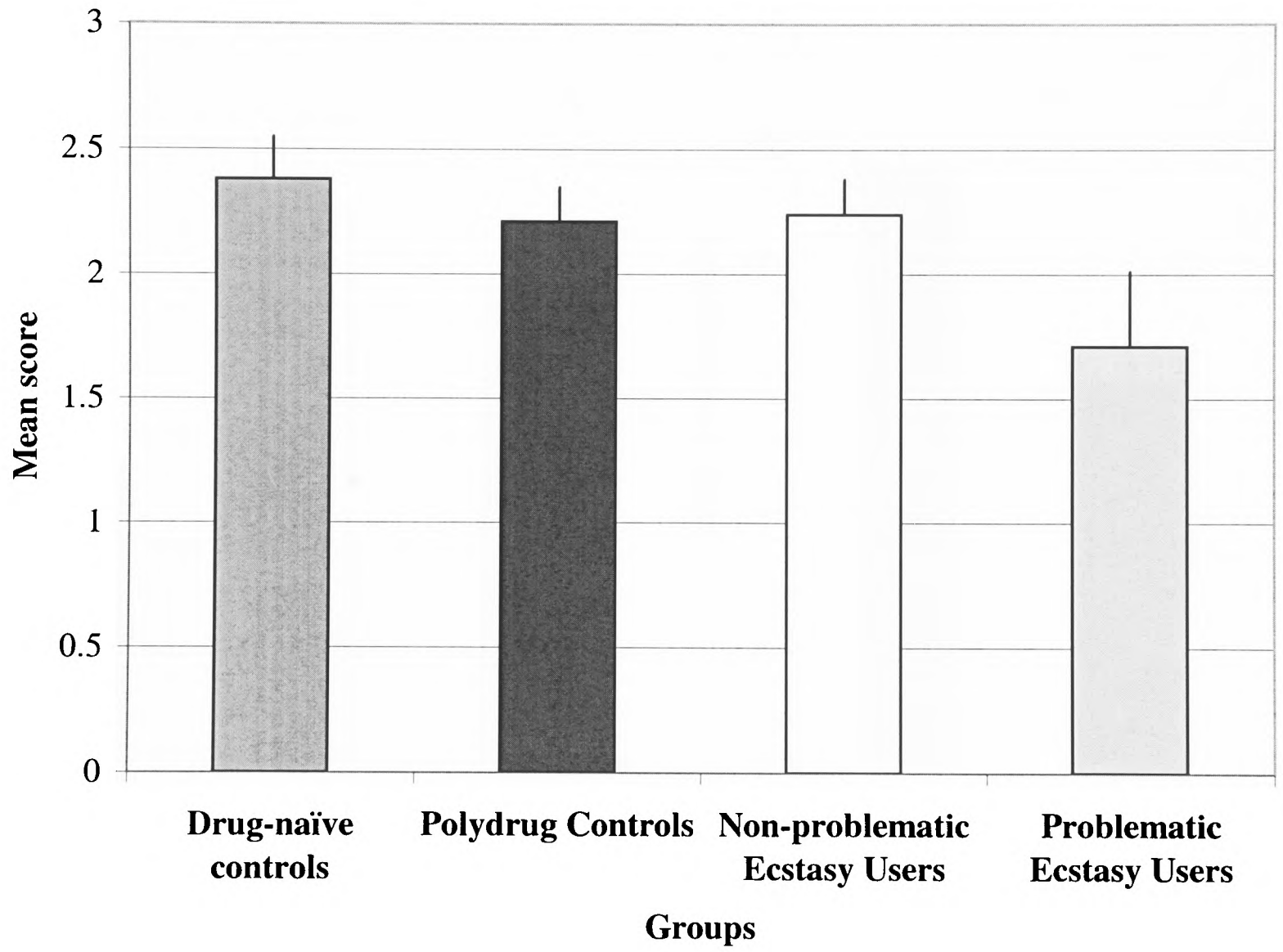


Figure 22. Comparison A: Mean errors made on the TOL (Bars indicate 1 standard error of mean)

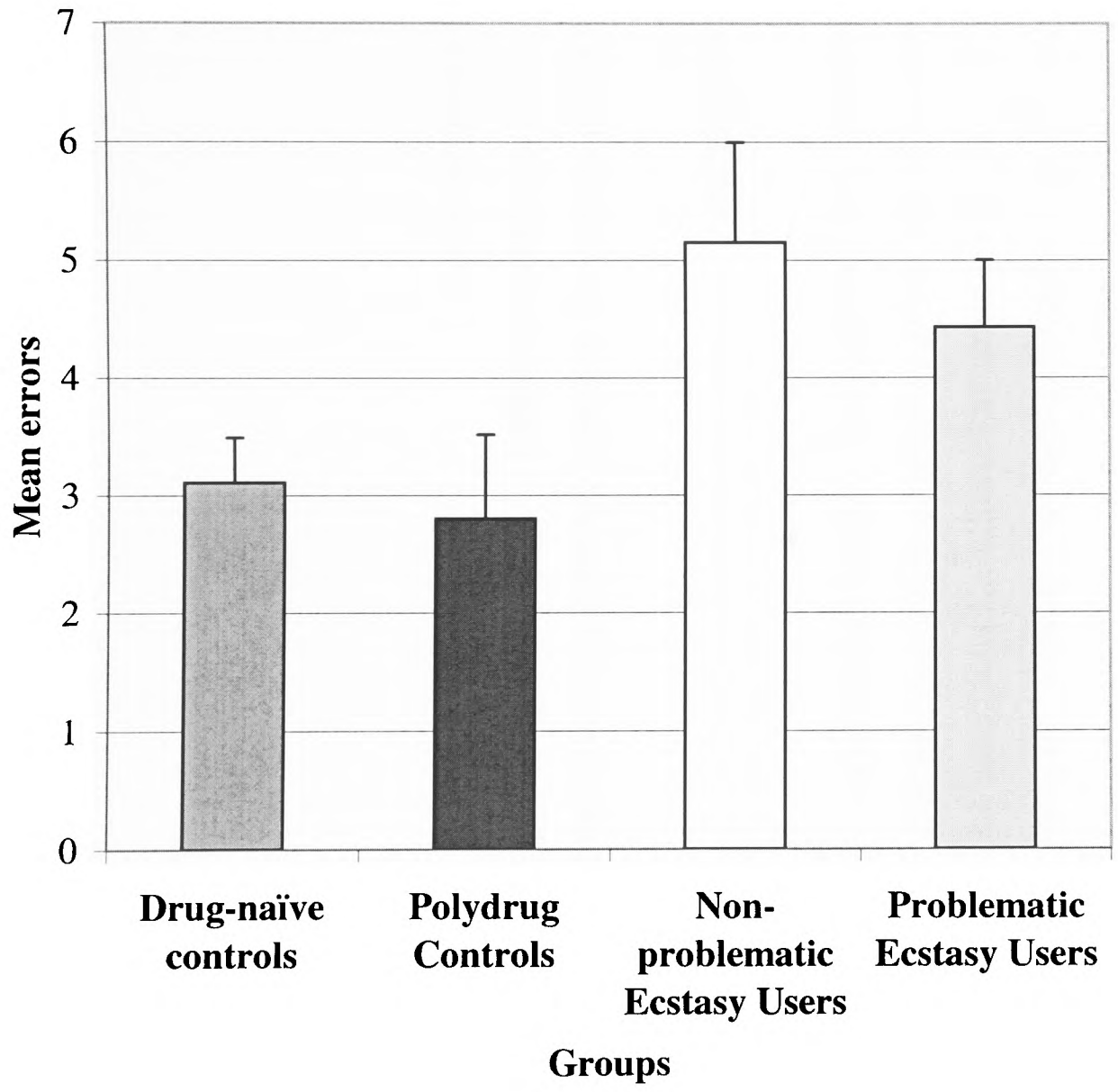
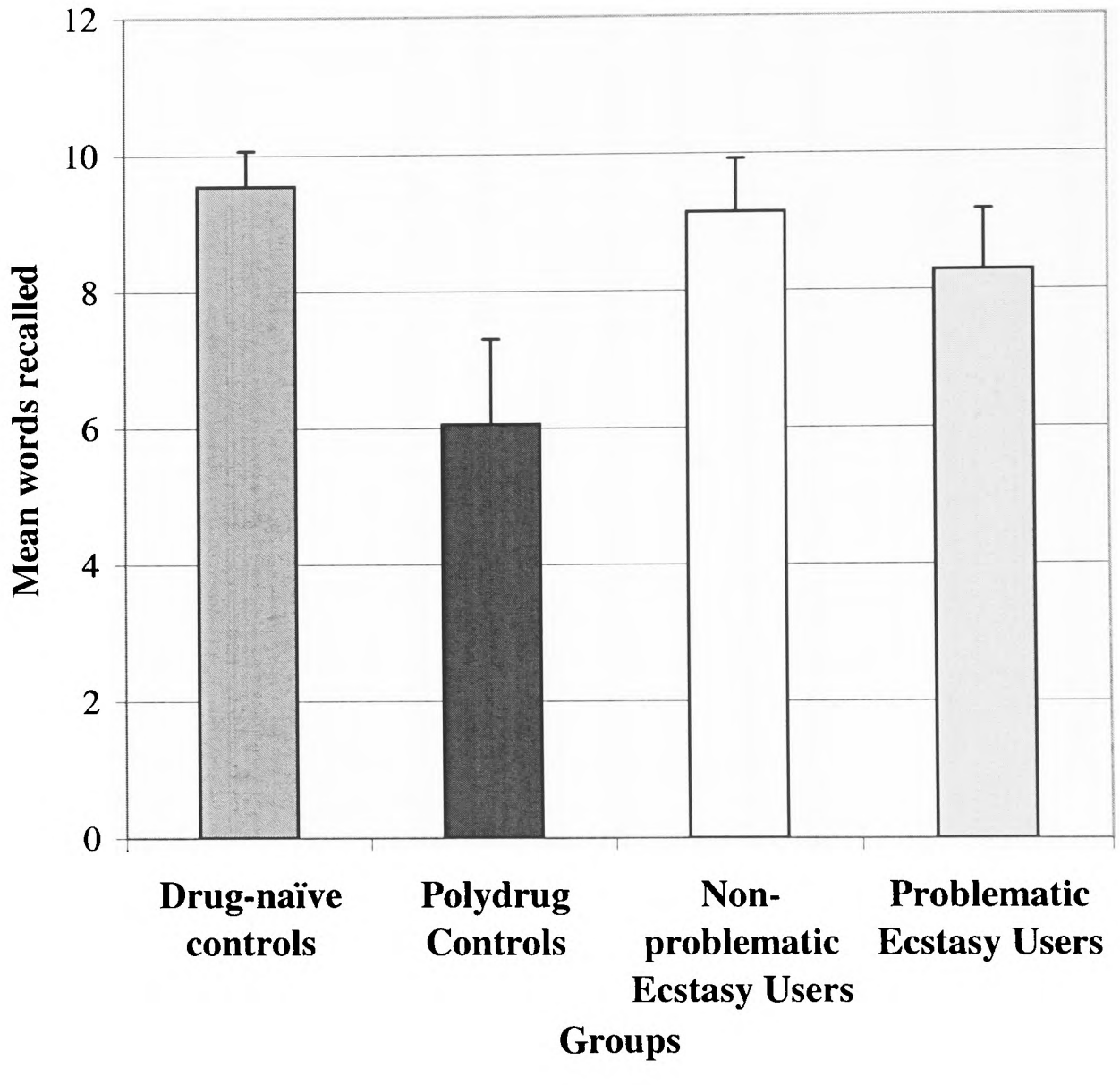


Figure 23. Comparison A: Mean delayed recall on the AVLT for all groups (Bars indicate 1 standard error of mean)



Comparison B: current drug naïve controls and data from chapter 5

Personal characteristics and drug data

Table 22 shows the demographic data and levels of alcohol and tobacco consumption for the current drug naïve controls, as well as the same data from the experimental groups in chapter 5. Significant group differences were found in current rating of health [$\chi^2 = 11.64$, $p = 0.009$], with drug-naive controls reporting significantly better health than current ecstasy users; and tobacco consumption [$\chi^2 = 25.31$ $p<0.001$] with drug-naive and polydrug controls consuming significantly lower amounts of tobacco per day compared to current and ex-ecstasy users. There were no significant group differences in age, gender and verbal IQ and alcohol consumption.

Measures of psychopathology

Table 23 shows data for all BSI subscales, for current drug naïve control group together with BSI data from chapter 5. Significant group differences were found on somatisation [$F(3,77) = 3.71$, $p = 0.015$] (figure 24), phobic anxiety [$F(3,77) = 10.03$, $p = <0.001$] (figure 25) and cognitive failures [$F(3,76) = 3.76$, $p = 0.014$] (figure 26) subscales. Drug-naive controls exhibited significantly lower scores on somatisation compared to current ecstasy users, significantly higher scores on phobic anxiety compared to polydrug controls, current and ex-ecstasy users; and significantly lower scores on the cognitive failures subscale.

Measures of cognitive performance

Table 24 indicates data for all cognitive assessment measures for the current drug naïve control group compared with the data from chapter 5. There were no significant group differences in any of the cognitive tasks.

Table 22. Comparison B: Group demographics and drug use data from chapter 5 and drug naïve controls (means and SDs).

	Drug-naïve Controls (C)	Polydrug Controls (P)	Current Ecstasy Users (E)	Ex-Ecstasy Users (Ex)	Group Effect p	Post Hoc Comparisons
Gender	10M / 10F[1]	6M / 14F	13M / 8F	14M / 6F	0.063	
Age	24.90 ± 4.27	27.95 ± 6.12	24.48 ± 3.4	27.1 ± 3.78	0.070	
Verbal IQ	109.05 ± 4.26	112.05 ± 7.48	111.57 ± 5.16	113.15 ± 4.36	0.116	
Current rating of health	3.85 ± 0.37	3.50 ± 0.69	3.29 ± 0.46	3.45 ± 0.69	0.009	E < C
Tobacco (Per day)	0.65 ± 2.00	3.30 ± 6.91	8.00 ± 6.46	12.25 ± 11.88	<0.001	C & P < E & Ex
Alcohol (Units per week)	6.25 ± 7.76	9.60 ± 10.15	14.43 ± 14.48	11.30 ± 11.62	0.232	

[1] M = male, F = Female

Table 23. Comparison B: Group BSI Scores from chapter 5 and drug naïve controls (means and SDs).

	Drug-naïve Controls (C)	Polydrug Controls (P)	Current Ecstasy Users (E)	Ex-Ecstasy Users (Ex)	Group Effect *p*	Post Hoc Comparisons
Negative symptoms						
Somatisation	0.22 ± 0.30	0.37 ± 0.34	0.63 ± 0.56	0.57 ± 0.50	0.015	C < E
Obsessive-compulsive	0.78 ± 0.58	1.05 ± 0.75	1.09 ± 0.73	1.28 ± 0.72	0.172	
Interpersonal sensitivity	0.55 ± 0.49	0.71 ± 0.70	0.69 ± 0.59	0.79 ± 0.60	0.649	
Depression	0.34 ± 0.44	0.53 ± 0.64	0.45 ± 0.63	0.65 ± 0.68	0.437	
Anxiety	0.37 ± 0.40	0.55 ± 0.68	0.56 ± 0.45	0.62 ± 0.56	0.483	
Anger/hostility	0.55 ± 1.32	0.49 ± 0.47	0.60 ± 0.49	0.67 ± 0.71`	0.914	
Phobic anxiety	0.48 ± 0.22	0.25 ± 0.30	0.13 ± 0.22	0.11 ± 0.21	<0.001	P,E & Ex < C
Paranoid ideation	0.65 ± 0.57	0.51 ± 0.38	0.58 ± 0.52	0.68 ± 0.73	0.781	
Psychoticism	0.24 ± 0.36	0.39 ± 0.56	0.41 ± 0.53	0.46 ± 0.46	0.515	
Negative psychobiology	0.60 ± 0.62	0.51 ± 0.38	0.49 ± 0.33	0.46 ± 0.42	0.934	
MDMA side effects	0.65 ± 0.44	0.99 ± 0.71	0.98 ± 0.68	1.04 ± 0.53	0.162	
Sexual functioning	0.40 ± 0.33	0.38 ± 0.34	0.59± 0.55	0.52 ± 0.48	0.340	
Cognitive failures	0.75 ± 0.56	1.14 ± 0.79	1.30 ± 0.76	1.51 ± 0.82	0.014	C < Ex
Positive Symptoms						
Feeling content with life	2.61 ± 0.81	2.40 ± 0.95	2.41 ± 0.94	2.49 ± 0.86	0.874	
Mood state	2.38 ± 0.72	2.30 ± 0.87	2.32 ± 0.87	2.37 ± 0.63	0.984	
Sociability	2.10 ± 0.71	2.22 ± 0.64	2.45 ± 0.77	2.43 ± 0.67	0.312	
Positive psychobiology	2.58 ± 0.76	2.22 ± 0.72	2.28 ± 0.88	2.36 ± 0.81	0.564	

Table 24. Comparison B: Cognitive assessment data from chapter 5 and drug naïve controls (means and SDs).

	Drug-naïve Controls (C)	Polydrug Controls (P)	Current Ecstasy Users (E)	Ex-Ecstasy Users (Ex)	Group Effect *p*
Story recall					
Immediate	8.10 ± 2.99	7.87 ± 2.95	8.33 ± 2.46	7.38 ± 2.50	0.714
Delayed	7.43 ± 2.69	7.15 ± 3.23	7.88 ± 2.91	6.33 ± 2.12	0.340
Prospective memory					
Remembering an appointment	1.90 ± 0.31	1.95 ± 0.22	2.00 ± 0.32	1.80 ± 0.52	0.434
Remembering a belonging	3.15 ± 0.75	3.35 ± 0.67	2.90 ± 0.89	3.25 ± 0.72	0.282
Tower of London					
Planning times	6.83 ± 3.24	7.48 ± 3.57	8.20 ± 4.23	9.31 ± 4.42	0.228
Solution times	4.52 ± 1.73	4.11 ± 0.96	3.78 ± 0.68	4.13 ± 1.81	0.398
Errors	3.11 ± 1.71	3.60 ± 3.71	3.90 ± 3.11	3.75 + 2.97	0.967
AVLT					
Immediate Recall Trial 1	6.10 ± 1.29	6.40 ± 1.79	6.19 ± 1.72	6.10 ± 2.00	0.939
Trial 2	8.85 ± 1.57	8.65 ± 2.62	9.48 ± 2.14	8.30 ± 1.92	0.338
Trial 3	10.45 ± 2.46	10.95 ± 2.58	10.33 ± 2.27	9.55 ± 2.16	0.318
Trial 4	11.55 ± 1.70	11.10 ± 2.65	11.43 ± 2.29	11.10 ± 1.65	0.870
Trial 5	12.10 ± 1.89	11.60 ± 2.44	11.62 ± 1.91	11.15 ± 1.98	0.551
Interference Trial	4.70 ± 1.69	5.45 ± 2.67	4.14 ± 1.28	4.40 ± 1.47	0.136
Trial 6	10.40 ± 2.68	9.70 ± 2.94	10.43 ± 2.62	10.1 ± 2.07	0.793
Delayed Recall	9.55 ± 2.31	10.30 ± 2.75	9.90 ± 2.13	9.25 ± 3.35	0.635
Number of Errors	1.65 ± 1.93	2.25 ± 2.59	1.57 ± 1.89	2.75 ± 3.26	0.391
Number of Repeats	6.35 ± 5.25	5.25 ± 4.39	4.43 ± 4.09	4.2 ± 3.76	0.406
Intrusion from list A	0.20 ± 0.41	0	0.0476 ± 0.22	0.10 ± 0.31	[2]
Intrusion from list B	0.25 ± 0.44	0.10 ± 0.31	0.19 ± 0.60	0.15 ± 0.37	0.750

[2] Invalid analyses due to floor effects

Figure 24. Comparison B: Mean BSI somatisation scores for all four groups (Bars indiatce 1 standard error of mean)

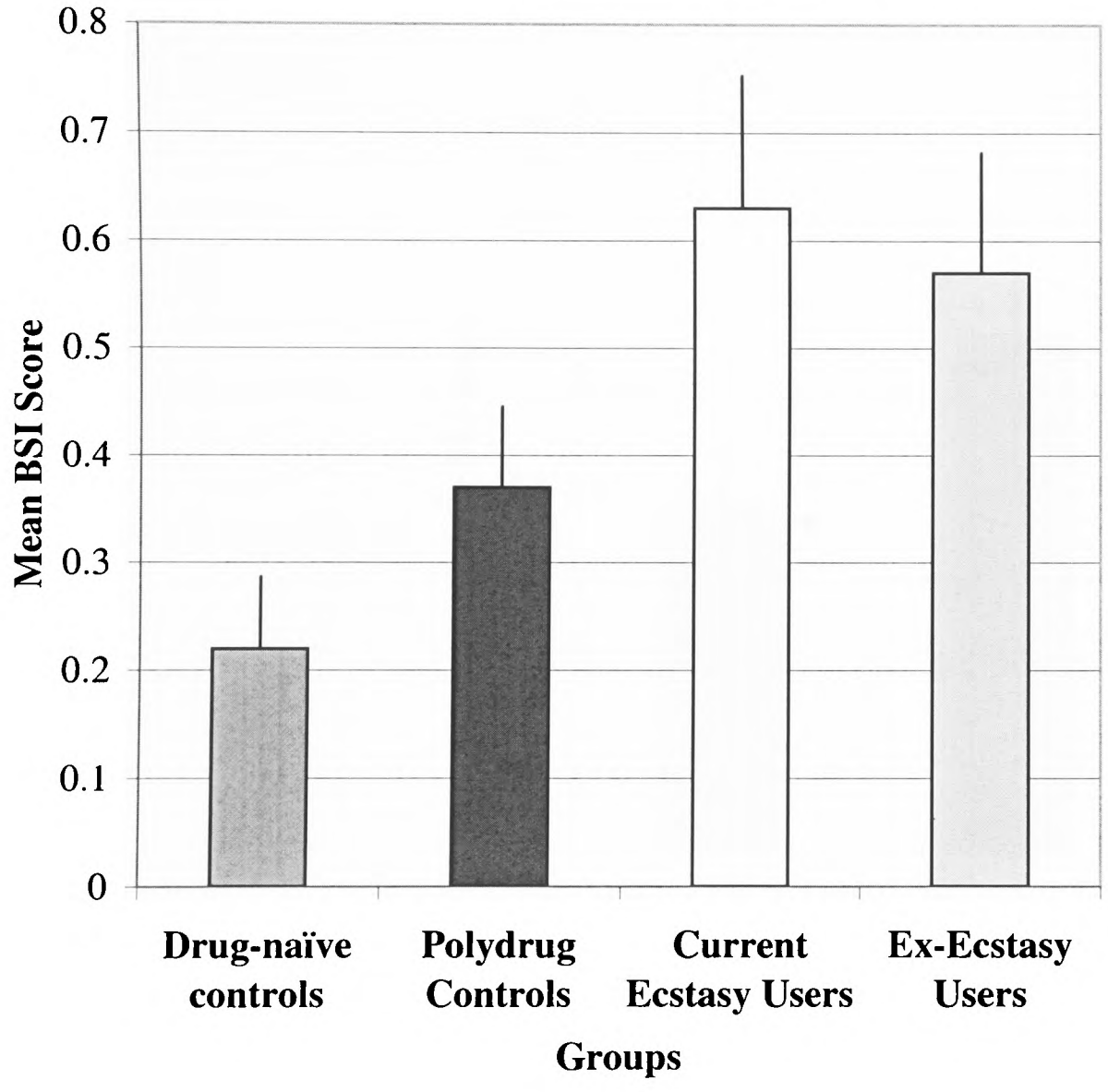


Figure 25. Comparison B: Mean BSI phobic anxiety scores for all four groups (Bars indicate 1 standard error of mean)

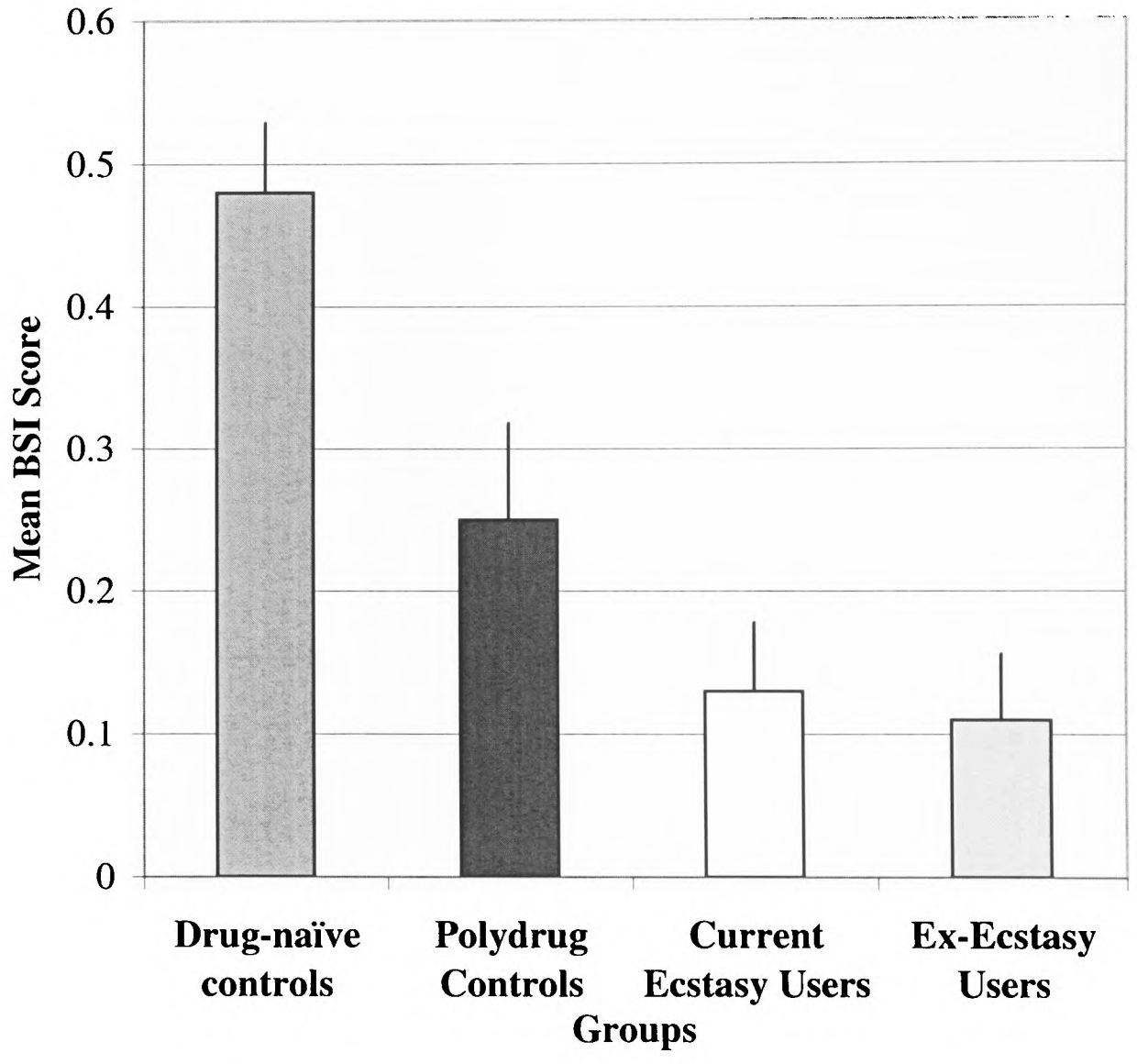
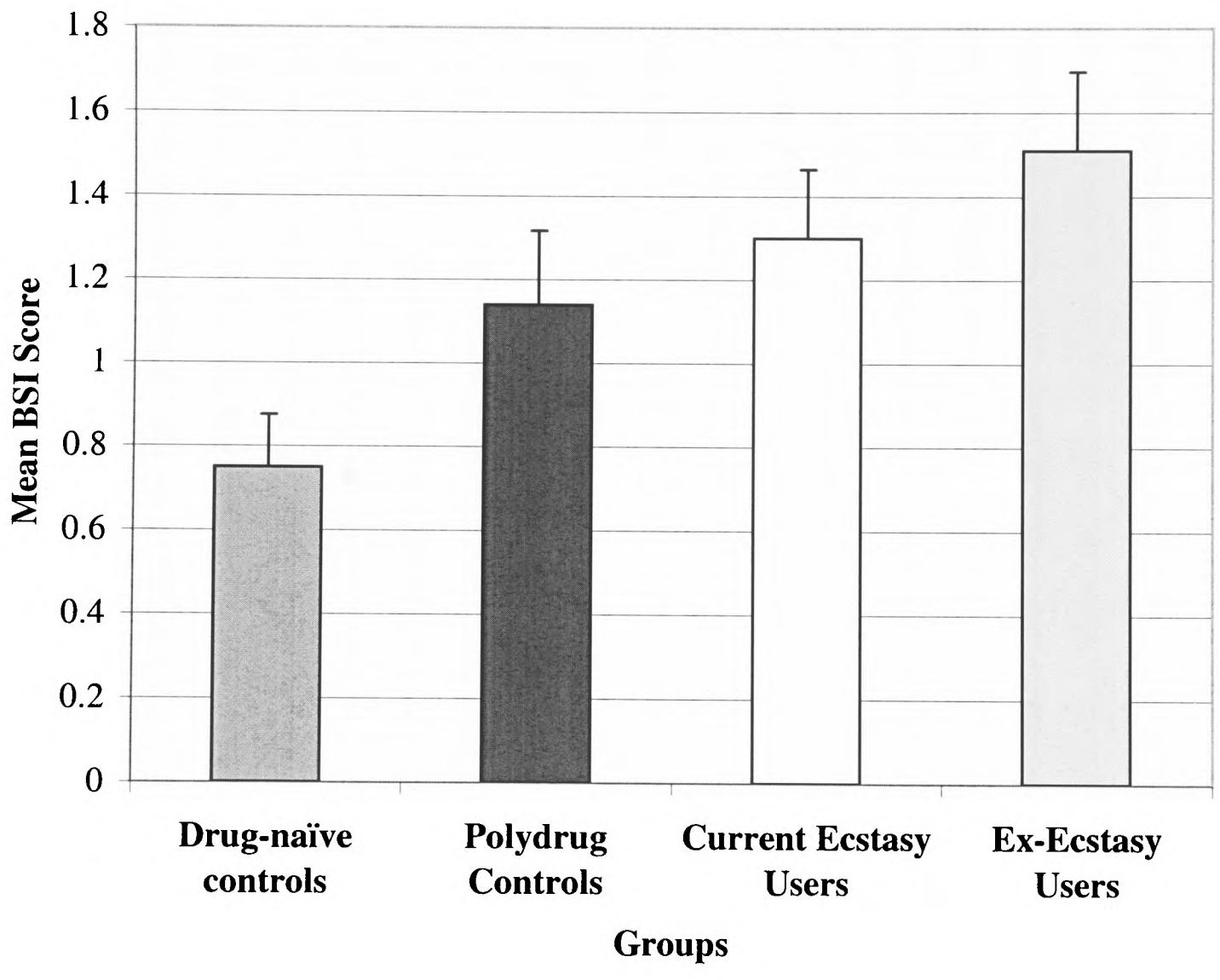


Figure 26. Comparison B: Mean cognitive failures in all four groups
(Bars indicate 1 standard error of mean)



DISCUSSION

The results of the current study concerning cognitive performance, indicates that with the introduction of a new drug-naïve control group, ecstasy users from the first empirical study (both non-problematic and problematic; chapter 3) were exhibiting trends of impairment in performance on the TOL; they were making more errors whilst completing the TOL compared to polydrug and drug-naïve controls. This may suggest that such impairments are selective problems of ecstasy use, since polydrug users did not show increased errors. This is consistent with previous evidence, where ecstasy users exhibited significantly more errors on completing a questionnaire than cannabis users (Rodgers et al, 2001), and significantly more errors on a spatial working memory task compared to polydrug users (Fox et al, 2002), and made significantly higher number of errors on the MFFT20 task compared to polydrug and drug-naïve controls (Morgan, 1998; Morgan et al, 2002). The fact that ecstasy users produce more errors on such cognitive tasks may indicate a lack of reflection (Rodgers et al, 2001) and be a manifestation of greater impulsivity in these users. Support for this later explanation comes from a study by Morgan (1998). Not only were an increased number of errors made by ecstasy users on the MFFT20 compared to polydrug and non-drug users, but ecstasy users also showed signs of elevated impulsivity on the Impulsivity, Venturesomeness and Empathy Questionnaire (IVE).

In the same comparison (A), it appears that polydrug controls from chapter 3 were also showing deficits on the delayed recall trial of the AVLT compared to drug-naïve controls (figure 23). This supports the suggestion that polydrug use may contribute to cognitive impairments. However, there were no impairments in any ecstasy user group compared to the drug-naïve controls, which suggests that in this case deficits may not be an artefact of polydrug use; especially since both ecstasy using groups used significantly higher amounts of other drugs than the polydrug controls. It is more likely that such deficits are caused by a factor independent to drug use. This finding does however support the notion that the polydrug control group in chapter 3, were showing memory deficits and this may account for the lack of evident memory deficits between the polydrug control group and ecstasy using groups. As such, this evidence strengthens the suggestion that the polydrug control group in that study (chapter 3) was not a reliable experimental group compared to previous research.

Concerning comparison B, the introduction of a new drug naïve control group did not demonstrate any statistical deficits in cognitive performance for both the polydrug and the ecstasy using groups from chapter 5. However, ex-ecstasy users reported significantly more cognitive failures than the drug naive controls (figure 26). This subjective reporting of cognitive deficits is not supported by the objective measures of cognitive performance. Ex-ecstasy users did not show signs of impairment on any of the cognitive tests. This disparity between subjective and objective measures of cognition, highlights the need to be cautious in relation to the reliability of self-report data concerning cognitive abilities in ecstasy users.

For the BSI data the results of the present study indicate that, that problematic ecstasy users (chapter 3 data) are now showing elevated symptoms on the MDMA side effects scale compared to drug-naive controls. These problematic users, who attributed their problems to ecstasy, also seemed to be showing increased reports of cognitive failures compared to polydrug and drug-naïve control groups. More importantly, non-problematic ecstasy users were displaying higher levels of somatisation and reported more cognitive failures compared to drug naïve controls only. This suggests that polydrug use causes somatisation symptoms, but only when used in conjunction with ecstasy, since there were no significant differences in this subscale between polydrug and drug naïve controls.

With the introduction of the new drug-naïve control group to the second empirical study (chapter 5; comparison B), current ecstasy users showed signs of elevated somatisation scores compared to drug naïve controls only. Again, this provides some evidence to suggest that polydrug use in conjunction with ecstasy causes significant somatisation effects, but not polydrug use alone. The second set of comparisons also showed that cognitive failures are perhaps more of an artefact of polydrug use, since polydrug users, current and ex-ecstasy users scored significantly higher numbers of cognitive failures than the drug-naïve controls, but did not differ from one another.

What is interesting to note is that the drug-naïve controls are themselves showing signs of phobic-anxiety, when compared to the groups from the first empirical study (chapter 3); they scored significantly higher than both ecstasy using groups and polydrug controls on this subscale of the BSI. This could be taken to suggest that ecstasy and polydrug use actually reduce the symptoms of phobic-anxiety, yet this is contrary to previous research where drug-

naïve controls have been shown to have reduced phobic-anxiety compared to ecstasy users (Parrott et al, 2001; Dugherio et al, 2001; Daumann et al, 2001 and Morgan et al, 2002).

The consistent new finding within the two new comparisons (A & B) of this chapter is that scores in (some) ecstasy users showed elevated somatisation scores (from both chapter 3 & 5) compared to drug-naive controls. This is consistent with findings of Parrott et al (2002), Morgan et al (2002) and Thomasius et al (2003). However, these studies also found ecstasy users to differ on other subscales of the SCL-90 and SCL-90-R compared to controls. The only ecstasy using group to show elevated signs of psychopathology in most scales of the BSI, within this current research programme, were those that reported problems from their ecstasy use. Thus, the psychopathological profile of problematic ecstasy users is actually closer to these previous findings, than is the case with the data from non-problematic users. This raises an important issue concerning the nature of those who choose to participate in 'ecstasy' research and whether participants perceive themselves to have problems or not, which they attribute to their ecstasy use (see chapter 8 for further discussion); such questions have not been addressed in previous research demonstrating elevated psychopathology in ecstasy users.

This study also highlights the effect ecstasy polydrug use has on reported ratings of health. Across both comparisons (A & B); ecstasy users (and problematic ecstasy users in comparison A) reported significantly poorer health compared to drug-naïve controls. Drug-naïve controls reported an average 3.85 on a rating scale from 1 to 4 (1 being bad health and 4 indicating good health). These findings support that of Morgan (1998) who found ecstasy users to display poorer health compared to non-drug users. Also, weight loss, infections, tremors and twitches (Parrott et al, 2002), lower back pain, headaches and stomach cramps (Cohen, 1995) have all been attributed to ecstasy use. Whether these health issues are a result of drug use or more to do with the lifestyle involved in recreational drug use is impossible to determine from this study, but this certainly warrants further investigation.

This current study attempted to address the validity of data in chapter 2 by determining whether ecstasy users showed signs of memory dysfunction and psychopathology. However, this has not been the case (with the exception of the somatisation symptoms – see above). The lack of significant findings between non-problematic ecstasy users and both polydrug controls and drug-naïve controls could suggest that regular ecstasy use is not always

associated with cognitive performance and psychopathology. There are other researchers that have failed to find cognitive deficits in ecstasy users compared to controls (Simon and Mattick, 2002; Gamma et al, 2001; Turner at al, 1998). One suggestion for this is that the MDMA content of ecstasy tablets has fallen and as a result ecstasy users are not necessarily consuming neurotoxic doses of MDMA, and hence are not showing any functional sequalae (Parrott, 2000). However, this is unlikely to be the case. Whilst acknowledging that the amounts of MDMA may be lower in ecstasy tablets compared to 10 years ago (Cole et al, 2002), ecstasy users within this research had consumed large amounts of the drug. In chapter 3, non-problematic ecstasy users reported a mean lifetime consumption of 264 tablets, and problematic ecstasy users reported 367 tables. In chapter 5, ecstasy users reported a mean lifetime consumption of 239 tablets, and ex-ecstasy users 185. In both these data sets, users had consumed similar amounts of ecstasy, and in some cases a lot more, compared to recent studies which have shown cognitive impairments in ecstasy users compared to drug naïve and polydrug controls (see, or example: Fox et al, 2001b & c; McCann et al, 2001; Reneman et al, 2001; Reneman et al, 2000; Gouzoulis-Mayfrank et al, 2000 and Morgan et al, 2002). It is therefore more likely that there is an alternative explanation for the non-significant findings in this study.

One explanation that could account for the lack of cognitive findings may lie in the reliability of the cognitive tests and the differences in administration between this study and other research. For example, with the AVLT administration, there is little uniformity in various procedural aspects, with varying rates of delayed recall from 15 to 40 minutes. There is also variation in filler activities between the last immediate recall trial and the delayed recall trial. In the studies detailed here (chapters 3 and 5) there was a large cognitive demand placed on participants between trial 6 and the delayed recall trial (with participants performing the prose recall task of the RBMT, the TOL and the NART in the interim), which may have affected consolidation of previously learnt material and hence produced difficulties in delayed recall. Such cognitive demands may be less in other studies which demonstrate deficits in delayed recall in ecstasy users compared to polydrug controls (e.g. Morgan, 1999; Fox et al, 2001c; Reneman et al, 2001).

The manual version of the TOL was used throughout this research. This is not a standardised test and is less commonly used within psychology research today, since more reliable computerised versions are available (e.g. CANTAB), which avoid variations in manual

dexterity. Finally, it has already been discussed in chapter 5 that the prospective memory components of the RBMT may not be sensitive enough alone as a measure for prospective memory, and it may have been more suitable to have used a graded measure of prospective memory; such as the PMQ which has previously been shown to indicate differences in ecstasy users compared to polydrug controls (Heffernan et al, 2001; Rodgers, 2000).

However, it is more likely that the inconsistent cognitive and psychobiological findings between ecstasy users, polydrug and drug naïve controls are due to atypical experimental group characteristics and performance. As previously discussed the drug naïve control group was actually showing higher symptom ratings related to phobic anxiety compared to ecstasy users. At the same time this drug naïve control group was actually performing lower than normative data on immediate recall of the AVLT, with immediate recall of 6.1 items out of 15: normative data suggests immediate recall should fall between the range of 6.3 and 7.8 (Lezak, 1995). Also, on recall scores of trial 5 of the AVLT, normative data indicates this should be between 12 and 14. However, drug naïve controls recalled at the low end of this spectrum with 12.1 words. Together, this data suggests the possibility that this drug naïve control group is not performing normally, or is, at least, at the very lower end of the normative spectrum. Thus any performance deficits in ecstasy user groups may be masked by poor cognitive performance in the drug-naïve control group. The question then arises, why are the control groups performing worse than expected?

One possible reason for the poor performance in the polydrug and drug-naïve controls found in this research could be due to sampling errors. Most of the polydrug control groups in the chapters 3 and 5, comprised predominantly of first year undergraduate psychology students. As part of a first year course requirement these students have to provide evidence of participating in three research studies in the academic year. Hence the reasons for taking part in this research differed to a majority of those who were allocated to the ecstasy using groups. This same issue was highlighted by Fox (2002) in her research, who also found such sampling errors. Those students who took part in the research as part of a course requirement were described as being far less motivated and focused than many of the ecstasy users who contributed. With this additional study incorporating a new control group of drug naïve participants, a concerted effort was made to avoid using these first year undergraduate psychology students, but the group was still made up of undergraduate students, who appeared more interested in taking part in research as a means to earning some money rather

than the research subject area itself. In contrast a majority of the ecstasy users were external volunteers, who had a vested interest in the study. Such motivational issues could, in these instances, have accounted for the discrepancies found in cognitive performance.

Therefore the most likely explanation for the atypical findings in the research conducted so far within this thesis, lies within methodological issues; specifically sampling errors with the control groups. As a result of the poor cognitive performance demonstrated by these groups (polydrug controls and drug naïve controls), cognitive deficits are not statistically evident in the ecstasy using groups. This is a more likely explanation to that originally proposed, which was that polydrug use in general produces cognitive deficits rather than ecstasy use. This raises the interesting possibility that the importance of controls is a testament to the relatively subtle deficits produced by ecstasy and other drug use. On one hand it could be argued that the subtle effects of ecstasy are not that important or more worryingly that the cognitive effects of ecstasy can easily go unnoticed.

The atypical findings with regard to psychopathological status are harder to account for using the explanation of an impaired control group. It is perhaps more likely, that polydrug use accounts for some of the discrepancies in the data. But most importantly, the individual's self-perception of problematic ecstasy use plays an important role, since the highest psychopathological symptoms have been found in ecstasy users who report problems which they specifically attribute to ecstasy use.

CHAPTER 7

Differences in Attributional Style Between Problematic and Non-Problematic Ecstasy Users: Locus of Control and Drug Attributions

INTRODUCTION

According to the data from these empirical studies, non-problematic ecstasy users do not appear to be demonstrating any significant cognitive differences compared to polydrug controls or drug-naïve controls. Non-problematic ecstasy users only displayed elevated levels of somatisation when compared to a group of drug-naïve controls (chapter 6), but no signs of psychopathology compared to polydrug controls. In these studies, the only sample of ecstasy users that appear to be showing any signs of psychopathological symptoms, are those that reported problems which they attributed to their ecstasy use (chapter 3 & chapter 4). The fact that these reported problems and their psychopathological status were independent of their patterns of ecstasy consumption highlighted the need for further investigation into the possible reasons underlying problematic ecstasy use. The aim of this current study therefore, is to explore one possible personality trait, which may contribute or help us understand the reporting of such problems, specifically in this group of ecstasy users.

In the first study, individuals were self-selecting themselves into problematic or non-problematic ecstasy using groups, on the basis that they experienced problems, which they *attributed* to their ecstasy use. This has lead to the suggestion that premorbid personality characteristics may play a role in attributing problems to ecstasy use. In a study by Dughiero et al (2001), psychopathological characteristics of ecstasy users were assessed with respect to premorbid personality traits as measured by the Cloninger Tridimensional Personality Questionnaire. Ecstasy users showed higher novelty-seeking scores compared to controls and in addition, showed higher scores than controls on the obsession-compulsion, phobic anxiety, psychoticism and sleep disturbance subscales of the SCL-90. MacInnes et al (2001) showed higher levels of depression, as measured by the Beck's Depression Inventory, in ecstasy users compared to non-drug using controls. These levels of depression were positively correlated with an external locus of control and self-report measures of life stress. Both these studies demonstrated differences in certain measures of personality, between ecstasy users and controls. However, neither studies addressed whether the ecstasy users self-perceived themselves as being problematic or not, or whether high levels of certain personality traits were more of less associated with possible ecstasy-induced problems.

Fox et al (2001a) addressed the issue concerning the self-perception of problems attributable to past ecstasy use, by examining differences in a group of problematic and non-problematic

ecstasy users in relation to both drug consumption and premorbid life adjustment variables. As with chapter 3, they found no group differences in relation to quantity and pattern of ecstasy use or in personal and family psychiatric history, yet problematic ecstasy users reported experiencing a greater number of negative interpersonal experiences prior to taking ecstasy. This finding suggests the need for the assessment of premorbid criteria when looking at problematic ecstasy use.

The present study sought to establish whether certain premorbid personality factors were important in contributing towards whether ecstasy users report problems, which they attribute to past ecstasy use. One particular personality characteristic that may be of importance is whether individuals attribute events to factors outside of their control e.g. externally, or attribute events to factors with their own control e.g. internally. This personality construct is referred to as the locus of control (LOC). It is thought to be a stable attribute of an individual's personality (Rotter, 1966) and is derived from the Social Learning Theory of personality (Rotter, 1954). He argues that for behaviour to occur in any specific psychological situation, there needs to be an expectancy that that behaviour will lead to a particular reinforcement in that situation. External LOC individuals believe reinforcers to be controlled by outside forces, such as luck, fate, the environment, powerful others or other factors outside their own control. Whereas, internal LOC individuals believe that reinforcers are controlled from within, contingent on their own actions or enduring personality characteristics (Rotter, 1966).

There has been considerable interest in the role of this personality construct and psychological distress, with the belief that individuals who have more of an external control orientation are likely to report higher levels of psychopathology and maladjustment than those with an internal control orientation. Amongst psychiatric inpatients, external LOC has been seen to be related to greater psychopathology (Archer, 1980). Amongst non-patient populations, studies have shown that LOC has tended to be positively correlated with psychological distress (D'Arcy & Siddique, 1984; Young & Washburn, 1992) and psychopathology (Hale & Cochran, 1987; Young & Washburn, 1992; Petrosky & Birkimer, 1991; Hoehn-Saric & McLeod, 1985; Archer, 1980). O'Leary et al (1976) examined the role of this personality construct amongst alcoholics. Alcoholics with an internal LOC exhibited the least psychopathology, whilst the greatest levels of psychopathology were found amongst alcoholics with an external LOC. A more recent study on inpatients, demonstrated that an

external LOC orientation for substance use behaviour was related to more days in treatment and a general external locus of control for life events; whilst an internal LOC was related to high self-efficacy for avoidance of drug use (Malin & Fordham, 2002). Taken together this research suggests that individuals, who exhibit psychological distress and drug using individuals, tend to have more of an external LOC orientation.

Fox et al (2001a) appears to support this notion in some respect by showing a difference between individual's perceptions of problems compared to the actual experience of problems. They suggested that problematic ecstasy users are attributing symptoms to their ecstasy usage, despite reporting a greater number of negative interpersonal experiences prior to taking ecstasy. Thus the main aim of the current study was to assess the relationship between self-reported problematic ecstasy use and the potential issue as to whether these individuals are attributing these problems to factors that are outside of their personal control (e.g. their ecstasy consumption), rather than attributing their problems to something that they have personal control over, i.e. LOC.

The present study also sought to investigate further the issue of polydrug use with regard to long term psychological effects reported by recreational drug users. Previous research suggests that the heavier the polydrug use alongside ecstasy, the higher the level of self-reported psychological symptoms as measured by the SCL-90 (Parrott et al, 2001). In addition, Morgan et al (2002) reported that psychopathology amongst ecstasy users was more associated with polydrug use rather than ecstasy per se. Thus, the present investigation was also an exploratory study, which sought to determine which drugs, if any, were associated with the long-term effects reported by some ecstasy-polydrug users. This was achieved by asking volunteers to indicate which drug or drug combinations, if any, they attributed to changes in their life experiences. These long-term changes in life experiences, where those that were used in the positive and negative effects scale in chapter 3.

The current study comprised a large scale survey, which included the personal history and drug use questionnaires used in the previous studies. The drug use questionnaire was slightly amended to include two new questions covering the frequency of ecstasy use and problematic use. The response options for the questions concerning the positive and negative changes in life experiences were also amended to allow for individuals to indicate which other drugs they attributed these changes too, if any, rather than just ecstasy use. The extent, to which

individuals attribute control to themselves, or to external factors, was assessed using the Locus of Control Scale (Rotter, 1966). This scale was used, based on the established literature concerning psychopathological symptoms and drug using population samples. Psychopathological status was assessed using the BSI, as used in previous studies. However, the subscale concerning MDMA effects was omitted, since it was seen that these items are associated more with the acute effects of ecstasy rather than the long-term effects and thus deemed as unnecessary for the aim of this particular study.

The grouping criteria used, within this study, consisted of ecstasy users who reported psychobiological problems that they attributed to their past ecstasy use (problematic ecstasy users), ecstasy users that did not report any problems from their usage (non-problematic ecstasy users), a polydrug group who had not used ecstasy (polydrug controls) and a non-drug using group who had not used any illicit substances (drug-naïve control group). A non-drug using group was included in this study, because conclusions from the previous study concerning polydrug and ecstasy using groups are flawed. The drug-naïve group did not follow exactly the same experimental protocol as many of the experimental groups they were subsequently compared to. As such, some group differences or lack of them may, in part, have been due to different demand characteristics and the different paradigms.

It is predicted that ecstasy users who report problems attributable to their past ecstasy use will report significantly higher psychopathological symptom scores than non-problem ecstasy users, who will also report greater psychopathological symptoms compared to polydrug controls and non-drug users. It is also predicted that problematic ecstasy users will differ significantly to non-problematic ecstasy users on the Locus of Control Scale (indicating a differing attributional style); demonstrating a higher external locus of control. The study also aims to explore which drugs, if any, are attributed to differing positive and negative life experiences,

METHOD

Participants

Participants were recruited through a number of techniques[1], including recruitment notices throughout the University of East London's e-mail system, posters around the University of East London and various clubs throughout London, and via an advertisement in the 'Big Issue' magazine (appendix P). First year undergraduate psychology students, who volunteered for the study, did so as part of a course requirement.

Two-hundred and eighty-eight volunteers participated in the study: 111 (37 male, 74 female) drug naïve participants, who reported no past drug use other than alcohol and nicotine; 62 (27 male, 35 female) polydrug users who had no history of ecstasy use but otherwise had used other illicit drugs; 62 (33 male, 29 female) ecstasy users, who reported ecstasy and other polydrug use but did not report problems from their past ecstasy use; and 53 (25 male, 28 female) problematic ecstasy users, who reported ecstasy and other polydrug use and also indicated that they had experienced problems which they attributed to ecstasy use. All participants were allocated to these groups using a post hoc method. Problematic ecstasy users were distinguished from non-problematic users by answering 'yes' to the question, 'Have you experienced any problems, which you attribute to your ecstasy use?' All participants gave written informed consent (see appendix Z) and The University of East London ethics committee approved the study (see appendix U for the application for ethical approval and confirmation of approval).

Assessment Measures

Drug Use

Each volunteer completed a questionnaire using either a hard copy (n= 46) or accessed and submitted on-line (n=242) via http://homepages.uel.ac.uk/K.Soar/ecstasy_qa.htm (part of the

University of East London's web-site). This questionnaire consisted of the same questions used in chapters 3, 5 and 6 linked to drug, alcohol and tobacco use. It was slightly modified to assess volunteers' current cannabis use and also address volunteers' past cannabis use. Questions regarding levels and patterns of ecstasy use were also taken from the previous studies in this thesis, with the addition of two new questions: the first assessing the frequency of ecstasy use and the second which allowed post hoc group allocation to problematic or non-problematic ecstasy groups (see above for question). All participants were then asked to indicate whether or not they had experienced a list of 7 positive and 21 negative changes in their life and which, if any, of six drugs (ecstasy, amphetamine, cocaine, LSD, cannabis and alcohol), they attributed this change to (appendix F).

Brief Symptom Inventory

Psychopathological status was assessed using the modified version of the BSI as used in previous studies, with the omission of the MDMA side effects subscale.

Locus of Control Scale (LOC; Rotter, 1966).

This scale is a 29-item, forced-choice test including 6 filler items, where participants had to select one statement of each pair (and only one), which they strongly believed to be the case. In some instances, both statements or neither statement may be believed in, in which case participants were instructed to select the one that they most strongly believed to be the case. The total score is the number of external choices made.

Statistical Analysis

Data analysis was conducted using SPSS 10. One-way ANOVAs were performed on the BSI data, demographic data and LOC scores to assess whether there were any group differences between drug-naïve, polydrug controls, ecstasy users and problematic ecstasy users. Where there were violations of homogeneity of variance (e.g. age and rating of health) the Kruskall Wallis test was employed. Post hoc analyses comprised of paired comparisons between

[1] The proportion of participants recruited by each source is unknown, due to the majority of participants completing the on-line questionnaire; which did not require individuals to indicate the manner in which they had heard about the study.

groups using the Tukey's HSD range statistic and Mann-Whitney test for the non-parametric equivalent. For these pairwise comparisons error corrections were employed by dividing the standard error rate ($\alpha = 0.05$) by the number of groups in the analysis, in this case $\alpha/3 = 0.017$, to reduce the risk of type 1 errors. Chi-squared was used to investigate any significant group differences with questions regarding gender, ethnicity, reported psychiatric history and family psychiatric history.

Drug use data violated the assumption of homogeneity of variance, despite attempts at transforming the data. Therefore Kruskall Wallis tests were employed. The independent samples t-test was used to assess differences in patterns of ecstasy use between the two ecstasy using groups.

To control for the significant group differences in age, data was re-analysed using analysis of covariance, to determine whether age was a statistically significant covariate, and if so, what effect this had on the statistical significance of any group differences. Again, co-variation for other drug use was not carried out for reasons given in the discussion of chapter 3.

After collapsing the two ecstasy using groups into one group named 'ecstasy users', Pearson Product Moment Correlational Analyses were conducted to assess the association between patterns of ecstasy use and scores on the LOC questionnaire and scores on the BSI. There were no statistical corrections made to these analyse to control for type 1 errors, thus it is important to note that significant findings should be treated with extreme caution due to the large number of correlations and potential chance occurrences.

Data concerning the positive and negative changes to life experiences and which, if any, drugs they attributed these changes to, are reported as percentages (tables 31-34; appendices). It was deemed inappropriate to conduct detailed inferential analyses on all of this data for a number of reasons. The first was that levels of drug use differed considerably across all four drug using groups. Secondly, respondents sometimes indicated more than one drug for each dimension on the questionnaire, yet it was difficult to establish whether they were referring to polydrug use as contributing to this change or whether individual drugs per se contributed to this change. Thirdly, not all cells were independent. Finally, if a chi squared test was conducted the expected frequency would be less than 5 on more than 20% of cases; therefore it would not have been statistically viable. However, data concerning the number of

respondents, in each of the four groups, who indicated they had experienced a change were analysed using a 4 x 2 Chi Squared test. Separate 2 x 2 Chi Square tests were used to establish between, which of the four groups, any statistical significant differences were. A significant level of 0.008 was used, in order to limit the possibilities of type 1 errors. For those respondents in the drug using groups who did indicate a change attributable to drug use, a 3 x 2 Chi Squared test was utilised to establish whether there were any significant differences between the number of respondents in each group who indicated more than one drug as indicative of positive and negative changes. Separate 2 x 2 chi square tests were used to establish which groups differed with the significance level set at 0.02 to limit any type 1 errors.

RESULTS

Group characteristics and drug data

Tables 25 and 26 show the demographic data for the participants, patterns of drug use and reported psychiatric history. There were no significant group differences for gender or health. However, there was a significant group effect of age [$\chi^2(3) = 19.51$, $p<0.001$], as non-problematic ecstasy users were significantly older than drug-naïve controls ($p=<0.001$). There was a significant difference in reported psychiatric history ($\chi^2(3) = 30.71$, $p<0.001$) and family psychiatric history ($\chi^2(3) = 18.84$, $p<0.001$), with a greater number of problematic ecstasy users reporting a psychiatric history compared to controls and ecstasy users (table 26). There was also a significant difference in ethnicity between groups ($\chi^2(12) = 45.78$, $p<0.001$), with drug naïve participants showing greater ethnic diversity than non-problematic ecstasy and problematic ecstasy users (see table 42 in appendix).

There were significant group differences on most levels of reported illegal drug consumption, amphetamine ($\chi^2(2) = 69.05$, $p<0.001$), cocaine ($\chi^2(2) = 68.97$, $p<0.001$), crack ($\chi^2(2) = 13.08$, $p = 0.001$), LSD ($\chi^2(2) = 60.93$, $p<0.001$), magic mushrooms ($\chi^2(2) = 43.37$, $p<0.001$), poppers ($\chi^2(2) = 57.01$, $p<0.001$), ketamine ($\chi^2(2) = 37.39$, $p<0.001$) and current ($\chi^2(2) = 11.42$, $p = 0.003$) and past cannabis use ($\chi^2(2) = 12.84$, $p = 0.002$), see table 25. Specifically, polydrug controls reported using significantly less amphetamine, cocaine, LSD, magic mushrooms, poppers, ketamine and current cannabis use, compared to non-problematic ecstasy and problematic ecstasy users; and significantly less crack and past cannabis use compared to problematic ecstasy users. Non-problematic ecstasy and problematic ecstasy users reported similar consumption of illegal drugs, with the exception of LSD and magic mushrooms, where the problem ecstasy group reported a significantly greater consumption of both drugs.

Drug naïve participants reported significantly less tobacco and alcohol use compared to polydrug controls, non-problematic ecstasy and problematic ecstasy users ($\chi^2(3) = 78.23$, $p<0.001$). Polydrug controls also reported significantly less tobacco use compared to non-problematic ecstasy and problematic ecstasy users, as well as significantly less alcohol use compared to ecstasy users ($\chi^2(3) = 75.04$, $p<0.001$).

Patterns of ecstasy use differed between the two ecstasy using groups. Problematic ecstasy users reported significantly higher lifetime consumption levels of ecstasy [$t(113) = -2.31$, $p = 0.025$] , average dosage levels [$t(109) = -3.09$, $p = 0.003$] and maximum dosage levels [$t(109) = -2.90$, $p = 0.005$] compared to non-problematic ecstasy users. However, there were no significant differences in duration of ecstasy use and length of abstinence periods from ecstasy use between the two ecstasy using groups (see table 25).

Problematic ecstasy users were also asked to indicate whether they had sought some form of help for their attributed problems (table 27). 32.1% (n = 17) reported that they had and, as shown in table 27, the most common help sought was from a GP (26.4%). 11.3% sought help from a psychiatrist and 9.4% sought help from a clinical psychologist or drugs service. The final 11.3% sought help from a variety of other organisations, which included counselling services.

Group differences

Locus of Control

Figure 27 illustrates the scores obtained on the LOC questionnaire for all four groups. Problematic ecstasy users scored lower than drug-naïve, polydrug controls and non-problematic ecstasy users, indicating a higher external LOC. However, this difference did not reach statistical significance [$F(3,284) = 1.226$, $p = 0.300$]. In order to further assess whether LOC was associated with problematic attributions, rather than ecstasy use, a post hoc ANOVA was conducted on LOC scores, using five groups by separating the problematic ecstasy users into two groups; those who reported problems and those who reported problems but had sought some form of help for them (consistent with the criteria from chapter 3). Data (see appendix; table 40) indicated that those problematic ecstasy users who had sought help for their attributed problems, reported a higher external locus of control compared to all other groups, including problematic ecstasy users who just self-reported problems and had not sought help. Again, these differences did not reach statistical significance [$F (4, 284) = 0.994$, $p = 0.411$], (see appendix; figure 33).

Table 25: Group demographics, drug use data and patterns of ecstasy use in drug-naïve, polydrug users, non-problematic and problematic ecstasy users

	Drug Naïve (N)	Non-ecstasy Polydrug Users (C)	Non-problematic Ecstasy users (E)	Problematic ecstasy users (P)	Group effect	Post Hoc Comparisons
Gender	37 M / 74 F	27 M / 35 F	33 M / 29 F	25 M / 28 F	0.065	
Age	23.72 ± 6.79	25.55 ± 7.02	25.24 ± 4.22	25.74 ± 5.14	<0.001	N < E
Current rating of health	3.34 ± 0.80	3.16 ± 0.96	3.15 ± 0.70	3.13 ± 0.79	0.269	
Patterns of ecstasy use:						
Average dose	-	-	1.82 ± 1.07	2.89 ± 2.25	0.003	E < P
Maximum dosage	-	-	4.19 ± 3.08	6.56 ± 5.38	0.005	E < P
Total consumption	-	-	117.27 ± 273.48	404.61 ± 871.36	0.025	E < P
Duration of ecstasy use (months)	-	-	59.30 ± 42.34	75.02 ± 47.55	0.075	
Months since last used	-	-	13.94 ± 20.40	17.22 ± 28.91	0.493	
Other drug use:						
Amphetamine	0	2.06 ± 5.69	26.58 ± 36.35	73.45 ± 154.39	<0.001	C < E, P
Cocaine	0	3.50 ± 13.64	24.48 ± 39.85	74.13 ± 273.74	<0.001	C < E, P
Crack	0	0	0.11 ± 0.45	2.23 ± 13.76	0.001	C < P
Opiates	0	0.10 ± 0.53	0.23 ± 0.58	1.17 ± 4.07	0.058	
Benzodiazepines	0	0.85 ± 3.84	2.11 ± 7.40	3.68 ± 8.43	0.005	
LSD	0	0.27 ± 1.33	8.11 ± 13.99	70.84 ± 278.80	<0.001	C < E, P : E < P
Magic Mushrooms	0	1.08 ± 4.41	15.18 ± 67.74	179.04 ± 733.17	<0.001	C < E, P : E < P
Solvents	0	0.15 ± 0.81	0.68 ± 3.86	10.00 ± 43.47	0.004	
Poppers	0	1.02 ± 2.83	28.85 ± 126.95	14.17 ± 19.16	<0.001	C < E, P
Ketamine	0	0	2.13 ± 10.23	5.66 ± 16.33	<0.001	C < E, P
Prozac	0	0.10 ± 0.56	0.18 ± 0.78	0.25 ± 1.65	0.662	
GHB	0	0	0.18 ± 0.92	3.06 ± 20.60	0.053	
Others	0	0.19 ± 0.94	0.18 ± 1.09	0	0.292	
Tobacco (per day)	0.80 ± 3.67	3.55 ± 5.76	6.84 ± 7.95	6.53 ± 7.18	<0.001	N < C, E, P : C < E, P
Alcohol (units per week)	4.16 ± 7.83	9.00 ± 10.99	15.02 ± 9.56	13.23 ± 14.45	<0.001	N < C, E, P : C < E
Current cannabis use (no. per month x no. years)	0	564.97 ± 2349.78	990.19 ± 1639.99	1092.91 ± 1709.50	0.003	C < E, P
Past cannabis use (no per month x no. years)	0	239.71 ± 429.09	956.83 ±2053.35	1238.07 ± 1846.14	0.002	C < P

Table 26: Reported psychiatric and family psychiatric histories for drug-naïve, polydrug users, non-problematic and problematic ecstasy users

	Participants				Immediate Family			
	Drug naïve	Polydrug users	Ecstasy users	Problem users	Drug naïve	Polydrug users	Ecstasy users	Problem users
Anxiety	3	4	6	14	5	12	5	19
Depression	9	9	14	22	31	22	22	32
Obsessive-compulsive disorder	0	1	0	1	0	2	2	2
Schizophrenia	0	0	0	1	1	2	4	5
Phobia	2	0	3	4	3	2	0	2
Panic Attacks	1	2	3	16	6	7	6	14
Eating Disorder	6	4	1	6	5	5	4	8
Alcohol and/or drug dependency	1	0	3	3	10	7	6	11

Table 27: Professional organisations where help/advice was sought by problematic ecstasy users

	% of problem users reported contacting organisation
General Practioner	26.4%
Clinical Psychologist	9.4%
Psychiatrist	11.3%
Drugs clinic/services	9.4%
Other	11.3%

Measures of psychopathology

Table 28 shows the group scores for all the subscales of the modified version of the BSI. With the negative subscales; problematic ecstasy users reported significantly higher levels of somatisation [$F(3,284) = 4.35$, $p = 0.005$] and negative psychobiology [$F(3,284) = 5.96$, $p = 0.001$] compared to drug naïve, polydrug controls and non-problematic ecstasy users (figures 28 & 29). Adjusted ANCOVA analyses, with age as a covariate (since age has shown to differ between groups - see table 25) showed there were no changes to the main effect of group on somatisation [$F(3,284) = 4.58$, $p = 0.004$], after co-varying for age [$F(1,286) = 1.68$, $p = 0.197$); and no change to the main effect of group on negative psychobiology [$F(3,284) = 6.33$, $p < 0.001$], after co-varying for age [$F(1,286) = 1.78$, $p = 0.183$].

Problematic ecstasy users reported significantly higher levels of depression [$F(3,284)=3.60$, $p=0.014$] and anxiety [$F(3,284) = 5.94$, $p = 0.001$] compared to drug-naïve and non-problematic ecstasy users (Figures 30 & 31). These main effects of group on depression [$F(3,284) = 3.68$, $p = 0.013$] and anxiety [$F(3,284) = 5.95$, $p = 0.001$] remained after co-varying for age.

Problematic ecstasy users and polydrug controls reported significantly higher obsessive-compulsive scores [$F(3,284) = 4.65$, $p = 0.003$] and cognitive failures [$F(3,284) = 5.09$, $p = 0.002$] compared to drug naïve participants. These main effects of group on obsessive-compulsive scores [$F(3,284) = 4.49$, $p = 0.004$] and cognitive failures [$F(3,284) = 5.05$, $p = 0.002$] remained after co-varying for age.

All drug using groups (polydrug controls; problematic and non-problematic ecstasy users) reported higher levels of sexual dysfunction compared to drug-naïve controls [$F(3,284) = 9.16$, $p<0.001$] (figure 32). Adjusted ANCOVA analyses showed that despite the covariate, age being significant [$F(1,286) = 5.26$, $p = 0.023$], the main effect of group on sexual dysfunction remained [$F(3,284) = 10.27$, $p <0.001$].

Finally, there were significant group differences on the anger subscale [$F(3,284) = 2.70$, $p = 0.046$], with drug-naïve controls showing lower scores than polydrug, non-problematic and

Table 28: Mean scores (SDs) across all dimensions for drug-naïve, polydrug controls, non-problematic and problematic ecstasy users

Symptom	Drug Naïve [N]	Polydrug Controls [C]	Non-problematic Ecstasy users [E]	Problematic ecstasy users [P]	Group Effect	Post Hoc Comparisons
Negative Symptoms						
Somatisation	0.46 ± 0.53	0.48 ± 0.56	0.45 ± 0.49	0.77 ± 0.64	0.005	N, C & E < P
Obsessive-compulsive	1.05 ± 0.77	1.41 ± 0.92	1.21 ± 0.74	1.47 ± 0.76	0.003	N < C & P
Interpersonal sensitivity	0.98 ± 0.89	1.14 ± 0.96	1.04 ± 0.88	1.38 ± 0.92	0.062	
Depression	0.69 ± 0.78	0.83 ± 0.82	0.74 ± 0.69	1.11 ± 0.89	0.014	N & E < P
Anxiety	0.63 ± 0.65	0.83 ± 0.87	0.63 ± 0.65	1.11 ± 0.82	0.001	N & E < P
Anger/hostility	0.65 ± 0.69	0.95 ± 0.89	0.81 ± 0.83	0.97 ± 0.91	0.046	
Phobic anxiety	0.37 ± 0.56	0.47 ± 0.71	0.36 ± 0.55	0.54 ± 0.69	0.285	
Paranoid ideation	0.88 ± 0.78	1.03 ± 0.86	0.85 ± 0.75	1.06 ± 0.75	0.306	
Psychoticism	0.58 ± 0.68	0.65 ± 0.74	0.66 ± 0.70	0.83 ± 0.77	0.216	
Negative psychobiology	0.86 ± 0.70	1.05 ± 0.84	0.99 ± 0.67	1.39 ± 0.84	0.001	N, C & E < P
Sexual functioning	0.47 ± 0.41	0.73 ± 0.55	0.76 ± 0.44	0.82 ± 0.58	<0.001	N < C, E & P
Cognitive failures	1.18 ± 0.98	1.66 ± 1.04	1.45 ± 1.00	1.73 ± 0.94	0.002	N < C & P
Positive Symptoms						
Feeling content with life	2.33 ± 0.91	2.22 ± 0.75	2.47 ± 0.71	2.23 ± 0.75	0.304	
Positive Mood state	1.92 ± 0.79	1.94 ± 0.73	2.34 ± 0.63	2.07 ± 0.83	0.004	N & C < E
Sociability	2.12 ± 0.80	2.28 ± 0.96	2.47 ± 0.72	2.29 ± 0.71	0.030	N < E
Positive psychobiology	2.17 ± 0.82	2.07 ± 0.66	2.37 ± 0.70	2.17 ± 0.73	0.164	

Figure 27: Mean scores on the LOC scale for all four groups. (Bars indicate 1 standard error of mean)

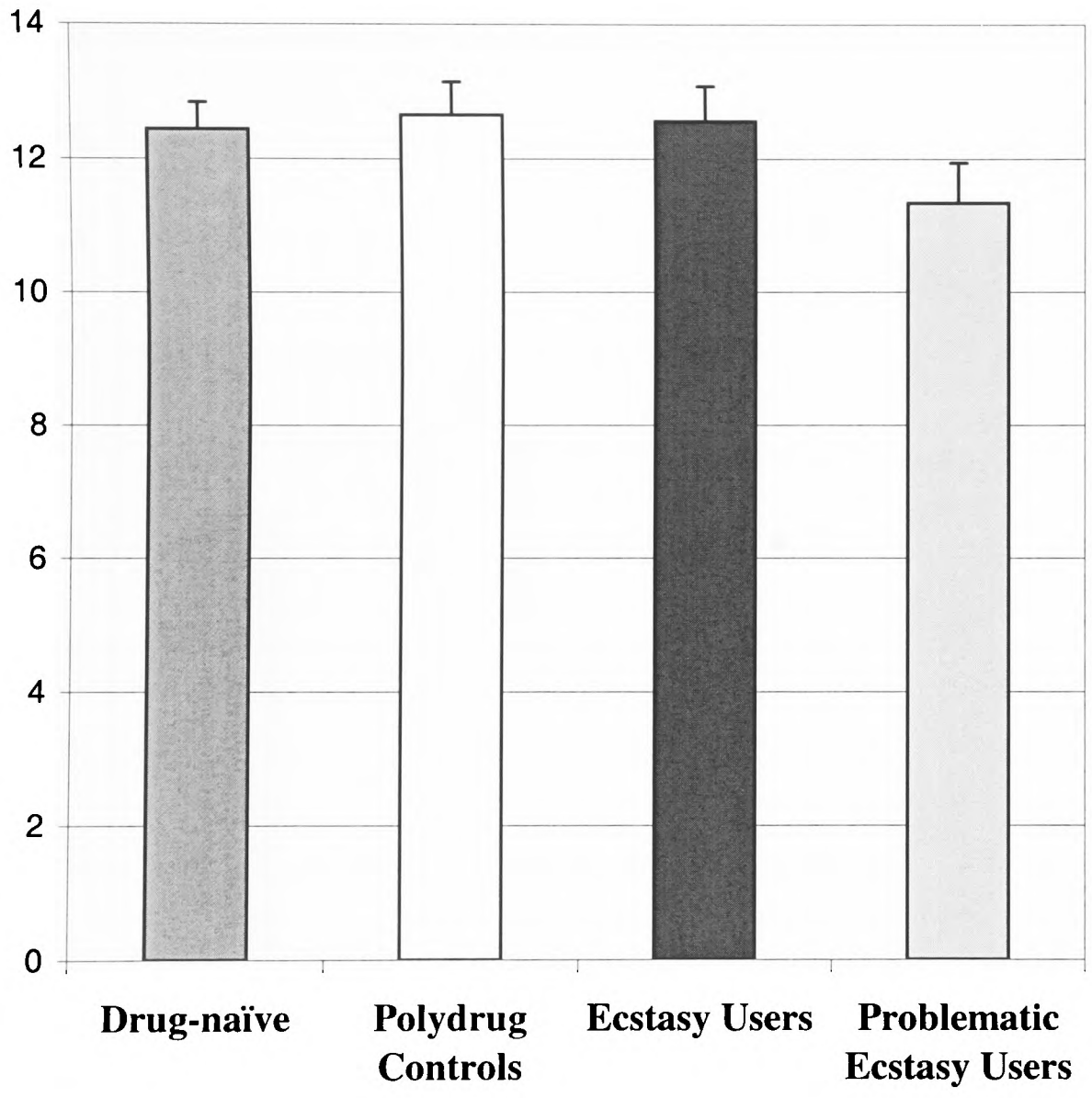


Figure 28: Mean BSI somatisation scores for all four groups.
(Bars indicate 1 standard error of mean)

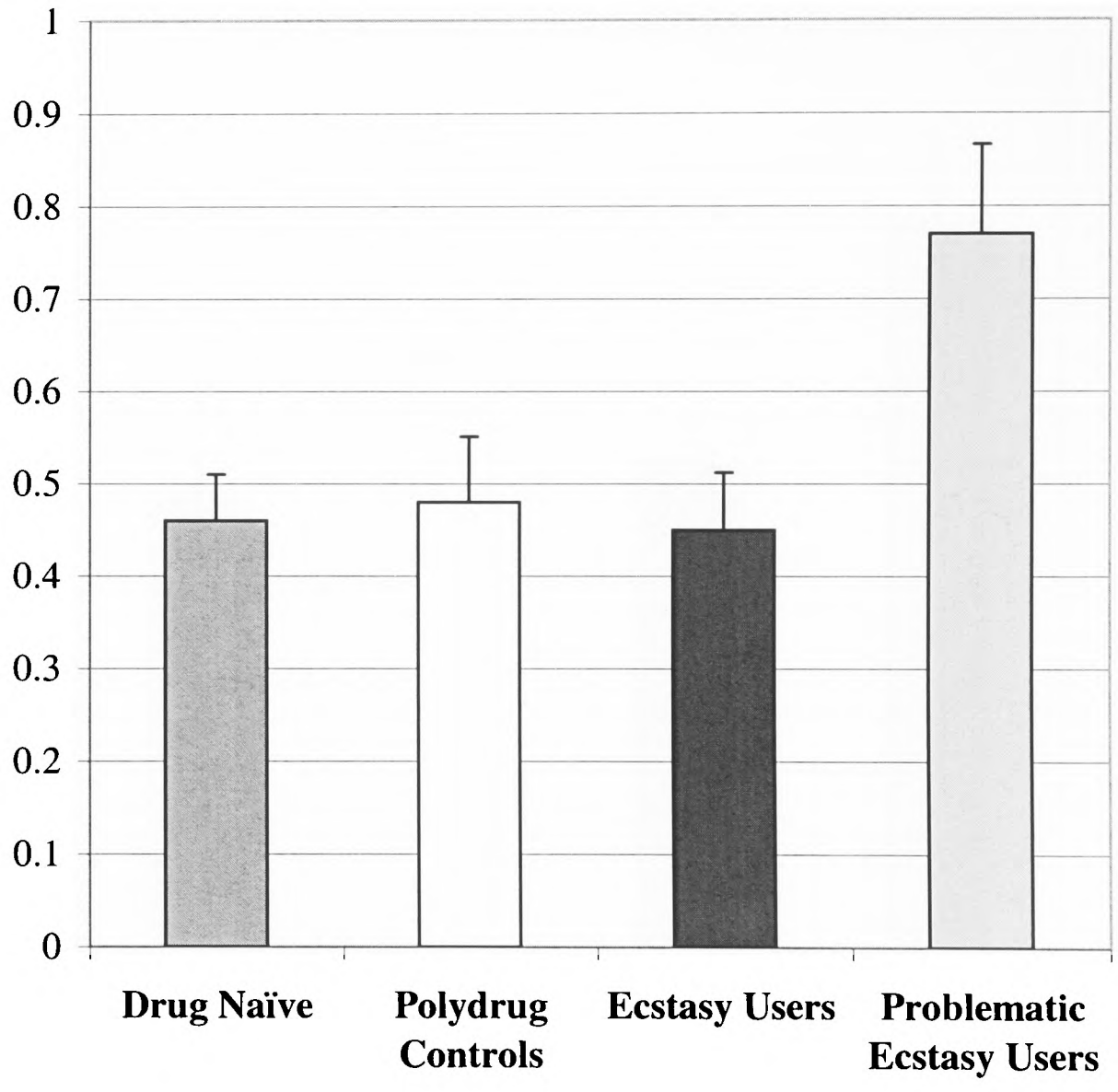


Figure 29: Mean BSI negative psychobiology scores for all four groups (Bars indicate 1 standard error of mean)

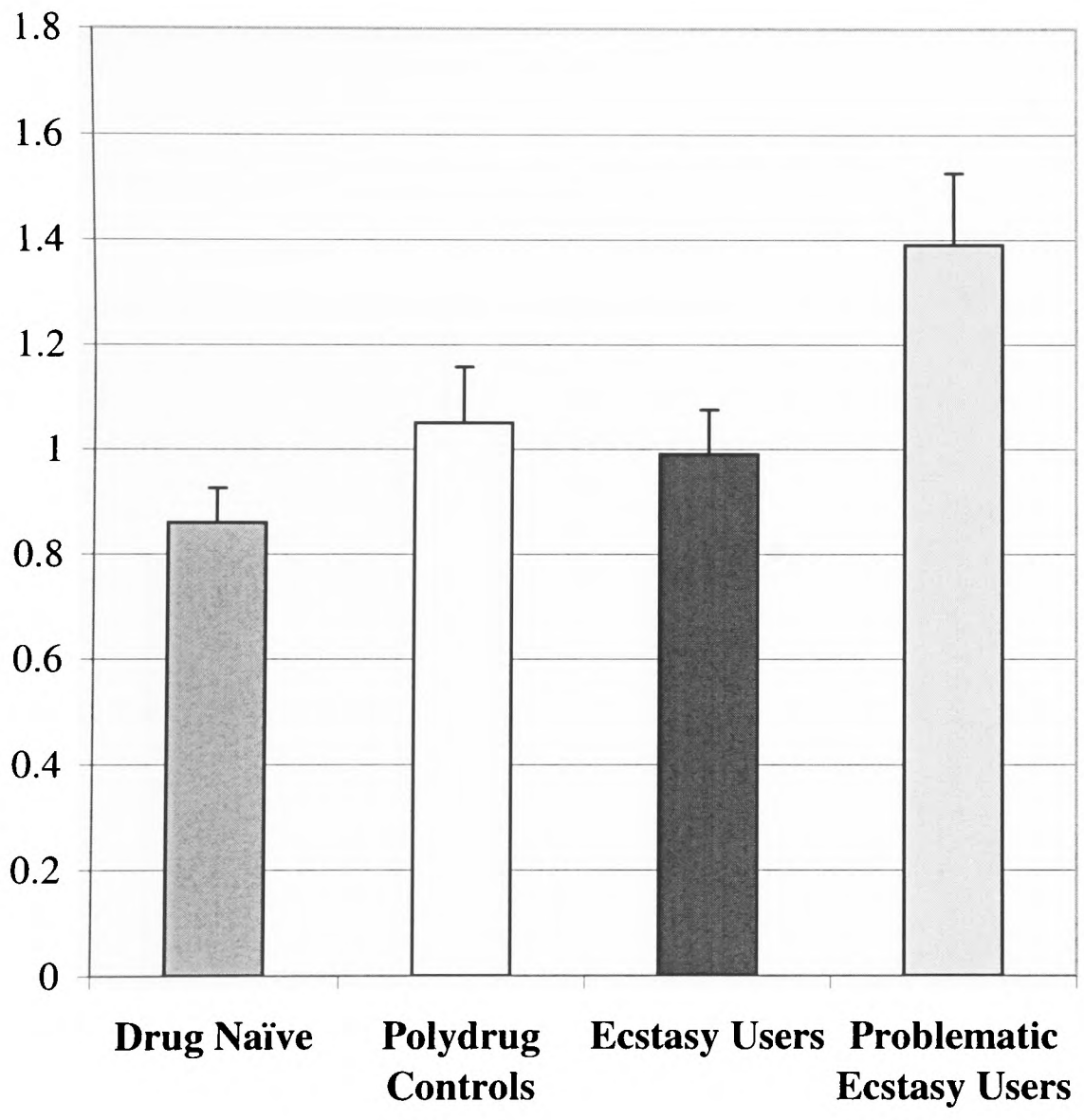


Figure 30: Mean BSI depression scores for all four groups (Bars indicate 1 standard error of mean)

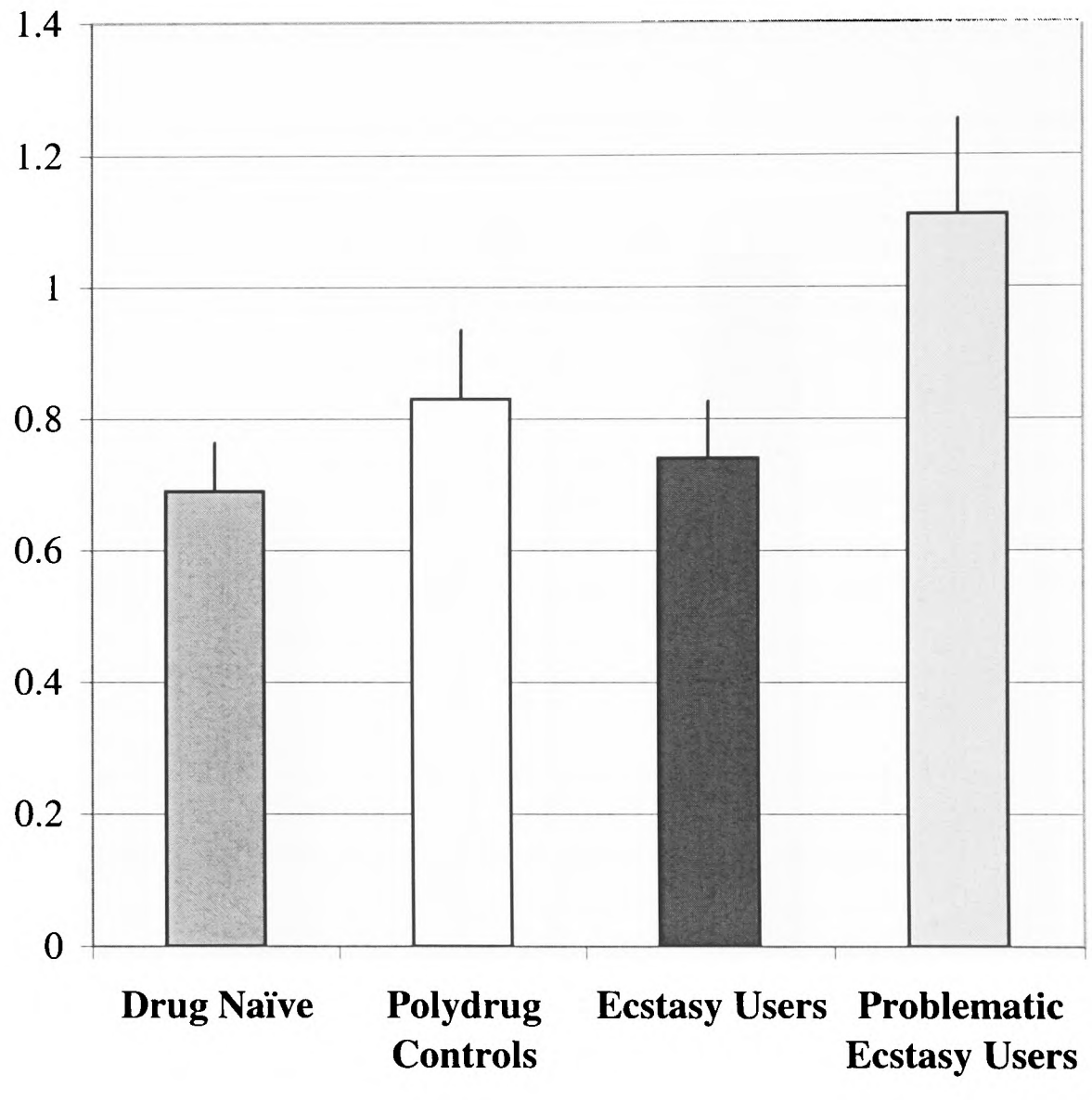


Figure 31: Mean BSI anxiety scores for all four groups.
(Bars indicate 1 standard error of mean)

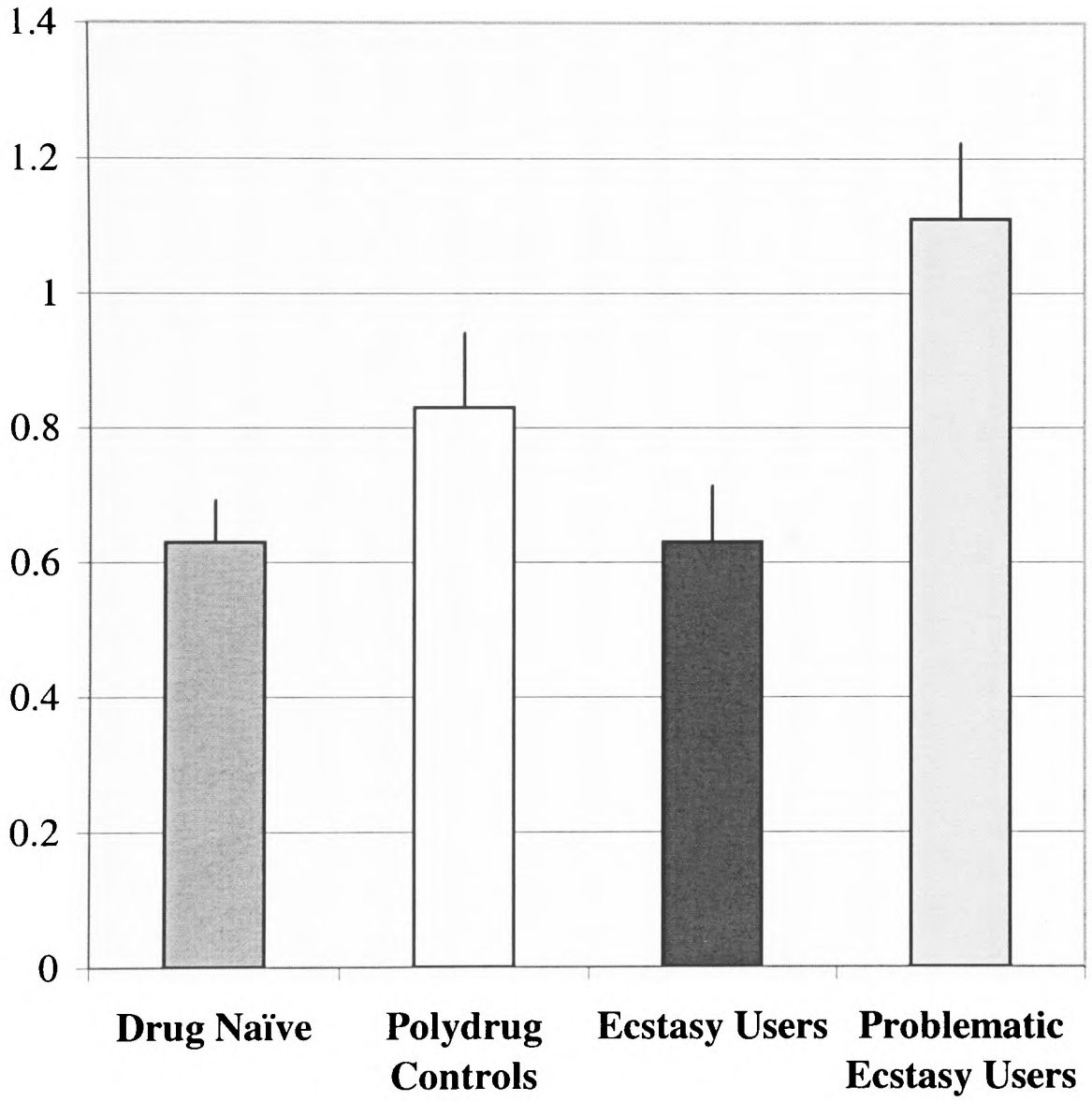
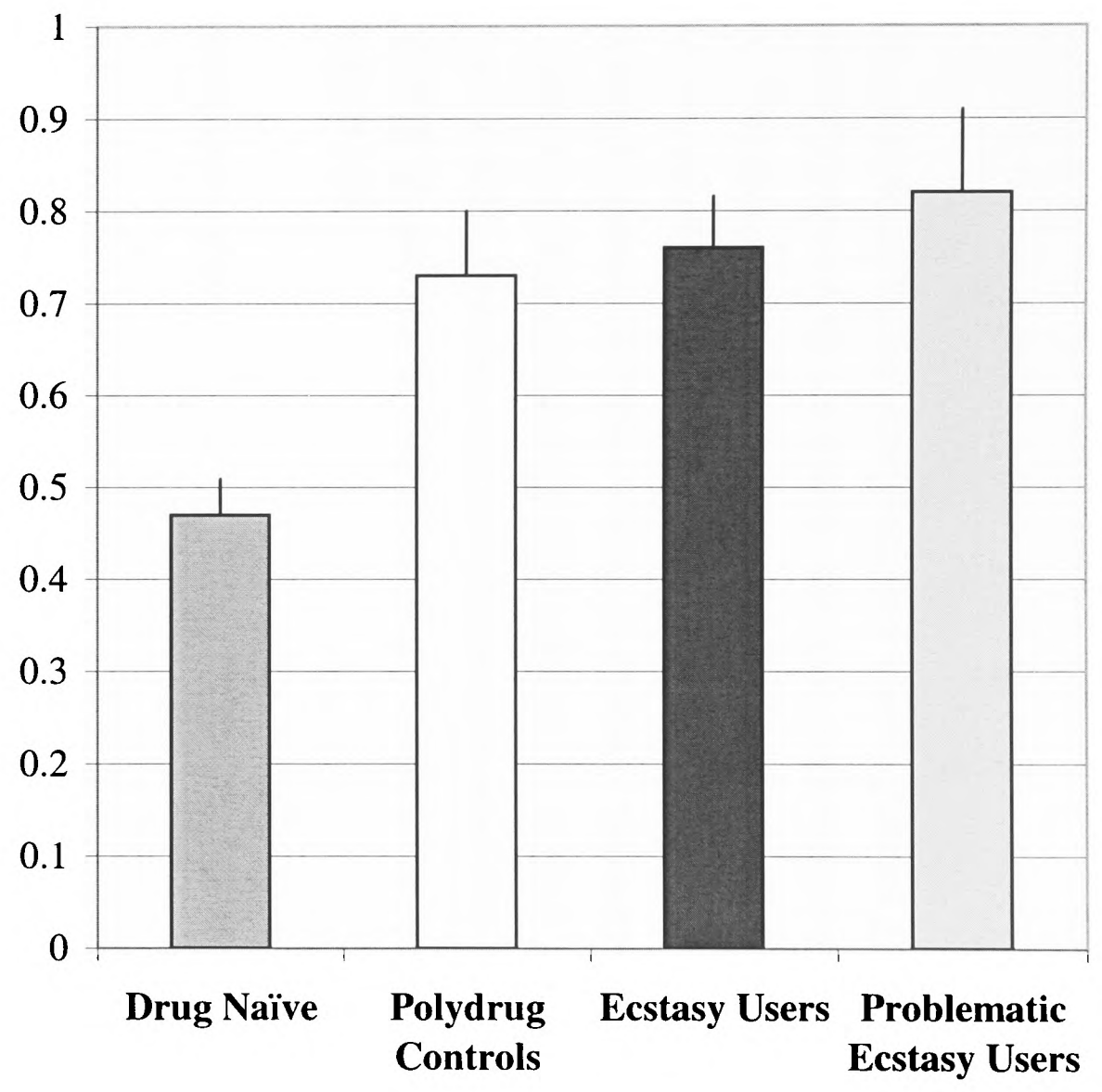


Figure 32: Mean BSI Sexual functioning scores for all groups (Bars indicate 1 standard error of mean)



problematic ecstasy users. However, these no longer remained significant following post hoc analyses.

With respect to the positive subscales of the modified BSI, there were significant group differences on positive mood $F(3,284) = 4.56$, $p = 0.004$], with non-problematic ecstasy users scoring significantly higher than drug naïve and polydrug controls. In the adjusted ANOCVA analyses the covariate, age, was significant [$F(1,286) = 7.78$, $p = 0.006$], however, the main effect of group on positive mood remained [$F(3,284) = 4.24$, $p = 0.006$]. Non-problematic ecstasy users also scored significantly higher than drug-naïve participants on the sociability subscale [$F(3,284) = 3.03$, $p = 0.030$]. This main effect of group on the sociability subscale remained in the adjusted ANCOVA analyses, [$F(3,284) = 2.79$, $p = 0.041$] after co-varying for age [$F(1,286) = 0.999$, $p = 0.318$].

Changes in Life Experiences Questionnaire

Tables 31 - 34 (appendices) show the percentages of drug naïve, polydrug controls, non-problematic and problematic ecstasy users who reported which positive and negative changes they have experienced in their life and which, if any, drug(s) they attributed these changes to.

Table 29 shows the number and percentage of drug-naïve, polydrug controls, non-problematic and problematic ecstasy users who reported that they had experienced positive and negative life changes. There were highly significant differences between groups for all life changes. A significantly higher number of people in the polydrug, non-problematic and problematic ecstasy user groups reported experiencing changes in empathy, a decrease in defensiveness, improved social functioning, increased feelings of well-being, obsessive thoughts, mood swings, less sociable, anxiety, paranoia, panic attacks, aggression, breathlessness, loss of organisation skills, motivational, memory and concentration loss, compared to drug-naïve controls. Polydrug users reported significantly less life experience changes compared to non-problematic and/or problematic ecstasy users in areas of spiritual enlightenment, enhanced sensations, obsessive thoughts, mood swings, depression, anxiety, paranoia, hallucinations, panic attacks, weight loss, sleep disruptions, but a greater number of polydrug controls reported memory problems compared to both non-problematic [$\chi^2 = 25.05$, $p<0.001$] and problematic ecstasy users [$\chi^2 = 11.43$, $p = 0.001$]. A significantly greater number of problematic ecstasy users reported life changes on all positive and negative items compared to

drug-naïve and/or polydrug controls and/or non-problematic ecstasy users. A greater number of problematic ecstasy users reported changes in panic attacks [$\chi^2 = 11.28$, $p = 0.001$], depression [$\chi^2 = 11.46$, $p = 0.001$], paranoia [$\chi^2 = 7.60$, $p = 0.006$] and general illness [$\chi^2 = 11.29$, $p = 0.001$], compared to non-problematic ecstasy users

Single drug attributions versus multiple drug attributions to changes in life experiences

Comparing percentages alone (see tables 31-34 in the appendix), polydrug users who did indicate changes, attributed them more to other factors than their drug use. Those ecstasy users who reported both positive and negative changes in their life, attributed these more to drug use than other non-drug factors. Non-problematic ecstasy users attributed use of a greater range of drugs to their changes, compared to problematic ecstasy users.

Chi squared results indicate that there were significant groups differences in the number of people who reported attributing life changes to more than one drug on a majority of life changes (table 30). These included the positive changes of increased empathy [$\chi^2 = 12.36$, $p = 0.002$], a decrease in defensiveness [$\chi^2 = 9.84$, $p = 0.007$], improved social/interpersonal functioning [$\chi^2 = 12.09$, $p = 0.002$], increased feelings of well-being [$\chi^2 = 13.79$, $p = 0.001$], a decrease in fear [$\chi^2 = 15.40$, $p<0.001$] and enhanced sensations [$\chi^2 = 6.02$, $p = 0.05$]. They also included the negative changes of obsessive thoughts [$\chi^2 = 9.91$, $p = 0.007$], aggression [$\chi^2 = 8.26$, $p = 0.016$], mood swings [$\chi^2 = 10.09$, $p = 0.006$], less sociability [$\chi^2 = 8.69$, $p = 0.013$], confidence loss [$\chi^2 = 7.69$, $p = 0.021$], anxiety [$\chi^2 = 15.50$, $p<0.001$], paranoia [$\chi^2 = 13.36$, $p = 0.001$], hallucinations [$\chi^2 = 7.96$, $p = 0.019$], backache [$\chi^2 = 4.48$, $p = 0.034$], sexual problems [$\chi^2 = 10.76$, $p = 0.005$], general illness [$\chi^2 = 9.13$, $p = 0.010$], weight loss [$\chi^2 = 6.23$, $p = 0.044$], loss of organisational skills [$\chi^2 = 8.92$, $p = 0.012$], and memory [$\chi^2 = 17.67$, $p<0.001$] and concentration loss [$\chi^2 = 15.21$, $p<0.001$].

Table 29: Number and percentage of drug-naïve, polydrug controls, non-problematic and problematic ecstasy users that reported that they had experienced positive and negative life changes

n / %	Drug-naïve n =111		Polydrug Users n =62		Non-problematic Ecstasy Users n = 62		Problematic Ecstasy Users n= 53		*P*
Positive life changes									
Increased empathy	28	25%	32	52%	44	71%	35	66%	<0.001
Decrease in defensiveness	20	18%	32	52%	32	53%	36	68%	<0.001
Improved social/interpersonal functioning	47	42%	49	79%	53	83%	44	83%	<0.001
Increased feelings of well being	40	36%	47	76%	44	36%	38	72%	<0.001
Decrease in fear	37	33%	38	61%	33	53%	28	53%	0.002
Spiritual enlightenment	21	19%	21	34%	30	48%	33	62%	<0.001
Enhanced sensations	30	27%	26	42%	40	65%	40	76%	<0.001
Negative life changes									
Obsessive thoughts	22	20%	25	40%	35	57%	36	68%	<0.001
Aggression	33	30%	31	50%	29	47%	29	55%	0.006
Mood swings	37	33%	37	60%	42	68%	45	66%	<0.001
Less sociable	31	28%	32	52%	36	58%	34	64%	<0.001
Confidence loss	41	37%	29	47%	30	48%	33	62%	0.024
Depression	35	32%	29	45%	33	53%	44	83%	<0.001
Anxiety	21	19%	29	47%	40	65%	39	74%	<0.001
Paranoia	13	12%	21	34%	34	55%	42	79%	<0.001
Hallucinations	5	5%	8	13%	21	34%	25	47%	<0.001
Panic attacks	4	4%	13	21%	14	23%	28	53%	<0.001
Phobias	10	9%	6	10%	7	11%	13	25%	0.032
Breathlessness	16	34%	25	40%	21	34%	25	47%	<0.001
Backache	32	29%	21	34%	18	29%	28	53%	0.016
Sex problems	12	11%	13	21%	17	28%	21	40%	<0.001
General illness	32	41%	27	44%	16	26%	30	57%	0.001
Weight loss	27	24%	18	29%	31	50%	38	72%	<0.001
Sleep problems	35	32%	28	45%	37	60%	38	72%	<0.001
Loss of organisational skills	19	17%	27	44%	27	44%	31	59%	<0.001
Motivational problems	32	29%	33	53%	36	58%	37	70%	<0.001
Memory loss	16	14%	60	97%	37	60%	40	76%	<0.001
Concentration loss	34	31%	36	59%	38	61%	54	86%	<0.001

Of those polydrug users who did indicate life changes attributable to drugs, they were significantly more likely to attribute these changes to just one drug rather than a combination of drugs, compared to non-problematic and/or problematic ecstasy users (table 30). This finding was relatively consistent across positive and negative life changes, except for spiritual enlightenment, confidence loss, backache and sexual problems. In addition, a significantly higher number of problematic ecstasy users attributed more than one drug to increased empathy [$\chi^2 = 7.01$, $p = 0.008$], decrease in fear [$\chi^2 = 6.62$, $p = 0.01$], obsessive thoughts [$\chi^2 = 6.19$, $p = 0.013$], aggression [$\chi^2 = 5.75$, $p = 0.016$], anxiety [$\chi^2 = 10.8$, $p = 0.001$], paranoia [$\chi^2 = 7.82$, $p = 0.005$], hallucinations [$\chi^2 = 5.37$, $p = 0.02$], sexual problems [$\chi^2 = 9.96$, $p = 0.002$], general illness [$\chi^2 = 9.13$, $p = 0.003$], loss of organisational skills [$\chi^2 = 7.25$, $p = 0.007$], memory loss [$\chi^2 = 10.89$, $p = 0.001$], concentration loss [$\chi^2 = 11.93$, $p = 0.001$] compared to non-problematic ecstasy users. A significantly higher number of non-problematic ecstasy users attributed more than one drug to improved social/interpersonal functioning [$\chi^2 = 10.94$, $p = 0.001$], increased feelings of well-being [$\chi^2 = 10.75$, $p = 0.001$] and mood swings [$\chi^2 = 5.36$, $p = 0.021$], compared to polydrug controls.

Specific Drugs Attributions to Positive Life Experience Changes

In establishing which specific drugs changes were attributed to, comparisons can only be made by comparing percentages (tables 31-34 in the appendix). Positive life experience changes, such as improved social/interpersonal functioning was strongly attributed to alcohol compared to any other drug across all four groups, with 18% of drug naïve participants, 45.2% polydrug controls, 43.5% non-problematic ecstasy users and 28.3% problematic ecstasy users attributing this change to alcohol. However, amongst non-problematic ecstasy users, ecstasy (35.5%) and cocaine (33.9%) also played a strong part, whilst amongst problematic ecstasy users this life change was attributed more to ecstasy than alcohol (45.3% vs. 28.3% respectively). A decrease in fear was also attributed mostly to alcohol compared to any other drug, amongst drug naïve (12.6%), polydrug controls (32.3%) and non-problematic ecstasy users (32.3%).

Table 30: Number of polydrug, non-problematic and problematic ecstasy users who attributed life changes to more than one drug

n / %	Polydrug Users		Non-problematic Ecstasy Users		Problematic Ecstasy Users		*P*
Positive life changes							
Increased empathy	5	23%	11	34%	21	68%	0.002
Decrease in defensiveness	4	18%	12	46%	18	62%	0.007
Improved social/interpersonal functioning	10	28%	28	65%	19	59%	0.002
Increased feelings of well being	5	18%	18	60%	16	62%	0.001
Decrease in fear	5	20%	11	41%	15	79%	<0.001
Spiritual enlightenment	2	22%	15	65%	15	54%	0.09
Enhanced sensations	6	30%	23	59%	23	62%	0.049
Negative life changes							
Obsessive thoughts	2	17%	8	27%	21	60%	0.007
Aggression	3	19%	6	23%	13	57%	0.016
Mood swings	3	18%	17	52%	28	63%	0.006
Less sociable	1	6%	9	46%	11	36%	0.013
Confidence loss	1	11%	4	20%	14	52%	0.021
Depression	3	25%	11	44%	20	49%	0.343
Anxiety	2	14%	8	25%	22	65%	<0.001
Paranoia	2	13%	9	27%	24	60%	0.001
Hallucinations	0	0%	4	20%	13	54%	0.019
Panic attacks	1	20%	2	25%	13	54%	0.187
Phobias	0	0%	1	50%	5	63%	0.747
Breathlessness	0	0%	2	13%	7	33%	0.097
Backache	0	0%	0	0%	8	40%	0.034
Sex problems	1	20%	1	7%	9	64%	0.005
General illness	3	43%	1	7%	14	54%	0.010
Weight loss	0	0%	8	29%	17	50%	0.044
Sleep problems	1	13%	14	42%	18	50%	0.152
Loss of organisational skills	4	29%	6	26%	19	63%	0.012
Motivational problems	5	33%	8	26%	12	35%	0.699
Memory loss	2	12%	9	25%	24	63%	<0.001
Concentration loss	7	32%	11	32%	29	73%	<0.001

Increased feelings of well-being were also attributed to alcohol amongst polydrug controls (21%) and non-problematic ecstasy users (25.8%), but also to cannabis (24.2%) in polydrug controls, whilst amongst non-problematic ecstasy users, ecstasy (25.8%) and cocaine (27.4%) were strongly implicated. Ecstasy was the strongest drug implicated (35.8%).in feelings of well-being with problematic ecstasy users.

Cannabis was reported as the reason behind enhanced sensations, by 22.6% of polydrug controls, yet ecstasy appeared to be the drug that non-problematic (54.8%) and problematic ecstasy users (56.6%) attributing enhanced sensations to the most, with LSD, cocaine and cannabis also being implicated in these two ecstasy using groups. Ecstasy use was a strong attributional factor for changes in spiritual enlightenment, with 27.4% of non-problematic ecstasy users and 30.2% problematic ecstasy reporting as such. Although non-problematic ecstasy users reported LSD to have been an equally contributing factor to changes in spiritual enlightenment. As expected, increased empathy was also attributed to ecstasy more than any other drug (45.2% and 45.3% respectively) amongst non-problematic and problematic ecstasy users, as was a decrease in defensiveness amongst problematic ecstasy users (35.8%).

Specific Drugs Attributions to Negative Life Experience Changes

Aggression appeared to be strongly associated with alcohol compared to any other drug and across all groups, with 24.2% of polydrug controls, 32.3% ecstasy users and 26.4% problematic users attributing this change to alcohol. Paranoia was most strongly associated with cannabis, compared to other drugs and across groups, with 21% of polydrug controls, 25.8% ecstasy users and 49.1% problematic ecstasy users implicating cannabis in this change. However, problematic ecstasy users also attributed paranoia quite highly to ecstasy (34%) and amphetamine (30.2%) use.

Cannabis use also appeared to be a strong factor compared to any other drug for motivational problems and loss of sociability in both ecstasy (30.6% and 22.6% respectively) and problematic ecstasy users (32.1% and 39.6%). Cannabis was also implicated in perceptions of concentration loss amongst problematic ecstasy users (24.5%) and also with memory loss amongst non-problematic ecstasy users (27.4%) compared to a low implication of ecstasy

attributed to memory loss in this non-problematic and problematic ecstasy users (only 4.8% and 13.2% respectively).

Hallucinations were mainly reported by problematic ecstasy users but were equally attributed to ecstasy and LSD use (24.5%). This is probably because this group reported significantly greater consumption levels of both ecstasy and LSD compared to the other drug using groups.

Ecstasy was a very strong attributional factor linked to depression (62.3%), anxiety (37.7%), panic attacks (34%), general illness (39.6%) and weight loss (39.6%) amongst problematic ecstasy users. Amongst this group, ecstasy was also implicated in obsessive thoughts, alongside cannabis use (30.2%). Whilst in the non-problematic user group, far fewer participants linked their ecstasy use to these negative symptoms. Mood swings were also strongly attributed to ecstasy, amongst ecstasy and problematic ecstasy users (25.8% and 54.7% respectively), but so too were the other stimulants, cocaine and amphetamine. Similarly both ecstasy using groups reported similar drug attributions with sleep problems.

Dose-related relationships

The self-reported lifetime consumption of ecstasy did not correlate with any measure on the BSI or locus of control scales. The reported average dose consumed, positively correlated with obsessive compulsive scores ($r = 0.210$, $p = 0.027$), anger ($r = 0.208$, $p = 0.029$), phobic anxiety ($r = 0.190$, $p = 0.046$) and psychoticism ($r = 0.193$, $p = 0.043$). But reported average dose consumed negatively correlated with the feeling content with life ($r = -0.262$, $p = 0.005$), positive mood ($r = -0.223$, $p = 0.019$) and sociability ($r = -0.196$, $p = 0.040$) subscales on the modified version of the BSI.

The largest dose of ecstasy on any one occasion positively correlated with obsessive compulsive scores ($r = 0.210$, $p = 0.027$), anger ($r = 0.246$, $p = 0.009$) and psychoticism ($r = 0.222$, $p = 0.019$), whilst it negatively correlated with the feeling content with life ($r = -0.302$, $p=0.001$) and positive mood ($r = -0.222$, $p = 0.019$) subscales on the modified version of the BSI.

Estimated lifetime consumption positively correlated with the average ecstasy dosage ($r = 0.597$, $p<0.001$), maximum number of ecstasy tablets that users reported consuming on a

single occasion ($r = 0.548$, $p<0.001$) and negatively correlated with the duration of ecstasy use ($r = -0.269$, $p = 0.005$).

Lifetime consumption of ecstasy also positively correlated with reported lifetime consumption of other drug use, including:- amphetamine ($r = 0.675$, $p<0.001$), cocaine ($r = 0.710$, $p<0.001$), LSD ($r = 0.713$, $p<0.001$), magic mushrooms ($r = 0.301$, $p = 0.001$), ketamine($r = 0.484$, $p<0.001$), GHB ($r = 0.208$, $p = 0.026$), solvents ($r = 0.682$, $p<0.001$) and current cannabis use ($r = 0.193$, $p = 0.039$). Average dose consumed in one occasion correlated with usage levels of amphetamine ($r = 0.250$, $p = 0.008$), ketamine ($r=0.549$, $p<0.001$), GHB ($r = 0.218$ $p = 0.021$), tobacco ($r = 0.301$, $p = 0.001$) and alcohol ($r = 0.272$, $p = 0.004$). Whilst maximum dosage consumed in one occasion correlated with amphetamine ($r = 0.248$, $p = 0.009$), ketamine ($r = 0.447$, $p<0.001$), tobacco ($r = 0.287$, $p = 0.002$) and alcohol ($r = 0.272$, $p = 0.004$) use.

Duration of drug use

The duration of ecstasy use was found to negatively correlate with the paranoia subscale ($r = -0.250$, $p = 0.010$) and positively correlate with the sociability subscale ($r = 0.212$, $p = 0.029$) of the modified BSI.

Locus of Control and drug use

LOC did not correlate with any measure of ecstasy use (maximum dosage, average dose, lifetime consumption, duration of use, time since last used), nor did LOC correlate with any lifetime consumption use of any other drug. However, LOC negatively correlated with the number of years cannabis had been consumed for ($r = 0.187$, $p = 0.005$)

Locus of control and the BSI

Scores on the LOC questionnaire positively correlated with depression ($r = 0.225$, $p = 0.016$) and psychoticism ($r = 0.224$, $p = 0.016$) subscales, indicating that a greater external attribution is associated with higher levels of depression and psychoticism. A more internal attribution style was associated with greater levels of contentment ($r = -0.220$, $p = 0.018$) and sociability ($r = -0.206$, $p = 0.027$).

DISCUSSION

The current study supports one of the main hypotheses, with problematic ecstasy users demonstrating significantly higher levels of psychopathology compared to non-problem ecstasy users, polydrug users and drug-naive controls on a number of the BSI subscales. Problematic ecstasy users reported higher scores for symptoms associated with somatisation, depression, anxiety, negative psychobiology and sexual dysfunction compared to non-problematic ecstasy users (table 28). However, despite similar patterns of other drug use between these two ecstasy using groups, problematic ecstasy users did report higher levels of ecstasy use (a significantly higher average dose, maximum dose and lifetime consumption), compared to non-problem ecstasy users (table 25). What is perhaps even more important, is that there were no differences in the duration of ecstasy use between the two ecstasy using groups, which suggests that problematic ecstasy use may be a function of the levels and intensity of ecstasy use. This is somewhat contrary to the initial suggestion in this thesis that problems associated with ecstasy use and psychopathological status were independent of patterns of ecstasy consumption, and also contrary to the findings of Fox et al (2001b), who found that problematic ecstasy use may not necessarily be dose-related.

The idea that it is the intensity of ecstasy use that possibly contributes or causes psychobiological problems is further supported by the dose-related effects found in this study. Higher average doses of ecstasy where associated with higher scores on the obsessive-compulsive, anger, phobic anxiety and psychoticism subscales, than lower average doses, in ecstasy users. Also, the higher the maximum amounts of ecstasy consumed on any one occasion the higher the scores on the obsessive-compulsive, anger and psychoticism subscales, in ecstasy users. This supports findings by Parrott et al (2002), who found that self-reported psychobiological problems attributed to ecstasy, were a direct function of the amount of times it was taken. However, these correlations need to be interpreted with caution because analyses have been conducted on ecstasy users as one large collapsed group (problematic and non-problematic) and not analysed as separate groups. As a result, the correlations might largely be a product of the very different ecstasy users. Additionally, there was no control for type 1 errors on what is arguably a large number of correlations, hence there is a higher probability that these significant findings were by chance.

This present study did not find any significant differences in the locus of control personality trait between the ecstasy using groups (table 25). Problematic ecstasy users demonstrated a trend towards lower external locus of control compared to non-problem ecstasy users (figure 27). However, this difference did not reach statistical significance, suggesting that this personality construct was not an important influence over whether or not some ecstasy users report more problems than other ecstasy users, which they attribute to their ecstasy use. There are, however, many other personality factors which could possibly contribute to or be associated with problematic ecstasy use. One important possible variable that has been highlighted within this study is psychiatric history. Problematic ecstasy users reported significantly greater personal and family psychiatric histories compared to non-problematic ecstasy users (table 26), suggesting a vulnerability to the development of psychological problems. Whether their ecstasy use contributes to or exacerbates the development of psychopathology is still to be determined. It may be the case that some, perhaps even all of these individuals, would have developed psychological problems independent of ecstasy use.

A limitation of this study is that these problematic ecstasy users were not asked to indicate details of the problems they attributed to their ecstasy use. Specific problems were only assessed indirectly via the questions pertaining to the changes in life experiences. Isolating the specific problems is difficult, based on the fact that problematic ecstasy users tended to implicate more of all other drugs when attributing negative long-term problems. It is interesting to note at this point, that whilst 58 participants self-perceived themselves as being problematic, only 17 (32.1%) reported having sought some form of help for their problems (table 27). These individuals tended to seek help via primary care services (GP, psychiatrists, clinical psychologists), with the GP being the first port of call. This is consistent with findings of Topp et al (1999) who found one fifth of their ecstasy using sample had received formal assistance from a health practioner for an ecstasy-related problem; and this was predominantly from a GP (11%). This help-seeking behaviour in ecstasy users has implications for health services; for example, GPs may benefit from the dissemination of ecstasy-related information.

The present study also lends some support to MacInnes et al (2001) who found higher levels of depression in ecstasy users compared to non-drug using controls, and that the levels of depression positively correlated with scores indicating an external LOC. In the present study, non-problematic ecstasy users showed higher levels of depression than drug-naive controls,

though this did not reach significance, but problematic ecstasy users did show significantly higher levels of depression compared to drug-naïve controls. In addition, correlational findings show that higher depression levels were associated with a greater external LOC. Therefore, there is support for the idea that ecstasy users tend to have higher levels of depression and thus a higher external LOC, but it must be made clear that external LOC is associated with the level of depression and not ecstasy use.

Parrott et al (2001) suggested that psychiatric symptoms and psychobiological problems are associated not only with ecstasy use but also with recreational polydrug use. The current study lends support to this, since ecstasy using groups exhibited higher levels of psychopathology on a number of subscales compared to polydrug controls, who also exhibited higher psychopathology on some subscales compared to drug-naïve controls. In addition both ecstasy using groups had used significantly more other recreational drugs compared to polydrug controls who, in turn, had obviously used significantly more substances than drug naïve controls. It could be concluded that this indicates that as polydrug use is increased so too is the risk of psychopathology. It appears that increasing use of other drugs is strongly associated with the increasing use of ecstasy, since the lifetime consumption of ecstasy use positively correlated with other common recreational drug use: i.e. amphetamine, cocaine, magic mushrooms, ketamine, GHB, solvents and cannabis.

Further support for the role of polydrug use in changes in life experiences, comes from the exploratory part of this study into positive and negative life changes attributed to differing recreational drug use. Ecstasy and problematic ecstasy users reported more positive and negative changes in life experiences (tables 29, 33 & 34) compared to polydrug and drug naïve controls (tables 29, 31 & 32). They also attributed these, more to drug use than 'other factors'. However, a greater number of polydrug controls reported changes compared to drug-naïve controls and also attributed these changes more to drug use than 'other factors', suggesting that polydrug use certainly plays a role in attributions related to life experiences (table 32). However, a greater number of ecstasy users appear to experience more life changes over and above those reported by polydrug users, with problematic ecstasy users experiencing the most (table 29). Ecstasy users (both non-problematic and problematic) also report life changes more to a combination of drugs than one specific drug, suggesting polydrug use in these ecstasy users has an impact on their life experiences. Ecstasy use plays a strong attributional role with regard to depression, anxiety, panic attacks, general illness and

mood swings, which is consistent to previous research. However, other drugs such as alcohol, amphetamine and cocaine also seem to be reported as playing a role; especially cannabis, which appears to play a strong attributional role with negative changes such as paranoia, memory loss, concentration loss, motivational problems and obsessive thoughts, (consistent with the findings of Morgan et al, 2002). This all lends support to the idea that research into the psychological effects of ecstasy clearly should not underestimate the contribution of other drug use/polydrug use.

Caution should also be taken in interpreting differences in 'drug attributions' between problematic and non-problematic ecstasy users. Even though a higher percentage of problematic ecstasy users attributed changes in life experiences to a greater range of drugs compared to non-problematic ecstasy users. A significantly higher number of problematic ecstasy users reported these changes to more than one drug (table 30) It is difficult to determine whether this is as a result of their 'problematic use' or the fact that they used significantly more hallucinogens and reported different patterns of ecstasy consumption. Problematic ecstasy users did report more negative changes related to ecstasy use, but they did also report having used significantly more ecstasy than non-problematic users (table 25).

LOC is well established as being linked to mental health related problems (Hale & Cochran, 1987; D'Arcy & Siddique, 1984; Young & Washburn, 1992; Petrosky & Birkimer, 1991; Hoehn-Saric & McLeod, 1985; Archer, 1980), even amongst drug using populations (O'Leary et al, 1976; Malin & Fordham, 2002) with higher rates of psychopathology relating to an external locus of control. The dose-related findings from this study supports this, since a greater external LOC orientation was associated with higher levels of depression and psychoticism. An internal LOC orientation was associated with higher levels of feeling content with life and sociability, indicating signs of psychological well-being (D'Arcy & Siddique, 1984). However, the hypothesis that problematic ecstasy users would demonstrate a more external locus of control orientation compared to non-problematic ecstasy users, may explain why they report higher psychopathology compared to non-problematic users. This hypothesis was not supported in this study. On the contrary, problematic ecstasy users reported a lower external locus of control to non-problematic ecstasy users (figure 27) and problematic ecstasy users who reported having sought help for their problems, reported an even lower external locus of control; although neither scores reached statistical significance

(figure 33, appendix). Therefore the LOC does not appear to be important in determining whether individuals report problems attributable to ecstasy within this study.

The higher percentage of problematic ecstasy users reporting life changes attributable to ecstasy, still suggests that attributional style may play some role in whether ecstasy users define themselves as problematic or not. This difference in attributional style may not necessarily be detected by the Locus of Control Scale (Rotter, 1966). The scale was chosen because of the extensive and consistent findings concerning psychopathology and externality LOC, and that the measure allows for the prediction of behaviour across a wide range of potential situations (Rotter, 1975). Whilst this later point was originally seen as a beneficial reason for using the LOC Scale, with hindsight it may have been beneficial to use a measure which would allow for a high prediction of behaviour in more specific situations, more closely related to the topic in question, for example the Multidimensional Health Locus of Control Scale (Wallston et al, 1978), which measures the degree to which an individual perceives that they themselves have control over their health or whether it is determined by chance.

The LOC is thought to be a stable personality variable based on behaviour focusing on future expectations. Hence is one premorbid psychosocial construct worth exploring in light of previous literature into its association with psychopathology. The fact that this study demonstrated an association with external LOC and some psychopathological dimensions strengthens the importance of such a personality factor in relation to psychological problems. However, its relationship with problematic ecstasy use is less clear. From this study, reported levels of psychiatric history (both personal and family) were higher in problematic ecstasy users, which does suggest that such traits are necessary factors for consideration when assessing problematic ecstasy use. In conclusion, the current study suggests that it is certain pre-existing factors, the intensity of ecstasy dosing and the role of polydrug use in relation to ecstasy use, which contributes to problematic ecstasy experiences.

CHAPTER 8

Overview of Thesis Research Findings

There is sufficient evidence from both clinical and empirical studies to suggest that ecstasy users demonstrate elevated psychopathology and cognitive impairments compared to non-ecstasy users, even when allowing for some of the many methodological confounds inherent in long-term recreational ecstasy research (see chapter 2 for details). In these studies it has been shown that ecstasy has been associated with elevated levels of psychoticism, phobic anxiety, obsessive-compulsive and anxiety symptoms. In addition, research points to selective cognitive deficits: in particular verbal memory (both recall and recognition), executive functioning, attentional abilities and working memory, including prospective memory. Many of these cognitive and psychological differences have also been shown to be related to altered brain serotonin functioning and in addition, further evidence suggests that cognitive impairments and psychopathology are dose-related.

However, there is currently a shortage of empirical evidence concerning whether or not any of these problems develop to an extent that they become problematic to the user. Topp et al (1999) reported that one fifth of ecstasy users had received treatment for an ecstasy related problem. Hammersley et al (1999) found that the heaviest users of ecstasy were more likely to report having been an inpatient in the last year. Further still the question pertaining to whether or not any of these problems are a direct function of their past ecstasy use has still to be resolved. Parrott et al (2002) reported that ecstasy-attributed problems were a direct function of the number of occasions on which the drug has been consumed. Alternatively, Fox et al (2001b) reported that psychological symptoms in "problematic" ecstasy users were unrelated to ecstasy use, but related to negative interpersonal relationships prior to taking the drug and less socially orientated motivations for using the drug.

This research thesis aimed to explore this issue of problematic ecstasy use and whether or not the role of premorbid issues and levels of drug use were integral to issues relating to the cause and effect of problematic drug use. The current chapter aims to provide an overview of the whole research programme, concerning the psychopathological and cognitive functioning of the problematic ecstasy users. The overview will be discussed in terms of the main differences, in terms of "premorbid" variables and levels of drug use between 'problematic' and 'non-problematic' ecstasy users. This will be followed by the main group differences in psychopathology and possible dose-related effects. It will also include an overview of group differences in cognitive functioning in terms of short term memory, executive functioning, everyday memory and reaction time, as well as dose-related effects. Interpretation of these

findings is also discussed in light of methodological constraints; highlighting potential improvements and the need for specific informative research.

OVERVIEW OF PROBLEMATIC AND NON-PROBLEMATIC ECSTASY USER PROFILES

The current thesis referred to 'problematic' ecstasy users as recreational ecstasy users who reported problems which they attributed to past ecstasy use; and which had developed to the extent that they had become problematic to the user. In the case of chapter 3, these problems were either clinically defined and/or had interfered with the individual's life to the extent that they had sought some form of help. Only 14 problematic ecstasy users could be recruited for this particular study, based on this 'problematic' criteria. In order to generate a larger sample of problematic ecstasy users, this definition was slightly changed in chapter 7, to those individuals who had developed problems which they strongly attributed to their past ecstasy use. With this slightly different inclusion criteria for 'problematic users', 53 problematic ecstasy users were identified, but only 17 of these (32% of problematic ecstasy users) had sought help for their problems. The most common sources of help that these individuals (in both groups; chapters 3 & 7) appear to have drawn upon was primarily from their local GP (93% in study 1 and 26% in study 4); although in a number of cases help was also reported to have been sought from clinical psychologists and psychiatrists, suggesting that they were clinically defined problems.

Problematic ecstasy users did not differ greatly on their levels of drug consumption compared with non-problematic ecstasy users. All ecstasy users reported using a wide range of drugs, including amphetamine, cocaine, LSD and cannabis use. Those problematic ecstasy users in the first study (chapter 3) tended to report more use of Prozac and monthly cannabis use than non-problematic ecstasy users. In the last study (chapter 7), problematic ecstasy users tended to have used more hallucinogens (LSD and magic mushrooms) compared to non-problematic ecstasy users. The individual from the 'problematic' case study (chapter 4), also reported consuming similar types of drugs to the problematic and non-problematic ecstasy users, but also reported quite an extensive use of benzodiazepines (post-ecstasy use). However, in general, within this research thesis, there were no consistently distinct patterns of drug use which enabled a clear differentiation to be made between problematic and non-problematic ecstasy users.

Concerning the levels of ecstasy consumption, in problematic and non-problematic ecstasy users, there was little difference between the two groups in the first study. However, there were significantly different patterns of ecstasy use between problematic and non-problematic ecstasy users in chapter 7. Here problematic ecstasy users reported significantly higher lifetime consumption levels of ecstasy, higher average dosage levels and higher maximum dosage levels compared to non-problematic ecstasy users. This provides some evidence to indicate that the problems reported by ecstasy users may be a function of their past ecstasy use.

Another issue which may play a contributory role in the development of problematic ecstasy use are possible premorbid factors such as psychiatric history. This is suggested by the evidence that problematic ecstasy users reported a more extensive level of psychiatric history (in both studies 1 and 4) and family psychiatric history (study 4) compared to non-problematic ecstasy users. However, there was no objective measure of psychiatric status of these users and it is difficult to establish from this thesis whether reported psychiatric histories occurred prior to ecstasy polydrug use, whether or not ecstasy use may have caused and/or contributed to more severe symptoms in pre-existing psychiatric problems and even whether they developed in the context of their drug use. However, the higher levels of family psychiatric history in some of these problematic ecstasy users, suggests that there may have been a predisposition to psychological problems. Finally, another factor which was explored within this research thesis was that of self-perception and whether or not individuals have a certain attributory style. Whilst the research did not indicate this was a significant contribution to problematic ecstasy use, problematic ecstasy users did indicate a slightly higher external locus of control compared to non-problematic ecstasy users. This trend was strengthened by an even higher external locus of control in a sub-sample of problematic ecstasy users (chapter 7) that had sought help for their attributed problems, compared to those who had not (appendix, figure 34). Whilst these differences in LOC did not reach statistical significance, the trends suggest that such personality factors may influence the development or certainly the reporting of problems related to ecstasy use, though this area warrants further investigation.

OVERVIEW OF PSYCHOPATHOLOGY FINDINGS

BSI and negative scales

Based on the current research programme it appears that problematic ecstasy users are consistently reporting significantly elevated scores on somatisation, depression and anxiety compared to polydrug drug controls and/or drug-naïve controls across all studies. Other areas of psychopathology that are elevated in problematic ecstasy users, compared to control groups include interpersonal sensitivity, phobic anxiety; paranoid ideation and psychoticism (chapters 3, 6 & case study). However, the current programme did not find any strong support for elevated scores on the psychobiological subscales (including poor appetite, overeating and difficulties in getting to sleep), sexual dysfunction, obsessive compulsive symptoms and anger/hostility in problematic ecstasy users.

Problematic ecstasy users also displayed consistently higher psychopathology scores compared to non-problematic ecstasy users (particularly for somatisation, depression, anxiety and negative psychophysiology) across all studies. In addition, scores were elevated in these individuals compared to non-problematic ecstasy users for interpersonal sensitivity, phobic anxiety, paranoid ideation and psychoticism in chapter 3 and in the case study.

The psychopathology evident in these problematic ecstasy users is consistent with many clinical case studies which have reported, in individual ecstasy users, anxiety related symptoms (Series et al, 1994; Creighton et al, 1991), depression (McGuire et al, 1994; Benazzi and Mazzoli, 1991; Cohen, 1996; Teggin, 1992; Schifano and Magni, 1994), panic attacks (Whitaker-Azmitia & Aronoson, 1989; Schifano and Magni, 1994; Pallanti & Mazzi, 1992; Windhaber et al, 1998; McCann & Ricaurte, 1992; McGuire et al, 1994); psychosis/ delusions and paranoid symptoms (e.g. Cassidy & Ballard, 1994; Series et al, 1994; Kennan et al, 1993; Van Kampen & Katz, 2001; Alciati et al, 1999). In addition, the elevated psychopathology in these problematic ecstasy users are also consistent with a large scale clinical survey, which identified 53% of its sample as being affected by one or more psychopathological problems, which included depression, psychotic disorders, and panic disorders (Schifano et al, 2000); and is also consistent with Parrott et al's (2002) report of raised levels of depression, mood fluctuation and anxiety reported by ecstasy users.

On first inspection of the data from this research thesis, it appears that there is a necessity to identify the 'problematic' and 'non-problematic' ecstasy user factor, within ecstasy-related research. The non-problematic data from the studies within this thesis do not appear to be consistent with the majority of the existing literature concerning cognitive and psychological deficits in ecstasy users. Conversely the data from the problematic ecstasy does fit in with the existing literature; i.e. problematic ecstasy users showing elevated signs of psychopathology, (see Parrott et al, 2001; Dugherio et al, 2001; Morgan et al, 2002; Daumann et al, 2001; Parrott, Sisk & Turner, 2000; Gamma et al, 2001; MacInnes et al, 2001; Thomasius et al, 2003 and Wareing et al, 2001). Few existing studies have addressed this factor of 'problematic' ecstasy use, thus any inconsistencies between the literature and comparisons made within this research programme could be explained by the general absence of attention to a distinction between problematic and non-problematic ecstasy users.

In order to help establish whether this issue does contribute to some of the inconsistencies between the data and the existing literature, data for all groups were compared to normative data. There are currently three published norms available for the BSI: based on 1) a sample of 1002 heterogeneous psychiatric out-patients; 2) a sample of 719 non-patient normal subjects; and 3) a sample of 313 psychiatric in-patients (Derogatis & Melisaratos, 1983). Comparing the non-problematic ecstasy users mean scores on the BSI from this current research programme, with those of normative data (table 36), it was seen that, with the exception of phobic anxiety in two studies, non-problematic ecstasy users are consistently reporting higher psychopathology compared to non-patient norms, but lower than psychiatric in-patients and out-patients. This possibly suggests that these non-problematic ecstasy users are showing elevated psychopathology relative to norms, but not compared to the current controls within this research programme. This suggests that the inconsistent findings between this group and existing ecstasy research may not just be because of the lack of distinction in prior research concerning problematic and non-problematic ecstasy use. Instead, it raises an important question about the nature and validity of the polydrug control groups used throughout this research. It could suggest that polydrug use may produce mild problems, and for many, these problems remain unnoticeable, but when comparing non-problematic ecstasy users with these polydrug users, elevated psychopathological scores in the non-problematic ecstasy users may be masked by the mild problems in polydrug users. This is further supported when comparing the non-ecstasy polydrug users with the normative data (table 35). These polydrug controls are consistently reporting higher psychopathology scores across all studies and dimensions

Table 35: Polydrug controls mean (SD) BSI dimension scores from the current studies compared to normative data consisting of non-patients, psychiatric out-patients and psychiatric in-patients (Derogatis & Melisaratos, 1983).

	POLYDRUG CONTROLS			Normative data		
Symptom	**Study 1**	**Study 2**	**Study 4**	**Non-patients**	**Psychiatric Out-patients**	**Psychiatric In-patients**
Somatisation	0.41 ± 0.37	0.37 ± 0.34	0.48 ± 0.56	0.29 ± 0.40	0.83 ± 0.80	1.01 ± 0.91
Obsessive-compulsive	1.10 ± 0.66	1.05 ± 0.75	1.41 ± 0.92	0.43 ± 0.48	1.57 ± 1.00	1.51 ± 1.07
Interpersonal sensitivity	0.81 ± 0.68	0.71 ± 0.70	1.14 ± 0.96	0.32 ± 0.48	1.58 ± 1.05	1.48 ± 1.11
Depression	0.58 ± 0.64	0.53 ± 0.64	0.83 ± 0.82	0.28 ± 0.46	1.80 ± 1.08	1.77 ± 1.21
Anxiety	0.68 ± 0.66	0.55 ± 0.68	0.83 ± 0.87	0.35 ± 0.45	1.70 ± 1.00	1.70 ± 1.15
Anger/hostility	0.46 ± 0.33	0.49 ± 0.47	0.95 ± 0.89	0.35 ± 0.42	1.16 ± 0.93	1.00 ± 0.97
Phobic anxiety	0.29 ± 0.33	0.25 ± 0.30	0.47 ± 0.71	0.17 ± 0.36	0.86 ± 0.88	1.07 ± 1.11
Paranoid ideation	0.67 ± 0.45	0.51 ± 0.38	1.03 ± 0.86	0.34 ± 0.45	1.14 ± 0.95	1.26 ± 1.02
Psychoticism	0.45 ± 0.54	0.39 ± 0.56	0.65 ± 0.74	0.15 ± 0.31	1.19 ± 0.87	1.26 ± 0.98

NB: for study 1 – see chapter 3
for study 2 – see chapter 5
for study 4 – see chapter 7

Table 36: Non-problematic ecstasy users mean (SD) BSI dimension scores from the current studies compared to normative data consisting of non-patients, psychiatric out-patients and psychiatric in-patients (Derogatis & Melisaratos, 1983).

NON-PROBLEMATIC ECSTASY USERS				Normative data		
Symptom	**Study 1**	**Study 2**	**Study 4**	**Non-patients**	**Psychiatric Out-patients**	**Psychiatric In-patients**
Somatisation	0.52 ± 0.38	0.63 ± 0.56	0.45 ± 0.49	0.29 ± 0.40	0.83 ± 0.80	1.01 ± 0.91
Obsessive-compulsive	1.31 ± 0.99	1.09 ± 0.73	1.21 ± 0.74	0.43 ± 0.48	1.57 ± 1.00	1.51 ± 1.07
Interpersonal sensitivity	0.59 ± 0.54	0.69 ± 0.59	1.04 ± 0.88	0.32 ± 0.48	1.58 ± 1.05	1.48 ± 1.11
Depression	0.44 ± 0.51	0.45 ± 0.63	0.74 ± 0.69	0.28 ± 0.46	1.80 ± 1.08	1.77 ± 1.21
Anxiety	0.44 ± 0.36	0.56 ± 0.45	0.63 ± 0.65	0.35 ± 0.45	1.70 ± 1.00	1.70 ± 1.15
Anger/hostility	0.65 ± 0.65	0.60 ± 0.49	0.81 ± 0.83	0.35 ± 0.42	1.16 ± 0.93	1.00 ± 0.97
Phobic anxiety	0.14 ± 0.39	0.13 ± 0.22	0.36 ± 0.55	0.17 ± 0.36	0.86 ± 0.88	1.07 ± 1.11
Paranoid ideation	0.68 ± 0.57	0.58 ± 0.52	0.85 ± 0.75	0.34 ± 0.45	1.14 ± 0.95	1.26 ± 1.02
Psychoticism	0.40 ± 0.41	0.41 ± 0.53	0.66 ± 0.70	0.15 ± 0.31	1.19 ± 0.87	1.26 ± 0.98

NB: for study 1 – see chapter 3
for study 2 – see chapter 5
for study 4 – see chapter 7

Table 37: Drug naïve controls mean (SD) BSI dimension scores from the current studies compared to normative data consisting of non-patients, psychiatric out-patients and psychiatric in-patients (Derogatis & Melisaratos, 1983).

	DRUG NAÏVE CONTROLS		Normative data		
Symptom	**Study 3**	**Study 4**	**Non-patients**	**Psychiatric Out-patients**	**Psychiatric In-patients**
Somatisation	0.22 ± 0.30	0.46 ± 0.53	0.29 ± 0.40	0.83 ± 0.80	1.01 ± 0.91
Obsessive-compulsive	0.78 ± 0.58	1.05 ± 0.77	0.43 ± 0.48	1.57 ± 1.00	1.51 ± 1.07
Interpersonal sensitivity	0.55 ± 0.49	0.98 ± 0.89	0.32 ± 0.48	1.58 ± 1.05	1.48 ± 1.11
Depression	0.34 ± 0.44	0.69 ± 0.78	0.28 ± 0.46	1.80 ± 1.08	1.77 ± 1.21
Anxiety	0.37 ± 0.40	0.63 ± 0.65	0.35 ± 0.45	1.70 ± 1.00	1.70 ± 1.15
Anger/hostility	0.55 ± 1.32	0.65 ± 0.69	0.35 ± 0.42	1.16 ± 0.93	1.00 ± 0.97
Phobic anxiety	0.48 ± 0.22	0.37 ± 0.56	0.17 ± 0.36	0.86 ± 0.88	1.07 ± 1.11
Paranoid ideation	0.65 ± 0.57	0.88 ± 0.78	0.34 ± 0.45	1.14 ± 0.95	1.26 ± 1.02
Psychoticism	0.24 ± 0.36	0.58 ± 0.68	0.15 ± 0.31	1.19 ± 0.87	1.26 ± 0.98

NB: for study 1 – see chapter 3
for study 2 – see chapter 5
for study 3 – see chapter 6

compared to the non-patient population norms, though lower scores than psychiatric in- and out-patients. Therefore polydrug controls themselves appear to be showing signs of psychopathology.

In response to the question about the validity and reliability of polydrug controls, a new drug-naïve control group was employed. Their cognitive and psychological profiles were statistically compared with those ecstasy and polydrug using groups in the previous two empirical studies (studies one and two), essentially providing two additional data sets (see chapter 6). However, the introduction of a new drug naïve control group only indicated elevated somatisation in non-problematic ecstasy users and no other psychopathological dimension. In study 4 (chapter 6), which also employed a drug naive control group, non-problematic ecstasy users, still did not show any signs of elevated psychopathology, with the exception of sexual functioning. Again, when comparing the psychopathological scores of the drug naïve controls with normative data (table 37), with the exception of somatisation levels in study 3, drug naïve controls were also consistently reporting higher mean psychopathology scores compared to non-patient norms. This does raise the possibility that perhaps higher scores here are, to a degree, a function of the sample cohort and testing environment (i.e. they are different to patient norms in terms of a number of possible factors – setting, expectations, motivation etc.).

Regardless of whether or not ecstasy users score within the clinical range or not, the BSI is still only a self-report method of clinical measurement. Self-report clinical measures are thought to have significant utility in that they can access exclusive information not ordinarily available through other methods of assessment. They reflect information derived directly from the patient or individual in question, with ease, which can be scored and interpreted with regard to clinical decisions (Derogatis & Melisaratos, 1983). There are problems, however, with relying on self-report data, which could be affected by personality characteristics, attitudes, values and other traits at the time of completion. It would be interesting therefore, in future research, to include a more objective assessment of psychopathology, such as the DSM-IV or equivalent, to validate those self-report data.

Another possible methodological confound which may account for some of the inconsistencies concerning psychopathological findings between ecstasy users in this research programme and the majority of the literature, concerns the differences in assessment of

psychopathology status. In the previous literature demonstrating elevated psychopathology scores in ecstasy users, the SCL-90 and SCL-90-R had been employed with fairly consistent results across some of its subscales (Parrott et al, 2000; Parrott et al, 2001; Dugherio et al, 2001; Daumann et al, 2001; Morgan et al, 2002; Thomasius et al, 2003). In the current research programme psychopathology was assessed using the BSI (Derogatis & Melisaratos, 1983), a shortened version of the SCL-90 and SCL-90-R, which has not been previously used to assess recreational ecstasy users. Yet other measures have been used to assess depression such as the Beck Depression Inventory (MacInnes et al, 2001), Hamilton Rating Scale (Gamma et al, 2001), D-S [Depression Scale] (Daumann et al, 2001) and anxiety - State-Trait Anxiety Inventory (Daumann et al, 2001) and have still shown ecstasy users to have elevated depression and anxiety compared to controls. However, with the exception of the final study (chapter 7) the BSI was modified to include additional items reflecting sexual functioning, cognitive failures, MDMA side effects and four positive dimensions. Adapting the scale in this manner, or any modification of any scale, raises questions concerning the reliability and validity of the changed measure (Bradley, 1994; Cole et al, 2002). It is possible that these additions may have disrupted the factorial dimensions of the scale. Therefore, each questionnaire item may not be measuring what it pertained to measure in the original questionnaire. As such the inventory might not be truly reflecting the psychopathological dimensions it aims to identify and the potential subtle selective differences in psychopathological symptoms between experimental groups.

The psychometric properties of the scale could have remained unchanged but this cannot be assumed. Parrott et al (2001) adapted the SCL-90 in the same manner, including additional subscales reflecting sexual functioning, cognitive failures, MDMA side effects and the same four positive dimensions and presented a number of reasons why they did not believe this to be a problem (see Parrott et al, 2002 for further detail). Their data on this modified SCL-90 was later subjected to factor analysis (Milani, personal communication). It was found that the original nine dimensions of the SCL-90 remained unchanged. It is suggested that the additional scales added to the BSI have also remained unchanged, as the two measures (SCL-90 and BSI) have been shown to measure essentially the same symptom constructs. Derogatis & Melisaratos (1983) demonstrated that the BSI strongly correlates with the SCL-90-R, with correlations being uniformly very high across all of the nine dimensions.

Milani (personal communication) did demonstrate that the four positive subscales of the modified version positively correlated with one another and failed to constitute as separate robust factors which separate from one another. Therefore the validity and reliability of the findings relating to these positive subscales are seriously questioned and interpretation is limited. However, the implications of this, on the overall findings of this research thesis are limited, since there were no consistent group differences on these positive subscales across all studies.

The psychometric properties of the original BSI subscales also need to be considered based on the same pattern of data across groups in both chapter 3 (see figures 1- 7) and chapter 6 (see figures 17-19). Whilst it has been suggested that these are group trends it does raise the issue concerning the validity of the individual subscales within this measure. Previous research using the SCL-90 (Parrott et al, 2001; Dugherio et al, 2001) and the SCL-90-R (Daumann et al, 2001) only demonstrated differences between groups in selective subscales. In retrospect, it would have been better to look at the correlations between subscales of the BSI, within this thesis, and possibly reduced the number of psychopathological variables to be analysed. This may have allowed for more specific areas of psychopathology to be identified in the ecstasy using groups and also account for some of the inconsistent findings in symptoms between these studies and studies which have used specific measures such as the Beck Depression used by MacInnes et al (2001) or the State-Trait Anxiety Inventory used by Daumann et al (2001). Additionally, having one single measure, like the BSI and SCL-90R, that assesses different pathologies could also be problematic, in that systematic negative responding could possibly inflate the severity of some of the factors or maybe lessen the severity of others; a further argument for using separate questionnaires/measures to measure specific pathologies, in future research.

It is possible that differences in the findings for the non-problematic ecstasy users compared to the majority of data in previous studies could be due to methodological issues. However, whilst these arguments may account for inconsistencies in the findings between non-problematic ecstasy users and controls, it does not account for the fact that problematic ecstasy users showed elevated psychopathology compared to non-problematic ecstasy users for somatisation, depression and anxiety, (in both studies one and four) and phobic anxiety, paranoid ideation, psychoticism and interpersonal sensitivity (study one). It therefore appears that there could feasibly be two distinct ecstasy using groups which differ to the extent of

presented psychopathology. Possible accounts for this difference will be presented later in this chapter.

Positive effects

The four separate positive dimensions were introduced to the BSI to address the criticisms from advocates of recreational ecstasy use, who have stated that researchers are biased and focus solely on the negative effects rather than the positive effects of ecstasy use (Parrott et al, 2001). These positive dimensions included: feeling content with life, positive mood states, sociability and positive psychobiology (for example, feeling healthy and proficient, enjoying dancing or music and feeling full of energy). Problematic ecstasy users consistently reported similar positive symptoms, in all dimensions, compared to drug naïve controls and polydrug controls. The only exception was in chapter 6, with problematic ecstasy users reporting lower levels of positive mood states compared to drug naïve controls; which was consistent with the increased levels of depression seen in these users.

The non-problematic ecstasy users from chapter 7 displayed significantly higher levels of positive mood state compared to drug-naïve and polydrug controls, and higher levels of sociability compared to drug naïve controls. Considering that this group of ecstasy users did not show any obvious or consistent signs of psychopathology suggests that they have received positive benefits from taking ecstasy. This finding in this particular group of ecstasy users (i.e. non-problematic users) appears to conflict with that of Parrott et al (2001), who demonstrated slightly lower scores for positive mood for all three polydrug using groups (non-ecstasy polydrug users, light ecstasy polydrug users and heavy ecstasy polydrug users). The current findings are, however, consistent with the frequent reports of reasons why individuals use the drug in the first instance; for increased positive mood, feelings of euphoria, increased physical and emotional energy and heightened sensual awareness (Downing, 1986; Liechti at al, 2000a; Liechti et al 2000b; Gamma et al, 2000; Cami et al, 2000; Liechti & Vollenweider, 2001). However, these positive benefits do not appear to be consistent in all non-problematic ecstasy users within this programme. In chapters 3, 5 and 6 non-problematic ecstasy users (including ex-ecstasy users in chapter 5) did not exhibit higher positive symptoms than other control groups. This is in agreement with Parrott et al's (2001) data for the sociability, positive psychobiology and feeling content with life subscales.

Though again, comparisons of this nature need to be made with caution, as this study did not make the problematic and non-problematic distinction. Additionally, such variations in research findings concerning these positive scales may reflect the potential methodological problem mentioned earlier, in using additional scales which have not been validated and assessed for internal consistency, and which may not (or did not) appear to represent separate factors (as previously discussed).

Dose-related effects

Concerning lifetime consumption of ecstasy use; none of the studies within this research programme indicated a consistent dose-related effect between any psychopathological dimensions; this is inconsistent with most previous research. Parrott, Sisk & Turner (2000) demonstrated that heavier ecstasy users (who had used on more than 20 occasions, with a mean of 371 occasions) reported significantly higher scores on several dimensions of the SCL-90 compared to non-using controls: including somatisation, obsessionality, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism and appetite. Also, Parrott et al (2001) found that SCL-90 psychopathology scores increased as the use of psychoactive drugs increased, and Milani et al (2000) demonstrated a positive correlation between the amount of ecstasy used and reported levels of anxiety, phobic anxiety, psychoticism, MDMA side effects and total negative feelings.

Contrary to lifetime consumption levels, the current data on the average dose consumed on any one occasion positively correlated with anger, phobic anxiety and sexual dysfunction (chapter 3) and obsessive-compulsive, anger, phobic-anxiety and psychoticism scales (chapter 7). The average dose consumed, negatively correlated with the positive subscales of feeling content with life, positive mood and sociability. These findings are consistent with previous research. Milani et al (2001) found that perceived problems in 'problematic ecstasy users' were related to the number of pills taken in a single occasion. In addition, Schifano et al (1998) also found that those consuming larger doses of ecstasy in a single evening, were at a higher risk of psychopathological disorders. It therefore appears that it may be the intensity of ecstasy dosage which is crucial in the development of psychopathology, rather than total ecstasy consumption. However, these possible dose-related effects could reflect corresponding increases in polydrug use, as well as ecstasy use, since heavier ecstasy users have been shown to display a higher lifetime consumption of other drugs including cannabis,

amphetamine, cocaine and LSD (Parrott et al, 2001; Milani et al, 2001), and these drugs alone have been associated with psychopathology (Lavik & Onstad, 1986; Newcomb & Bentler, 1986; Newcomb, Scheier & Bentler, 1993; Mass et al, 2001).

OVERVIEW OF COGNITIVE FINDINGS

Short-term Memory

Within the current research programme short-term memory was measured using two tests: the Auditory Verbal Learning Test (AVLT; Rey, 1964) and the story recall component of the Rivermead Behavioural Memory Test (Wilson et al, 1991). The AVLT has been extensively used to evaluate memory functioning in normal samples and in a variety of clinical samples concerning different medical and psychiatric conditions (Lezak, 1995). Both problematic ecstasy users (including the individual examined for the case study) and non-problematic ecstasy users did not show any signs of impairment on short-term verbal recall memory as measured by the AVLT and RBMT story recall (compared to polydrug or drug naïve controls) in any of the studies. The current findings, concerning short-term verbal recall as measured by the AVLT, are inconsistent with the majority of previous research which has demonstrated impairments in AVLT scores, for both immediate and delayed recall, in ecstasy users (Fox et al, 2001c; Reneman et al, 2000; Reneman et al, 2001). However, others such as Thomasius et al (2003), have reported similar AVLT results. Previous research findings on the RBMT story recall have been less consistent. Morgan (1999) and Morgan et al (2002) showed deficits in story recall in ecstasy users, with similar patterns of ecstasy consumption to those in this thesis. However, in agreement with current findings, Thomasius et al (2003) and Morgan (1998) did not find evidence for story recall impairments in ecstasy users.

There are no available norms for the RBMT story recall task, but there are a number of available norms for the AVLT (Lezak, 1995; chapter 16). However, for the purposes of this research, data was compared with norms based on an Australian sample of 20 to 29 year olds of average intelligence published by Geffen et al (1990). These norms were preferable for comparison compared to other available norms, because they provide data for adults within the same age range, similar educational attainment and report the same recall trails as used in the current research programme; these are all factors that can potentially account for variances

in scores on this test (Mitushina, Kyle & D'Elia, 1999). When compared to normative data across all trials of the AVLT, all ecstasy using groups appeared to be performing below norms (table 38), suggesting that ecstasy users are possibly exhibiting short term verbal recall impairments. As mentioned before in the context of the psychopathological findings, this brings into question the validity of the polydrug control groups.

When comparing the polydrug controls with the normative data (table 39), this group can be seen to be consistently recalling fewer mean words per trial in comparison with normative data in all trials and across all studies. Therefore polydrug controls themselves appear to be showing signs of memory deficits. However, even when trying to compensate for this methodological issue by introducing a new drug-naïve control group (see chapter 6), no cognitive deficits were evident in any ecstasy using group. The drug naïve group did however highlight the significantly poor performance displayed by the polydrug controls on delayed recall trial. However, even this new drug naïve group performed below what would be expected compared to a normative data set. Thus, whilst the research programme does not provide any direct evidence that ecstasy users are showing signs of short-term verbal memory dysfunction, this is possibly due to poor control groups rather than the absence of cognitive impairments in ecstasy users.

Executive Functioning

Executive functioning was measured using the original manual version of the Tower of London task (Shallice, 1982), which purported to measure strategic aspects of executive functioning. Since participants were required to manually rearrange the balls, the task also examined psychomotor control. Neither the planning times nor these motor response times (represented by 'solution times') were found to differ between ecstasy using groups (problematic, non-problematic or ex-ecstasy users), polydrug controls and drug naïve controls, throughout this research programme. The individual case study, however, did show increased motor response times and planning times compared to polydrug controls and both non-problematic and problematic ecstasy users. However, this cognitive impairment could, in part, have been a consequence of the extensive psychopathological problems displayed in this particular individual, rather than just ecstasy use, since many psychiatric disorders can have an effect upon cognitive functioning (Velligan et al, 2002; Zilberman et al, 2003).

Table 38: Problematic, non-problematic and ex-ecstasy users mean (SD) AVLT recall scores from the current studies compared to normative data based on 20 to 29 year olds of average intelligence (Geffen et al, 1990).

	PROBLEMATIC ECSTASY USERS		NON-PROBLEMATIC ECSTASY USERS			
AVLT	**Study 1**	**Case Study**	**Study 1**	**Study 2**	**Study 2 Ex-users**	**Normative Data**
Immediate Recall						
Trial 1	5.93 ± 1.77	5	6.75 ± 1.48	6.19 ± 1.72	6.10 ± 2.00	**8.4 ± 1.2**
Trial 2	8.57 ± 2.41	8	9.50 ± 1.88	9.48 ± 2.14	8.30 ± 1.92	**10.8 ± 1.9**
Trial 3	9.43 ± 2.95	11	10.35 ± 2.32	10.33 ± 2.27	9.55 ± 2.16	**11.3 ± 1.6**
Trial 4	11.00 ± 2.08	11	11.70 ± 1.95	11.43 ± 2.29	11.10 ± 1.65	**12.2 ± 1.8**
Trial 5	11.00 ± 2.72	12	11.60 ± 1.73	11.62 ± 1.91	11.15 ± 1.98	**12.2 ± 2.2**
Interference Trial	4.86 ± 2.25	5	4.80 ± 1.58	4.14 ± 1.28	4.40 ± 1.47	**6.5 ± 1.8**
Trial 6	9.79 ± 2.69	7	10.50 ± 2.95	10.43 ± 2.62	10.1 ± 2.07	**11.1 ± 1.7**
Delayed Recall	8.29 ± 3.32	7	9.15 ± 3.45	9.90 ± 2.13	9.25 ± 3.35	**10.6 ± 2.4**

NB: for study 1 – see chapter 3
for study 2 – see chapter 5

Table 39: Polydrug and drug naïve controls mean (SD) AVLT recall scores from the current studies compared to normative data based on 20 to 29 year olds of average intelligence (Geffen et al, 1990).

	POLYDRUG CONTROLS		DRUG NAÏVE CONTROLS	
AVLT	**Study 1**	**Study 2**	**Study 3**	**Normative Data**
Immediate Recall				
Trial 1	6.30 ± 1.79	6.40 ± 1.79	6.10 ± 1.29	**8.4 ± 1.2**
Trial 2	8.80 ± 2.24	8.65 ± 2.62	8.85 ± 1.57	**10.8 ± 1.9**
Trial 3	10.80 ± 2.67	10.95 ± 2.58	10.45 ± 2.46	**11.3 ± 1.6**
Trial 4	10.80 ± 2.46	11.10 ± 2.65	11.55 ± 1.70	**12.2 ± 1.8**
Trial 5	11.55 ± 2.26	11.60 ± 2.44	12.10 ± 1.89	**12.2 ± 2.2**
	5.70 ± 2.64	5.45 ± 2.67	4.70 ± 1.69	**6.5 ± 1.8**
Interference Trial				
Trial 6	9.10 ± 2.81	9.70 ± 2.94	10.40 ± 2.68	**11.1 ± 1.7**
	6.05 ± 5.60	10.30 ± 2.75	9.55 ± 2.31	**10.6 ± 2.4**
Delayed Recall				

NB: for study 1 – see chapter 3
for study 2 – see chapter 5
for study 3 – see chapter 6

That groups of ecstasy users did not display any impairment on the TOL task relative to controls, is somewhat inconsistent with previous literature using the same measurement. Schifano et al (2001), Milani and Schifano (2000) and Fox et al (2001b) have all shown that ecstasy users, with similar levels of ecstasy use to participants in the studies in this thesis, perform significantly worse than controls on the manual version of the TOL. Studies which have not demonstrated executive deficits in ecstasy users on the TOL task have used the computerised versions of the task (Fox et al, 2002 and Morgan, 1998). There is no normative data currently available that relates to the manual version of the TOL (there are only 'norms' for the computerised CANTAB version), thus no valid comparisons or interpretations can be made concerning the general performance of ecstasy users and the validity of the control groups. However, the above observations regarding the poorly performing controls are quite likely to have affected the outcome of these trials.

Everyday Memory (including cognitive failures)

Everyday memory was measured using the Rivermead Behavioural Memory test, a battery of twelve psychological tests which assess the skills necessary for adequate functioning in normal life rather than performance on experimental tasks (Wilson et al, 1991). The overall profile and screening scores associated with this test battery did not differ between non- and problematic ecstasy users, polydrug or drug naive controls, in any of the empirical studies. Only the individual, RW, displayed poor performance on everyday memory measured by the RBMT. However, looking at the separate components of the RBMT, problematic ecstasy users performed poorly on the 'immediate delivery of a message' test compared to non-problematic ecstasy users, and 'remembering a first and second name' component compared to polydrug controls in the first study (chapter 1). Thus, cognitive impairments in everyday memory in ecstasy users is comparable to previous literature (Schifano et al, 1998; Milani and Schifano, 2000; Rodgers et al, 2001) but only in those ecstasy users that are defined as problematic ecstasy users, not in the non-problematic users. However, as this conclusion is based just on the one study here, which employed the full RBMT, these findings should be viewed with caution.

The small and limited impairments in everyday memory as measured by the RBMT may be due to the lack of sensitivity to the subtle memory deficits thought to be associated with ecstasy. The RBMT is designed as a screening instrument to detect brain damage (Wilson et

al, 1989) and, as such, this particular cognitive test may not be suitable for detecting subtle memory deficits, whether due to brain damage or the introduction of a drug or stressor (Wall et al, 1994; Wills et al, 2000). One future possibility for objectively assessing everyday memory in ecstasy users is to use the Extended Rivermead Behavioural Memory test (ERBMT) which doubles the amount of material involved in the assessment, by combining material from the different forms of the test. This is thought to increase the sensitivity to detect memory problems, by increasing the level of difficulty (Wall et al, 1994).

Self-perceived everyday cognitive performance was measured by the cognitive failures dimension of the modified BSI, which consisted of questions concerning the self-perception of a variety of cognitive slips over the previous 4 weeks. Problematic ecstasy users reported a significantly greater number of cognitive failures compared to drug naïve controls, though this finding was not consistent throughout the research (only in chapter 7). Non-problematic ecstasy users did not report elevated levels of cognitive failures compared to control groups. Again, this finding concerning self-perceived cognitive performance in non-problematic ecstasy users, appears to conflict with other studies (Rodgers, 2000; Heffernan et al, 2001; Fox et al, 2001b), where as the finding in problematic ecstasy users, support these previous studies. Again, as mentioned earlier, comparisons of this nature need to be made with caution as these previous studies did not make this distinction between problematic and non-problematic use.

Prospective Memory

Chapters 5, 6 and 7 failed to show any significant deficits in prospective memory in recreational ecstasy users compared to polydrug and drug naïve controls. This again, is inconsistent with the literature, where prospective memory deficits in recreational ecstasy users, compared to polydrug controls, have been demonstrated (Heffernan et al, 2001; Rodgers et al, 2001). This discrepancy may possibly be due to the different assessment measures used between studies. Prospective memory in the current studies was assessed using components taken from the RBMT (e.g. remembering an object and remembering to ask for an appointment). The reliability and validity of using these components alone has not been established with regard to assessing and measuring prospective functioning. Also, scoring these items was based on that used in the RBMT, which is based in turn on the whole test battery being utilised, and thus may be an unrepresentative scoring of prospective

memory alone. Bearing this in mind, it would be more ideal for prospective memory to be assessed, as a concept on its own, using a standardised prospective memory questionnaire as used in previous studies (i.e. Prospective Memory Questionnaire; Heffernan et al 2001, Rogers et al, 2001), but also to develop an objective assessment which is reliable and valid at measuring this cognitive function.

Reaction Time

A choice reaction time task was employed in study 1 (chapter 3). Neither ecstasy using groups showed any deficits on times compared to one another or the polydrug control group. This is consistent with most of the previous literature concerning unimpaired reaction time abilities in ecstasy users (Parrott et al, 1998; Rodgers, 2000; Fox et al, 2001b; Semple et al, 1999). The two previous studies that did demonstrate impaired reaction times in ecstasy users, only did so compared to drug-naïve controls (Croft et al, 2001) and in very heavy users, who had used considerably larger amounts of ecstasy (a mean of 741 tablets; Verkes et al, 2001) than any ecstasy using group within this research. Thus it appears that this cognitive process is relatively intact in ecstasy users and it was for this reason that reaction times were not measured in the subsequent studies.

Dose-related effects

According to the current research there were no dose-related effects of ecstasy (with respect to lifetime consumption, average dose and largest dose) on measures of reaction time, executive functioning, immediate and delayed RBMT story recall and cognitive failures. This agrees with the majority of the literature employing these cognitive assessment measures (Parrott et al, 1998; Verkes et al 2001; Morgan et al, 1998; Morgan et al, 1999; Thomasius et al, 2001).

However, dose-related effects were consistently found in the 'remembering name' task of the RBMT (lifetime consumption, average dose and largest dose), immediate AVLT recall (average and largest dose) and delayed verbal recall (average and largest dose). These results are in line with the psychopathological dose-response effects, it appears that it may be the intensity of ecstasy dosage on one or more occasions, rather than total ecstasy use, which is

crucial to the development of selective cognitive deficits concerning (AVLT assessed) immediate and delayed verbal memory.

Methodological issues concerning the variability in cognitive task administration

It has been suggested that inconsistencies between the cognitive findings from this current research programme and those in the existing literature may reflect poor control groups in these studies for valid statistical comparisons (chapter 6). However, it could also be partially due to variation in administration of the cognitive tasks between the procedures used in this thesis and previous research studies. It is acknowledged that there is little uniformity in administration of the AVLT (Lezak, 1995). Whilst the current studies employed the same number of AVLT trials as previous studies (e.g. Reneman et al, 2001 & 2001), there are a number of differences in task administration compared to existing literature. One inconsistency is the absence of a recognition trial, as reported in the studies by Reneman et al (2000 & 2001). Secondly, the interval between trial presentation and delayed recall in each of the present studies varied; since the length of delay was dependent on completion of other cognitive tasks within that time period. This variation in delay is inconsistent compared to previous literature, which has stipulated a specific time period (e.g. 20 minutes in Reneman et al (2001) and Thomasius et al (2003), and 30 minutes in Fox et al (2001)).

This latter issue, concerning cognitive activities in the interval period, also varies between studies, both within this current research programme and in previous literature. This in itself could account for differences in performance (Lezak, 1995). Finally, the time given for participants to recall the word lists is not described by researchers in any previous papers using this task; nor was it strictly controlled for within the current research programme. According to the instructions provided by Rey (1964), the time for word recall should be 60 seconds for the first trail and 90 seconds for all subsequent trials. Such lack of uniformity in procedures could account for some of the variance in the research findings (Lezak, 1995).

Similar arguments can be applied to the atypical RBMT story recall findings, especially concerning the delay period. Studies that have shown deficits in ecstasy users have tended to use a delay interval of 40-50 minutes, filled with a number of cognitively demanding tasks (Morgan, 1999; Morgan et al, 2002). The current research programme used a delay period of no more than 20 minutes, similar to the interval time used by Thomasius et al (2003).

Finally, it has been stressed that there is a necessity for standardised administration for the TOL, as differences in instruction and cueing, influence performance across all levels of difficulty on this task (Unterrainer et al, 2003). This is especially the case within this current research programme, since the manual TOL was employed, which increases the chances of error and variability in administration. This could possibly account for discrepancies in findings in executive functioning between this research and previous investigations.

ALTERNATIVE INTERPRETATIONS AND LIMITATIONS

Methodological problems are undoubtedly a very possible candidate for helping explain the discrepancies between the thesis findings and the ecstasy literature, as outlined above. In particular the issue of the inadequate controls, who were actually appearing to show signs of cognitive deficits and elevated psychopathology compared to normative data, questions the validity and reliability of these groups for comparisons and interpretations concerning ecstasy user's cognitive performance and psychopathological status. However, whilst these arguments may account for the inconsistencies in the performance between non-problematic ecstasy users and controls, the question still remains as to why problematic ecstasy users are showing signs of elevated psychopathology and some selective cognitive dysfunction, even compared to non-problematic ecstasy users.

Patterns of ecstasy use

It is difficult to ascertain whether the greater number and severity of psychopathological symptoms, and the cognitive deficits in problematic ecstasy users, relative to non-problematic ecstasy users, are due to differences in patterns of ecstasy use. From chapter 3, there were no significant differences in any patterns of ecstasy use compared to non-problematic ecstasy users (i.e. average dose, maximum dose on any one occasion and total lifetime consumption). However, chapter 7 indicated that problematic ecstasy users reported a significantly higher average dose of 2.89 compared to 1.82 tablets in non-problematic ecstasy users. They also reported a significantly higher maximum dose on any one occasion of 6.56 compared to 4.19 tablets in non-problematic ecstasy users; and a higher lifetime consumption of ecstasy of 404.61 compared to 117.27.

When comparing the patterns of ecstasy use of those problematic ecstasy users across the two studies, it appears that it may be the intensity and frequency of using ecstasy that may contribute to psychopathological symptoms in these ecstasy users. Problematic ecstasy users consumed much higher levels of ecstasy in their lifetime (404.61 in chapter 7 and 367.36 in chapter 3), compared to non-problematic ecstasy users (263.55 in chapter 3 and 117.27 in chapter 7). They had also consumed this higher level of ecstasy in a shorter period of time (61.29 months in chapter 3 and 75.02 months in chapter 7) compared to those non-problematic ecstasy users in study 1 and study 4 (83.7 months and 87.42 months respectively). The issue of intensity of dosing is also consistent with the dose-related effects discussed earlier for the psychopathological scores and selective cognitive deficits.

One important methodological limitation concerning the interpretation of differing patterns of ecstasy use between groups is that, as with the majority of published studies, it is impossible to obtain an objective assessment of MDMA consumption in these ecstasy using groups. The research into the long-term effects of recreational ecstasy use is based on the model of MDMA-induced serotonergic neurotoxicity. This model assumes that recreational ecstasy users are actually consuming doses of MDMA that are actually neurotoxic. However, differences in self-report patterns of ecstasy use, between user groups, may not necessarily reflect differences in MDMA consumption, since there is no control over MDMA administration, nor is there any confirmation of the dose and the purity of MDMA taken.

There is little quality control on the streets regarding the content of ecstasy tablets (see Parrott, 2004 for a comprehensive review), with considerable variation in the composition of tablets, even with tablets which are physically similar in appearance and have the same brand name (Sherlock et al, 1999; Bell et al, 2000). Analyses of tablets sold as ecstasy have shown that they do generally contain MDMA, but that levels of the compound vary. Sherlock et al (1999) examined 25 tablets handed in under amnesty in the UK and found active doses of MDMA to be approximately 80-150mg. Weir (2000) examined a larger sample of 69 tablets sold as ecstasy in Europe between 1995 and 1997. Of the 30 that contained MDMA, levels ranged from 2mg to 149mg. Some studies have even reported samples of ecstasy tablets with MDMA levels as high as 180mg and 200mg (O'Connell & Heffron, 2000 and Christopersen, 2000, respectively). The most recent study by Palenicek et al (2002) reports levels ranging from 30mg to 100mg of MDMA per tablet.

Ecstasy tablets have also shown to include analogues of MDMA and other active substances: such as MDEA (3,4-methylenedioxy-N-ethylamphetamine), MDA (3,4-methlyenedioxyamphetamine), caffeine, amphetamine, methamphethamine, paracetamol, ketamine, ephedrine, aspirin, pheneylethylamine dextromethorphan (DXM), pseudoephedrine, and salicylates (Schifano, 1998; Sherlock et al, 1999; Weir 2000; Palenicek at al, 2002; Baggott et al, 2000). Reports of unusual or unexpected effects from ecstasy therefore may be explained by the presence of these other substances in ecstasy tablets. Ecstasy tablets are rarely if ever contaminated with toxic impurities (Schifano, 1998; King, 2000), but approximately 8-10% of drugs sold as ecstasy, contain no active ingredient whatsoever (Weir, 2000; Baggott et al 2000). The likelihood of consuming MDMA in an ecstasy tablet varies depending on the batches available at that time, size of the sample examined and geographical location of where the tablets are obtained (Parrott, 2004). From an Italian sample, of at least 20,000 tablets, Schifano (1998) found that 85-90% of tablets contained MDMA as the active ingredient. A study from the Czech Republic found that over 80% of tablets tested contained only MDMA (Palenicek et al, 2002), whereas latest reports suggest that non-MDMA tablets are rare, with purity levels between 90 and 100% (Parrott, 2004).

It is clear that there are uncertainties over the chemical constituents of ecstasy tablets, and these may be an important confounding factor when assessing the effects of MDMA-induced neurotoxicity and when comparing ecstasy user groups. One can only provide an estimate when calculating MDMA intake in human studies, which until recently has been the average dose of 100mg (Bolla et al, 1998; Christopersen, 2000). However, Cole et al (2002) suggest evidence that the quality of the ecstasy tablet has actually declined since the beginning of the 1990's. In their analysis of 80 ecstasy tablets, MDMA content ranged from 20-109mg, but the mean content was 60-69mg, much lower than the 100mg commonly assumed in past empirical studies (for example, Bolla et al, 1998). Debate still continues though, since in a review of this question, Parrott (2004) argues that since the late 1990's the proportion of ecstasy tablets containing active MDMA has actually increased to a comparatively high level again. Needless to say, the changes (regardless of whether it is an increase or decrease) in MDMA content need to be taken into account when interpreting potential differences in patterns of ecstasy use within and between user groups.

Other drug use

Throughout the research programme all ecstasy using groups reported using significantly more, other drugs than polydrug controls. This polydrug use is in line with epidemiological findings which suggest that ecstasy users are more likely to be polydrug users (Webb et al, 1996; Pederson & Skrondal, 1999; Topp et al, 1999; Winstock et al, 2001; Strote et al, 2002; Arria et al, 2002). Riley et al (2001) reported that 81% of their sample reported mixing drugs and/or alcohol. A majority of ecstasy users (92.1%) report co-administration of cannabis (Strote et al, 2002), but ecstasy use also has a high association with other drugs such as amphetamine, LSD, amyl/butyl nitrate, cocaine, tobacco and alcohol (Webb et al, 1996; Riley at al, 2001; Topp et al, 1999). These drugs alone have been shown to be associated with various psychopathological symptoms (Mass et al, 2001; Lavik & Onstad, 1986) and cognitive impairments (Horner et al, 1999; Ling et al, 2003; Pope et al, 2003; Pope et al, 2001 Demir et al, 2000; Blume, 2001; Stein et al, 1997 and Hoff et al, 1996). Polydrug use has also been associated with higher ratings of psychopathology (Milani et al 2000; Parrott et al 2000). It is thus possible that the psychopathological and cognitive findings in problematic ecstasy users within this research may be due to wider polydrug use. However, despite problematic ecstasy users reporting significantly more use of most other drugs compared to the polydrug controls, they only reported significantly higher levels of LSD and magic mushrooms than non-problematic ecstasy users in chapter 7, and Prozac and monthly cannabis use in chapter 3. This would seem to undermine the idea that the elevated symptoms in problematic ecstasy users are due to differences in levels of other drug consumption.

Another area for consideration is the long-term implications of possible interactions of various drugs, when consumed in combination with or directly following and/or preceding ecstasy use and whether the use of one drug will enhance the potential toxicity of other drugs at a later time. At present little is known of the pharmacological effects of these drug interactions and whether they may possibly enhance or protect toxicity. For example, amphetamine has been shown to enhance the level of MDMA-induced neurotoxicity (O'Loinsigh et al, 2000); whilst alcohol has been shown to have a neuroprotective effect against MDMA induced neurotoxicity (Miller & O'Callaghan, 1994). It is likely that administering such drugs together produces slightly different effects compared to using ecstasy alone. Hernandez-Lopez et al (2002) addressed the combination of MDMA and alcohol in a double-blind, double-dummy randomised crossover trial consisting of nine male

volunteers. MDMA used in combination with alcohol induced longer lasting euphoria and well-being than MDMA or alcohol alone, whilst MDMA actually reversed the subjective sedation induced by alcohol. Verheyden et al (2003) reported that participants who took cannabis, alcohol and cocaine in conjunction with ecstasy reported higher scores on a acute positive effects of the drug, suggesting that the subjective pleasurable effects of these drugs are additive. Further still, they showed that users who had used cocaine in conjunction with their ecstasy use scored higher on the acute negative and positive effects compared to ecstasy users that had not used cocaine, whereas those who had used amphetamine and ecstasy together reported higher physical effects than those that had not. A more recent study has also implicated the additive effect nicotine has on neurocognitive functioning in ecstasy users (Friend et al, 2004). These findings may be of possible clinical significance considering that these substances are commonly co-administered, and considering that ecstasy users are almost exclusively polydrug users. The exploratory findings from study 4 (chapter 7) support this claim to some extent, with problematic ecstasy users attributing various problems to various drugs and combinations of their drug use, not just ecstasy use. It could also be speculated that the intensity of ecstasy use in the problematic group could mean that this group were also more likely to have used a number of combinations of drugs in a shorter period of time compared to non-problematic ecstasy users, again increasing the possibility of even greater neurotoxic injury and subsequent functional consequences. Future studies, comparing ecstasy users who use ecstasy alone, with ecstasy users that use it in conjunction with other drugs such as alcohol, cannabis, cocaine and amphetamine are needed. Similar questions also need to be asked pertaining to their patterns of use, akin to those asked of ecstasy users (e.g. average consumption and maximum consumption on each occasion and duration of usage). This future study, may shed some light into the clinical implications of drug interactions.

Whilst reported patterns of ecstasy and other drug use is a possible explanation for the differences in problematic ecstasy users compared to non-problematic ecstasy users, there are important methodological limitations concerning this interpretation. Throughout all the five studies, profiles of individual's ecstasy and other drug use was based solely on self-report data with no biological assays to verify this data. Self-report data is not always reliable. These reports are unlikely to be wholly accurate and may often underestimate or overestimate ecstasy consumption, especially considering the variety of chemicals sold under the name of ecstasy. They may also under- or overestimate their usage either because of fears about confidentiality or to heighten their 'street credibility'. Also, retrospective accounts of drug

use history rely on memory; both the theoretical model of MDMA toxicity and the evidence of cognitive performance in ecstasy polydrug users problematise the reliability and use of self-report.

Biochemical markers could have been employed in this research programme in order to verify self-report drug use data. Hair analysis has been proposed as a method of providing long-term qualitative and quantitative information concerning individuals' retrospective drug use (Kikura et al, 1997; Allen & Oliver, 2000). In addition, through using methods such as chromatography/mass spectrometry (GC/MS; Allen & Oliver, 2000) or by ion mobility spectrometry (IMS; Keller et al 1998) the detection of deposits of MDMA, its metabolites and other compounds in the hair shaft can be found, therefore confirming whether MDMA has actually been ingested, since not all tablets sold as ecstasy contain the psychoactive ingredient MDMA (Weir, 2000; Baggott et al 2000; Parrott, 2004). Kikura et al (1997) detected MDMA in all hair samples from 7 individuals who reported that they had used ecstasy and also Semple at al (1999) reported that hair analysis generally confirmed the drug history given by participants. A recent large-scale study of 110 volunteers that compared drug concentrations analysed by GC/MS, with self-reported drug histories showed a concordance rate of greater than 50% between self-report drug history levels and levels detected using hair analysis and concluded therefore that there is some reliability in self-report data on drug use (Cooper et al, 2000). However, this still leaves approximately 50% of self-report data that does not match with levels detected by hair analysis. Additionally, Cooper et al (2000) failed to find any correlation between the reported numbers of ecstasy tablets consumed and the levels detected in the hair. Thus, whilst hair analysis may give some objective indication of drug use, it can only be used for a medium term of drug usage (e.g. 6-12 months), as measurement of previous drug use is solely reliant on hair length, and in addition, consistency and reliability of this method has yet to be established.

Perhaps a more immediate application of biochemical assay could be in the process of confirming more short-term drug taking and abstinence, in particular, given that the half-life of MDMA in animals is between 1 and 2 hours, a 2-week abstinence period prior to cognitive and psychopathological assessment was deemed sufficient to rule out any withdrawal or possible residual effects of the drug. However, the current research programme failed to objectively confirm that individuals were abstinent from ecstasy for two weeks prior to cognitive and psychopathological assessment, or even absent from other drugs on the day of

assessment. Since participants knew that payment was given for completion in all studies (with the exception of the last one), it is possible that they avoided being excluded from taking part, by fabricating when they had last consumed drugs. To avoid such issues urine and/or blood samples need to be used on the days of assessment to confirm the necessary period of abstinence/presence from drugs. Urine and blood screens have proved to be consistent with self-reported drug histories by Schifano et al (1998) and Sherlock et al (1999) reported that 29 of 31 respondents who reported taking ecstasy tablets on the night of the study actually had MDMA present in their urine. However, Curran (2000) argues that whilst blood and urine screens can detect drugs like cannabis 2 to 3 weeks after use, amphetamines such as MDMA can only be detected 24 hours to 48 hours after the last dose. Therefore, ideally a combination of hair analysis (assessing drug use in the previous 4 weeks) and urine analysis need to be used for verification of self report data and drug abstinence. However, there are still limitations with hair analysis verification as mentioned earlier.

Pre-existing Differences

One possible explanation for the emergence of two distinct groups of ecstasy users, may be due to pre-existing vulnerabilities in individuals (i.e. in those individuals that report problems associated with their ecstasy use). In the current research programme, a greater number of problematic ecstasy users (both in chapters 3 and 7) reported previous psychiatric histories compared to non-problematic ecstasy users and in, chapter 7, a greater number of them had a family history of psychiatric illness. Thus, pre-existing psychiatric differences may have contributed to these 'ecstasy-related' problems in one of two ways. Firstly, it may be the case that these individuals had a genetic pre-disposition for such psychopathological problems, hence the difference in psychiatric history between the two ecstasy using groups. The classic diathesis model for mental health, proposes that the combined impact of genetic predisposition and an environmental stressor, produces a given negative mental health outcome (Gabbard & Goodwin, 1996). In the individuals assessed here, their ecstasy use may have constituted this significant external stressor by negatively modulating normal brain function. In less vulnerable individuals, ecstasy use alone may not be sufficient for the emergence of psychological problems.

Secondly, these problems, regardless of whether they were caused and/or influenced by genetic and/or environmental factors, may have existed prior to their ecstasy use. There is the

possibility that the onset of psychopathological problems may have preceded rather than followed initiation of ecstasy and other drug use, and thus was a cause, rather than an effect of ecstasy use, since poor premorbid adjustment is associated with increased drug use. The retrospective nature of the studies in this research programme and in previous research means that this issue has not been addressed. In a prospective-longitudinal study in a non-clinical sample, Lieb et al (2002) found that in a majority of cases (88%), ecstasy and other polydrug use was actually secondary to the onset of DSM-IV mental disorders and psychological problems. These pre-morbid disorders consisted mainly of specific phobia (98.4%), social phobia (76.6%), alcohol abuse/dependence (78%), and somatoform conditions (73.2%). In an additional prospective-longitudinal study, it was revealed that ecstasy use was secondary to the onset of DSM-IV mental disorders in the majority of cases, and the risk of initiation of ecstasy use was higher in those individuals who presented themselves with a mental disorder at baseline. However, the relationship between drug use and vulnerability to psychopathology is not always that simple. Brady et al (1993) reported that whilst females were more likely to suffer from depression and other affective disorders prior to their drug use, males were more likely to develop depression after the onset of drug use, indicating that psychiatric factors may precede or contribute to the initiation of drug use in females, but be more consequential to drug use in males. This finding was later supported by Zilberman et al (2003) who reported that females where more likely to use drugs as a result of mood and anxiety disorders, whereas males were more likely to show psychiatric problems after the onset of drug use. Due to the methodological design of the current research programme it is difficult to ascertain whether the psychopathology in problematic ecstasy users were primary or secondary to their drug use, additionally, gender differences was not the focus of the research.

Similar pre-existing vulnerability factors could account for the differences in cognitive abilities between the non-problematic and problematic ecstasy users, though group differences for these capacities were weaker and less consistent. It is also possible that the selective cognitive deficits presented in the problematic ecstasy users, but not in the non-problematic ecstasy users, are actually secondary to their psychopathological problems, rather than ecstasy per se. This is of particular salience since the problematic ecstasy users were consistently showing signs of elevated depression and anxiety. Depression and anxiety disorders both have a potential to effect cognition by producing a slowing of psychomotor abilities (Lezak, 1995), a prevailing "frontal" cognitive profile (Goodwin, 1997), deficits on the TOL task, visual search task (Beats et al, 1996) and executive functioning (Purcell et al,

1997) and distractibility and attentional disorders (Eysenck, 1982). Cognitive dysfunction itself is part of the DSM-IV diagnostic criteria for depression, anxiety and other axis I and II disorders.

These possible arguments may account for the development of problematic ecstasy use. Such pre-existing factors could also account or certainly contribute to the patterns of ecstasy use. For example, a slightly depressed or anxious individual may need to consume more ecstasy tablets in order to achieve the subjective effects similar to those experienced by 'normal' individuals and/or part of their ecstasy usage, is a form of self-medication for these pre-existing pathologies. Both these issues may explain the differential patterns of ecstasy usage between the problematic and non-problematic ecstasy users in this research.

Previous studies assessing the cognitive and psychopathological effects of ecstasy use have not explicitly addressed such premorbid issues, which could potentially limit the interpretation of their findings. One of the key challenges for future research is to attempt to screen for and control these possible pre-morbid psychological characteristics in ecstasy users, before concluding that ecstasy is a primary risk factor for the onset of certain psychopathological problems.

Secondary personality traits

Secondary personality differences between non-problematic and problematic ecstasy users may also play a role in the discrepancies between the two groups in psychopathology scores and cognitive performance. It is well established that childhood problems and personality traits such as antisocial behaviours, sensation seeking and impulsivity, are associated with an increase risk of experimenting with controlled drugs and developing substance abuse problems (Bardo et al, 1996; Hawkins et al, 1992; Zuckerman et al, 1994; Hatzitaskos et al, 1999; Clark et al, 1998). This would be consistent with studies showing elevated scores on trait impulsiveness in ecstasy users compared to controls (Morgan, 1998; Morgan et al, 2002; Montgomery & Butler, 2001a & b). These secondary personality factors are also associated with lower serotonergic functioning (Linnoila et al, 1993; Virkkunen et al, 1995). It may be plausible that the problematic ecstasy users within this research programme displayed premorbid personality differences compared to non-problematic ecstasy users, which may have caused and/or contributed to the development of problems.

These personality traits alone may account for the psychopathological scores and cognitive deficits in the problematic ecstasy users, since many of these personality traits, independent of drug use, are also associated with poorer cognitive performance and increased risk of developing adult psychopathology (Zuckerman & Neeb, 1979; Hawkins & Trobst, 2000). Previous studies on ecstasy users have shown differences in impulsiveness (Morgan et al, 1998; Parrott, Sisk & Turner, 2000; Montgomery & Butler, 2001a & b), sensation seeking (Daumann et al, 2001) and novelty seeking (Dughiero et al, 2001; Montgomery & Butler, 2001) compared to controls. In many of these studies, ecstasy users have also shown elevated levels of psychopathology (Parrot, Sisk & Turner, 2000; Morgan, 1998; Daumann et al, 2001; Dugherio et al, 2001). Additionally, in a pharmacological challenge study using d-fenfluramine, Gerra et al (1998) actually found correlations between prolactin changes and novelty seeking scores in ecstasy users. Laviola et al (1999) reported that both elevated novelty seeking scores and an interrupted monoaminergic functioning were both associated with adolescent ecstasy use compared to controls, suggesting there may be a premorbid condition or personality style/trait involving some 5-HT deficiency in ecstasy users. However, again these studies did not define whether the ecstasy users considered themselves to be problematic or not; but they highlight that such premorbid states, especially ones that are known to be related to low 5-HT function, could contribute to a misleading impression that cognitive deficits and increased psychopathology are caused by problematic ecstasy use.

There is support for personality traits interacting with problematic ecstasy use, at some level. Fox et al (2001b) examined the differences between self-reported problematic (psychological, emotional and somatic problems) and non-problematic ecstasy users in relation to both consumption and premorbid life adjustment variables. The problematic ecstasy group had significantly higher scores on all scales of the SCL-90 compared to the non-problem group. However, their self-perceived problematic use was shown to be unrelated to their drug use but instead to negative interpersonal relationships prior to taking the drug and less socially orientated motivations for using the drug.

The last empirical study of the current research thesis attempted to explore a potential personality indicator of problematic ecstasy use on the basis of attribution and, specifically, whether individuals that self-perceived themselves as problematic had a different locus of control to those ecstasy users that did not perceive themselves as problematic (chapter 7).

Despite the fact it has been shown that higher rates of psychopathology are related to an external locus of control (Hale & Cochran, 1987), this personality construct was not found to be of importance in determining whether individuals reported problems attributable to ecstasy use in the current study. However, the fact that a higher percentage of problematic ecstasy users reported life changes attributable to ecstasy suggests that some form of attributional style may still play some role in problematic ecstasy use.

It therefore appears that in future research, there is a need to incorporate an objective assessment of secondary personality factors. Of particular importance is the need to control for axis II disorders, such as a personality disorder, as well as axis I disorders, which previous research has tended to ignore.

Serotonergic Neurotoxicity

The fundamental underlying assumption in the current and previous research is that recreational-ecstasy use causes serotonergic neurotoxicity (see chapter 1 for details) and the functional consequences of this neurotoxicity are thought to be in behavioural domains influenced by serotonin (see chapter 2 for details). Whilst the problematic ecstasy users are displaying evidence of elevated psychopathology and also some cognitive deficits, non-problematic users are not. Based on this assumption, it could be suggested, perhaps controversially, that the non-problematic ecstasy users have not incurred significant or indeed any serotonergic neurotoxic injury whereas the problematic ecstasy users have.

There are arguments, and supportive evidence from both animal and human research, to suggest that there may be a critical threshold of serotonergic activity below which functional sequalae develops. It is possible that problematic ecstasy users may be more vulnerable to the neurotoxicity of ecstasy by virtue of a lower serotonergic 'injury' threshold. Individual 5-HT neurons may be more robust in some users and thus this injury threshold is not reached, therefore not developing functional problems. Or perhaps, more likely, that some individuals have lower levels of 5-HT to begin with and less serotonergic injury is needed to reach this critical threshold.

Heuther et al (1997) argues that this threshold is hard to predict from animal models as there are a number of important species differences. Even within the same species there are genetic

differences in individual vulnerabilities (Zhou et al, 1996). Also, the dose of MDMA required to cause serotonergic damage, depends on state parameters such as age, health state, environmental temperature, environmental surroundings and fluid supply. Bowyer et al (1994) and Broening et al (1994 & 1995) showed that if hyperthermia is elicited in animals whilst under the influence of MDMA, serotonergic neurotoxicity was enhanced. However, a more recent study which assessed both serotonin depletion and behavioural measures (anxiety, cognition and depression) at different ambient temperatures at the time of drug administration, produced different findings. McGregor et al (2003) showed that, in rats, hyperthermia at the time of MDMA administration was not necessary to produce serotonergic depletion and subsequent long-term anxiety and depression. In addition, poorer cognition was only observed in the rats at the highest ambient temperature. Such inconsistent findings continue to fuel the debate concerning whether or not the extent to which human recreational ecstasy users 'chill out' whilst on ecstasy, affects neurotoxicity and functional consequences. Another important area of inquiry, which may shed light on the inconsistencies in the ambient temperature debate concerns the age of initiation of ecstasy use. This factor may also account for differences in the problematic and non-problematic ecstasy users within the current research.

Newcomb et al (1993) found that whilst teenage polydrug use had few effects on adult mental health, specific drug use (for example, cannabis and cocaine use) in adolescence and changes in these patterns in young adulthood, predicted later psychopathology. Adolescent onset of substance use disorder, compared with adult-onset, resulted in higher rates of depression (Clark et al, 1998), and in alcoholics, early-onset alcoholism resulted in more depression and anxiety symptoms compared to late onset alcoholism.

Early onset cannabis users, but not late onset users, exhibited significantly longer reaction times than controls (Ehrenreich et al, 1999). Also there were differences in cerebral blood flow (higher in early-onset; Wilson et al, 2000). However a subsequent study, only found differences in early versus late onset cannabis use on verbal IQ but not other areas of cognition. This research suggests that early onset of drug use might have the effect of disrupting the developmental processes that leads to successful adaptation during adolescence, such that adolescent drug use appears to increase the risk of developing drug-related problems (Laviola et al, 1999). This inconsistency in age of onset in humans could be accounted for by the different drug using populations and the different pharmacological

actions. However, the discrepancy could also be accounted for by possible age-related metabolic differences in individuals and metabolic handling of certain drugs.

Morley-Fletcher (2004) noted that early differences in metabolism of MDMA play a role in the behavioural changes associated with the drug and that these effects are detectable at the adolescent stage. Differences in MDMA metabolism have also been reported in humans (Kreth et al, 2000), as well as animals. Polymorphic enzyme cytochrome P450 2D (CYP2D6) is involved in the metabolism of a broad array of drugs. Kreth et al (2000) and Ramamoorthy et al (2002) have shown that individuals who lack fully functioning CYP2D have a reduced ability to metabolise MDMA. Since unexpected adverse effects of drugs are often related to their metabolism, it is possible that the differences in the capacity to metabolise ecstasy, specifically MDMA, may determine or modulate inter-individual acute toxic reactions (Schifano, 2004) and potentially long-term ecstasy-related neurotoxicity, and have an impact on the development of ecstasy-related problems in particular individuals. Thus it could be speculated that the problematic ecstasy users within this research programme may, with regard to metabolism, have a predisposing genetic risk to the adverse effects of ecstasy.

A number of alternative arguments for the discrepancy in findings between the problematic ecstasy and non-problematic ecstasy users within this current research programme have been discussed. Whilst these propositions are plausible, suggestions for the differences between the two ecstasy using groups may need to be verified with the use of biochemical assays, further analyses and additional studies, before any firm conclusions can be drawn. But according to these interpretations it does appear that ecstasy use is more toxic and is a higher risk factor for the development of adverse psychopathology and cognitive dysfunction in some populations of ecstasy users more than others. This may be due to patterns of use, predisposing genetic risks, premorbid differences, personality and environmental factors and the age of onset; or possible some multi-factorial combination of such influences.

Recruitment Strategies:

Definitions of problematic ecstasy use

Whilst possible accounts have been discussed concerning the differences in non-problematic and problematic ecstasy users within the current research programme, there is still the need to

account for the discrepancies between the current findings and the previous literature on ecstasy use, cognition and psychopathology. Methodological issues concerning valid and reliable control groups seem to be the likely explanation (as previously addressed), but the discrepancy could be accounted for by the differing criteria for inclusion into drug user groups. Studies that have demonstrated elevated psychopathology and cognitive deficits in ecstasy users compared to polydrug controls (e.g. Dugherio et al, 2001; Daumann et al, 2001, Thomasius et al, 2003; Parrott, Sisk and Turner, 2000; Parrott et al, 2001; Morgan et al, 2002; Reneman et al, 2001) do not define whether or not the ecstasy users employed in their research considered themselves as problematic. Parrott, Sisk and Turner (2000) and Parrott et al (2001) did not state any exclusion criteria and there was no objective assessment of psychiatric status in the ecstasy users employed in their studies. Morgan et al (2002) did exclude participants who reported a psychiatric history, but there was still no objective assessment of ecstasy user's psychiatric status at the time the research was conducted. In these studies, therefore, it is possible that their samples of ecstasy users could have consisted of both problematic and non-problematic ecstasy users, hence it is difficult to address whether the research findings concerning the problematic ecstasy users in this current study are consistent with that of previous research.

Even within this research programme the inclusion criteria differs between studies for 'problematic ecstasy users'. In the first study (chapter 3) problematic users were defined as recreational users of ecstasy who reported problems which they attributed to past ecstasy use, and which had to be clinically defined and/or to interfere with the individual's life to the extent that they had sought some form of help. In chapter 7 there was a looser, less stringent definition: ecstasy users who reported problems that they attributed to their past ecstasy use. Thus, the latter group could have consisted of ecstasy users not defined as problematic ecstasy users according to the criteria in chapter 3. This difference may also have accounted for differences in scores in problematic ecstasy users between studies. However, when BSI data from chapter 7 was analysed using the 'problematic ecstasy user' criteria from the first study (chapter 3), the problematic ecstasy users (both help seeking and non-help seeking users) were still reporting higher psychopathological scores on a number of subscales (appendix, table 39). The only difference appeared with the depression and anxiety subscales, where 'help seeking' problematic ecstasy users appeared to be reporting higher depressive and anxiety symptoms (appendix, table 41). These findings suggest that for ecstasy use to be problematic to the user, it is not necessary or crucial for them to have sought help for their

problems. Individual problematic perceptions and attributions appear to be valid in representing whether ecstasy use is problematic or not.

Thus, when comparing the current findings with that of the previous literature it is important to bear in mind the inclusion and exclusion criteria for ecstasy users, employed in studies, when interpreting their findings. There is also a need within future ecstasy research to be clear on the definition of 'problematic' ecstasy use before drawing any conclusions concerning ecstasy and the development of clinical problems.

Adequate control groups & recruitment strategies

One of the main issues that has arisen throughout this thesis is the limitation of data interpretation due to poor control groups. Initially it was thought that the inconsistent findings between non-problematic ecstasy users and polydrug controls were possibly confounded by the extent and nature of polydrug use. The study in chapter 6 attempted to address the possible role of polydrug use in relation to cognitive and psychopathological deficits, in ecstasy and non-ecstasy polydrug users, by including a drug-naïve control group. However, the inclusion of this fourth experimental group failed to identify any further cognitive deficits or psychopathology in the drug using groups. In fact, these drug-naïve controls were actually showing symptoms relating to phobic anxiety, above levels exhibited by polydrug controls, ex-ecstasy and current ecstasy users, which in itself may have impacted upon their cognitive performance. It is therefore necessary for a suitable control group to be established for adequate comparisons to be made on cognitive and psychopathological functioning in drug using groups. Control groups should consist of individuals with similar lifestyles and backgrounds to other experimental groups and also be screened for psychiatric and premorbid personality disorders using an objective diagnostic tool.

It was observed, during data collection, that the participants who volunteered for these studies did so for a variety of (often conflicting) reasons. Like some studies, and more specifically case studies, this research relied on participants presenting themselves as problematic ecstasy users. Many of those that self-selected themselves in the 'problematic' group, in the first study, had a very strong personal interest in the study, perhaps in an attempt to gain understanding and insight into the cause of the problems which they attributed to their past ecstasy use. This confirms the belief of Cole & Sumnall (2003), who suggested that ecstasy

research consists of samples of individuals who are coming forward to confirm their fears about adverse effects that have been raised in the media profile. However, many (but not all) of the current ecstasy users who still advocated ecstasy use, volunteered to take part to try and dispel the belief that ecstasy can contribute to cognitive and psychopathological dysfunction. Certainly, asking for "non-problematic" ecstasy users could result in attracting ecstasy users who are from a very different cohort of users compared to those used in existing studies. Regardless of the reason for volunteering, it could be argued that ecstasy users that contribute to these studies are highly motivated participants with their own personal agenda for contributing to the ecstasy research. In contrast, most of the polydrug and drug-naïve controls who volunteered, did so more for financial reward. Such variations in motivations for taking part in research could possibly have confounding effects on research outcomes and certainly warrants further investigation when documenting ecstasy-related effects.

In addition to conflicting motivational issues, the lifestyles of experimental groups differed to varying degrees, which could also affect variances in cognitive and psychopathological performances. Current ecstasy users are unlikely to have the same lifestyle patterns as non-drug using controls or cannabis using controls. They tend to have repeated circadian disruption, extended aerobic exercise and altered patterns in appetite, which could all effect or contribute to cognitive and affective states (Turner et al, 2000). This differs somewhat to ex-ecstasy and problematic ecstasy users, who are no longer, part of that clubbing lifestyle, and also to polydrug and drug naïve controls. Also, the polydrug and drug-naïve controls tended to be recruited mainly using the snowball technique rather than through advertisements in clubs and clubbing magazines. Using the snowballing technique to recruit participants has the obvious potential bias, in that it may limit recruitment of individuals from particular social networks and subcultures and in the case of this research predominantly consisted of undergraduate students. The work presented here raises the question as to whether research should avoid using undergraduate students as a control sample, since their possible lack of motivation and interest in the studies may have prevented them from performing to the best of their abilities, which could account for the poor cognitive performances throughout this research programme.

To avoid the possible motivational and lifestyle confounds raised in using drug-naïve or polydrug control groups to potentially demonstrate the cognitive and psychopathological profiles of ecstasy users, it would be of interest to use a sample of other drug using groups

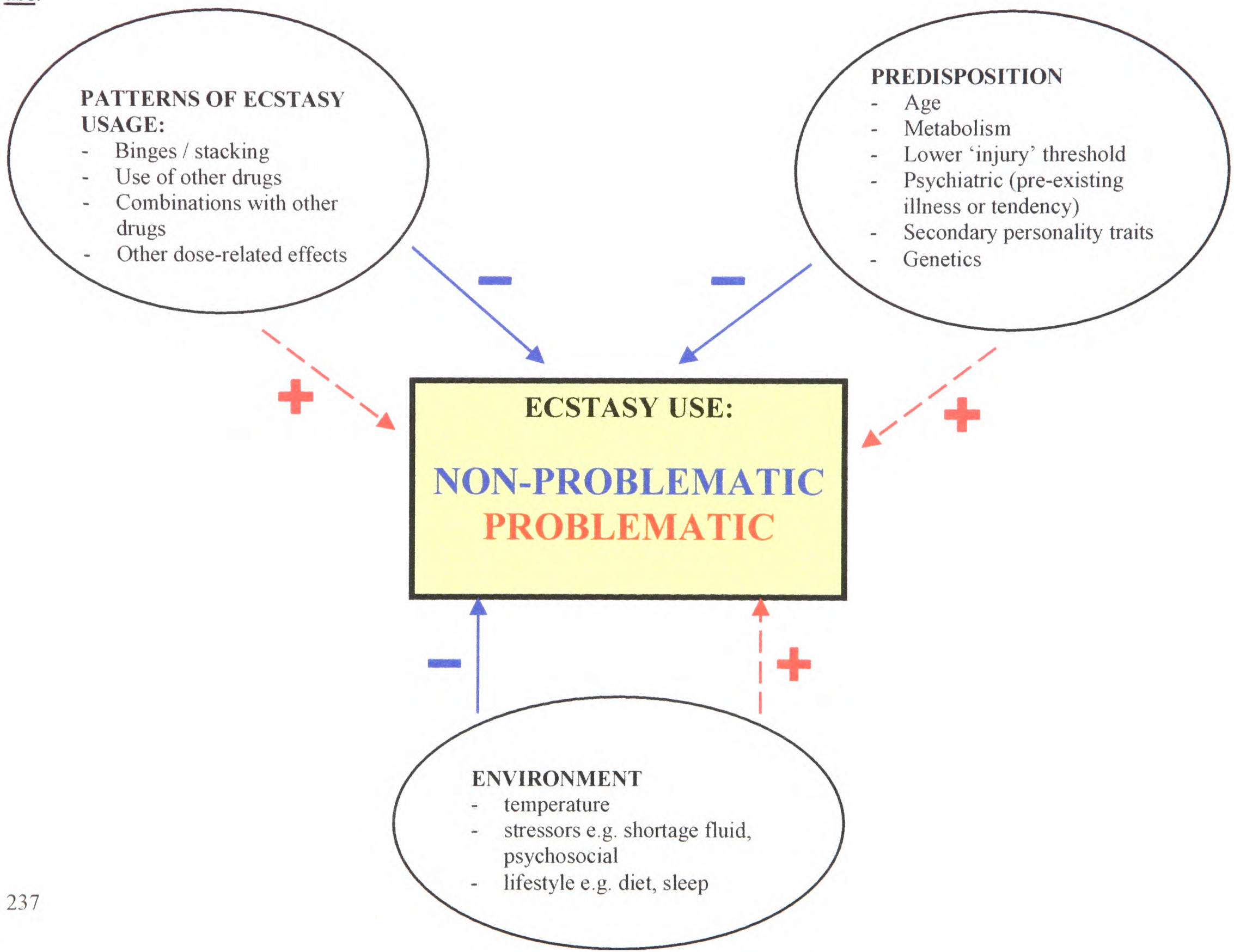
e.g. heroin or cocaine users. It has been acknowledged that chronic use of illicit drugs may be associated with a more general profile of neuropsychological deficits (Rogers & Robbins, 2001) and psychopathology. For instance, not only have executive disturbances been found in ecstasy users (Morgan, 1998; Bhattachary & Powell, 2001; Verkes et al, 2001; Morgan et al, 2002; Fox et al, 2002), but also in cannabis users (Pope et al, 2003), cocaine users (Stein, 1997; Bolla et al, 1998; Minnes, 1998), and heavy alcohol drinkers (Blume, 2001). However, there may be subtle differences between different classes of drugs. For instance, cannabis is associated with short term memory deficits on free-recall and learning tasks, as well as attentional tasks; cocaine is associated with executive deficits, visuo-spatial abilities, psychomotor speed and manual dexterity; and opiates tend to produce marked deficits on 'frontal' tasks (Rogers & Robbins, 2001). Further work in these directions could lead to 'profiling' and perhaps an understanding of cognitive and psychopathological deficits unique to or exacerbated by ecstasy.

SUMMARY

This chapter has provided an overview of the findings from the current research programme in relation to previous literature. It appears that ecstasy users self-select themselves into two distinct groups, those that do not perceive themselves to be largely problematic or at least do not attribute problems to their past ecstasy use and those that report problems which they associate with their ecstasy use. However, the nature and severity of these problems vary between individuals, as supported by the cognitive and psychopathological assessment results. This chapter has highlighted that problematic ecstasy users, rather than non-problematic ecstasy users, reported a number of psychopathological symptoms (in particular elevated somatisation, depression and anxiety), and also demonstrated selective cognitive impairments. Problematic ecstasy use could be in part due to slight differences in patterns of ecstasy use, with the suggestion that the intensity of drug use may contribute to the development of psychopathology, although there also appears to be other contributory factors that play a role in the emergence of psychopathology, within this sub-sample of ecstasy users (e.g. pre-existing problems, predisposition and environmental factors).

It is suggested that there is some multi-factorial combination of these individual factors which influence the extent and nature of the development of a problematic ecstasy profile. This proposed model is summarised in the following diagram (diagram 1). It is hypothesised that the more contributory factors that are present within an individual, the more likely that

Diagram 1: A diagrammatic model summarising the potential factors which influence the development of problematic ecstasy use.



problematic ecstasy use will develop. For example, an individual who has a strong predisposition to psychiatric problems, altered metabolism of MDMA and a lower neurotoxic 'injury' threshold is more likely to develop problems if they use high amounts of ecstasy on each occasion, in conjunction with other drug use. This would then be exacerbated further if this drug use occurred in a hot, crowded environment with little fluid and a shortage of sleep.

The proposed model can also account for the inconsistency in psychopathological and cognitive deficit research findings between non-problematic ecstasy users from the current research thesis and that of previous literature. The model would propose that these non-problematic ecstasy users within this thesis, have fewer 'risk' factors present in the context of their ecstasy use compared to ecstasy using samples (which may include both problem and non-problematic ecstasy users as noted earlier) in other research studies which document psychopathological and cognitive differences. The model also shows areas where 'protective' possibilities exist, in terms of harm reduction 'use advice', particularly if, as is perhaps highly likely, it is a combination of factors.

Such harm-reduction advice would be in line with, and in addition to, those strategies that are already employed by many ecstasy users (Panagopoulos & Ricciardelli, 2005). In particular the model may highlight those individuals that could be more vulnerable to developing ecstasy related problems. For example, if there are known mental health problems within an individual's family, it would be advisable for that person to avoid using ecstasy as a recreational drug as they could have an elevated risk of developing ecstasy-related problems. Further still, if individuals know that they are genetically deficient in the hepatic enzyme CYP2D6 (the enzyme that regulates MDMA metabolism), they too are more likely to have a toxic reaction to ecstasy consumption, as well as the potential for developing longer term problems and are advised not to consume the drug. However, if such 'at risk' individuals, and indeed the general population of ecstasy users, still choose to use ecstasy, advice on patterns and consumption of ecstasy usage could hopefully help reduce the overall risk of developing ecstasy related problems. This advice could include guidance on safer dosing: by limiting ecstasy binges; ideally only consuming small amounts of ecstasy at any one time; allowing a period of at least 2 weeks between ecstasy usage, in order to allow for the acute and sub-acute effects to diminish; limiting or avoiding cocktails of drugs, specifically amphetamine and cocaine use in conjunction with ecstasy use (since these drugs have shown to enhance MDMA neurotoxicity). Additionally, raising awareness of the environment that ecstasy is

consumed in could potentially reduce the risk of developing ecstasy-related problems. This would include appropriate regulation of body temperature, allowing periods of rest in a quiet room, not allowing the body to become too hot, maintaining an adequate water supply and further avoiding dehydration by avoiding the consumption of alcohol. Further, exerting control over other lifestyle factors such as ensuring appropriate sleep and a balanced diet could help the body to restore and maintain normal functioning. However, future research needs to address and understand the relative weighting of each factor within this model in order to provide appropriate and specific 'protective' advice. In addition, such objectives must be tempered by the possibility that some risk factors are not easily assessed or knowable, and that the possibility of ecstasy as a sole determinant of pathology remains key for some individuals.

However, caution needs to be taken when interpreting the specific assessment scores of ecstasy users, in this thesis, in relation to other ecstasy using samples, due to the inherent and particular methodological issues possibly affecting the studies presented. This mainly concerns the validity and reliability of an adequate control group. Opportunities to strengthen the research paradigms used within this research thesis concern addressing many of the methodological issues raised. In summary, these include:

- Improving recruitment strategies to ensure recruiting control groups which are appropriately matched to ecstasy using groups, in that they display similar lifestyles, sleep and diet patterns and, more importantly, other drug use, so as to achieve greater experimental control.
- Focusing further on the different combinations of drug use in conjunction with ecstasy use, in order to assess the possible interactions and differences in the long-term effects of these combinations, in relation to cognitive and psychopathological indices.
- Use of bio-markers (e.g. urine and hair analysis) to verify drug use in conjunction with the self-report data, in order to improve the reliability of type and quantity of different drug use.
- Exploring the age of onset of ecstasy use and its potential long-term effects, especially in relation to differences in metabolic rates, and subsequent cognitive and psychopathological differences.

- Improving assessment of psychopathological status, and including a more objective assessment measure (e.g. DSM IV).
- Improving assessment of cognitive functioning; including an objective measure of prospective memory; using a computerised version of the TOL to avoid manual errors in presentation and scoring of the test; and possibly use the extended version of the RBMT to increase the sensitivity of detecting everyday memory problems.
- Assessment of secondary personality traits, existing psychopathology and possible individual predispositions will help us contextualise the effects of ecstasy, but also, perhaps, help us to identify probable "at risk" populations of ecstasy users.

However, the issue of causation within this problematic ecstasy/MDMA research area will only be truly inferred by conducting a controlled prospective-longitudinal study assessing serotonin, secondary personality factors, indices of predisposition, cognitive and behavioural functioning in MDMA-naïve individuals that are randomly assigned to MDMA or placebo conditions. Only then can it be shown that recreational ecstasy use causes neurotoxic injury and cognitive and psychological problems, and whether these develop to the extent that they become problematic to the user. However, because MDMA has been shown to have neurotoxic effects on animal brains after just a single dose (Ricaurte et al, 1988), such studies are unlikely to occur. Thus, this further highlights the crucial need for researchers to document the conditions under which psychopathology and cognition remain unimpaired in ecstasy users, just as it is important to describe the situations where deficits develop. As Parrott (2003) argues, researchers who find unimpaired performance profiles should be encouraged to submit their findings for publication, and perhaps, in line with this suggestion, a function of journal editorship should be to consider the publication of non-findings.

REFERENCES

Allen DL, Oliver JS (2000): The use of supercritical fluid extraction for the determination of amphetamines in hair. Forensic Science International 107: 191-199.

Akunne HC, Soliman KFA. (1994): Serotonin modulation of pain responsiveness in aged rat. Pharmacology, Biochemistry and Behaviour, 48(2): 411-416.

Arria AM, Yacoubian GS, Fost E. (2002): Ecstasy use among club rave attendees. Arch Paediatric Adolescent Medicine, 156: 295-296.

Alciati A, Scaramelli B, Fusi A, Butteri E, Cattaneo ML, Mellado C. (1999): Three cases of delirium after "Ecstasy" ingestion. Journal of Psychoactive Drugs. 31(2): 167-170.

Archer RP. (1980): Generalized expectancies of control, trait anxiety, and psychopathology among psychiatric inpatients. Journal of Consulting & Clinical Psychology, 48(6): 736-742

Askenazy F, Caci H, Myquel M, Darcourt G, Lecruiber Y. (2000): Relationship between impulsivity and platelet serotonin content in adolescents. Psychiatry Research, 94: 19-28.

Bardo MT, Donohew RL, Harrington NG. (1996): Psychobiology of novelty seeking and drug seeking behaviour. Behaviour Brain Research, 77: 23-43.

Baggott M, Heifets B, Jones RT, Mendelson J, Sferios E, Zehnder J. (2000): Chemical analysis of ecstasy pills. The Journal of the American Medical Association, 284(117):2190

Batel P. (2000): Addiction and schizophrenia. European Psychiatry, 15:115-122.

Battaglia G, Sharkey J, Kuhar MJ, de Souza EB. (1991): Neuroanatomic specificity and time course of alterations in rat brain serotonergic pathways induced by MDMA (3,4-methylenedioxymethamphetamine): assessment using quantitative autoradiography. Synapse, 8(4): 249-60.

Battaglia G, Yeh SY, De Souza EB. (1988): MDMA-induced neurotoxicity: parameters of degeneration and recovery of brain serotonin neurons. Pharmacology Biochemical. Behaviour, 29(2): 269-74.

Beats BC, Sahakian BJ, Levy R. (1996): Cognitive performance in tests sensitive to frontal lobe dysfunction in elderly depressed. Psychological Medicine, 26:591-603.

Becker U, Laakmann G, Baghai T, Pfiffer B, Kauret G. (1995): Depression and direct central serotonin. European Neuropsychopharmacology, 5(3):273

Bell SEJ, Burns DT, Dennis AC, Matchett LJ, Speers JS. (2000): Composition profiling of seized ecstasy tablets by Raman spectroscopy. Analyst, 125: 1811-1815.

Benazzi F, Mazzoli M. (1991): Psychiatric illness associated with "ecstasy". The Lancet 338: 1520.

Bhattachary S, Powell JH. (2001): Recreational use of 3,4-methylenedioxymethamphetamine (MDMA) or 'ecstasy': evidence for cognitive impairment. Psychological Medicine, 31: 647-658.

Blier P, Seletti B, Gilbert F, Young SN, Benkelfat C. (2002): Serotonin 1A receptor activation and hypothermia in human: lack of evidence for a presynaptic mediation. Neuropsychopharmacology, 27(2): 301-308.

Blume AW. (2001): The Central Executive Model: An examination of its utility to predict changes in drinking behaviour among people abusing alcohol. Dissertation Abstracts International: Section B: The Sciences & Engineering, 62(5-B): 2476.

Bolla KI, Cadet JL, London ED. (1998): The neuropsychiatry of chronic cocaine abuse. Journal of Neuropsychiatry & Clinical Neurosciences,10(3): 280-289.

Bolla KI, McCann UD, Ricaurte GA. (1998): Memory impairment in abstinent MDMA ('ecstasy') users. Neurology, 51(6): 1532-1537.

Bone PI, Ramos GP, Villalba YP, Valle FJ. (2000): Persisting and late onset psychotic disorder due to consumption of ecstasy (MDMA). Nota Clinica, 25(1): 61-65.

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, JF, Davies DL, Schmued L, Broening HW, Newport GD, Slikker W Jr, Holson RR. (1994): Further studies of the role of hyperthermia in methamphetamine neurotoxicity. Journal Pharmacology Experimental Therapeutics, 268: 1571-1580.

Bradley C. (1994): Adapting Scales and Procedures: The limits of reliability and validity. Handbook of Psychology and Diabetes: A guide to psychological measurement in diabetes research and practice. Chapter 16: 379-388.

Brady KT, Grice DE, Dustan L, Randall, C. (1993): Gender differences in substance use disorders. American Journal of Psychiatry, 150:1070-1711.

Broening HW, Bacon L, Slikker W. (1994): Age modulates the long-term but not the acute effects of the serotonergic neurotoxicant 3,4-methylenedioxymethamphetamine. Journal of Pharmacology and Experimental Therapeutics, 271(1):285-293.

Broening HW, Bowyer JF, Slikker W. (1995): Age-dependent sensitivity of rats to the long-term effects of the serotonergic neurotoxicant (+/-)-3,4-methylenedioxymethamphetamine (MDMA) correlates with the magnitude of the MDMA-induced thermal response. Journal Pharmacology and Experimental Therapeutics, 275(1): 325-333.

Brown GL, Goodwin FK, Ballenger JC, Goyer PF, Major LF. (1979): Aggression in humans correlates with cerebrospinal fluid metabolites. Psychiatry Research, 1:131-139

Buchert R, Thomasius R, Nebeling B, Petersen K, Obrocki J, Jenicke L, Wilke F, wartberg L, Zapletalova P, Clausen M. (2003): Long-term effects of "ecstasy" use on serotonin transporters of the brain investigated by PET. Journal of Nuclear Medicine, 44(3): 375-384.

Cami J, Farre M, Mas M, Roset PN, Pausevida S, Mas A, San L, de la Torre R. (2000): Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects. Journal of Clinical Psychopharmacology, 20(4): 455-466.

Cassens, G, Inglis, A, Appelbaum, P S. (1990): Neuroleptics: effects on neuropsychological function in chronic schizophrenic patients. Schizophrenia Bulletin, 16(3):477-499.

Cassidy G, Ballard CG. (1994): Psychiatric sequelae of MDMA (ecstasy) and related drugs. Irish Journal of Psychological Medicine, 11(3): 132-133.

Chang L, Ernst T, Grob CS, Poland RE. (1999): Cerebral ^{1}H-MRS alternations in recreational 3,4-methlylenedioxymethamphetamine (MDMA, "ecstasy") users. Journal of Magnetic Resonance Imaging, 10: 521-526.

Chang L, Grob CS, Ernst T, Itti L, Mishkin FS, Jose-Melchor R, Poland RE. (2000): Effect of ecstasy [3,4-methlylenedioxymethamphetamine (MDMA)] on cerebral blood flow: a co-registered SPECT and MRI study. Psychiatry Research: Neuroimaging Section, 98: 15-28.

Christophersen AS. (2000): Amphetamine designer drugs – an overview and epidemiology. Toxicology Letters, 112-113, p.127-131.

Clark DB, Kirisci L, Moss HB (1998): Early adolescent gateway drug use in sons of fathers with substance use disorders. Addictive Behaviours, 23(4): 561-566

Cleghorn JM, Kaplan RD, Szechtman B. (1990): Neuroleptic drug effects on cognitive function in schizophrenia. Schizophrenia Research, 3(3):211-219.

Coccaro EF. (1989): Central serotonin and impulsive aggression. British Journal Psychiatry, 155:52-62.

Cohen RS. (1995): Subjective reports on the effects of the MDMA ('ecstasy') experience in humans. Prog. Neuropsychopharmacology & Biological Psychiatry, 19: 1137-1145.

Cohen RS. (1996). Adverse symptomatology and suicide associated with the use of methylenedioxymethamphetamine (MDMA; "ecstasy"). Biological Psychiatry 39: 816-818.

Cohen RS, Cocores J. (1997). Neuropsychiatric manifestations following the use of 3,4-methylenedioxymethampehetamine (MDMA; "ecstasy"). Prog. Neuropsychopharmacology & Biological Psychiatry, 21: 727-734.

Colado MI, Granados R, O'Shea E, Esteban B, Green AR. (1998): Role of hyperthermia in the protective action of clomethiazole against MDMA ('ecstasy')-induced neurodegeneration, comparison with the novel NMDA channel blocker AR-R15896AR. British Journal Pharmacology, 124(3): 479-84.

Cole JC, Bailey M, Sumnall HR, Wagstaff GF, King LA. (2002): The content of ecstasy tablets: implications for the study of their long term effects. Addiction, 97: 1531-1536.

Cole JC, Sumnall HR, Wagstaff GF. (2002): Methodological problems with ecstasy and the SCL-90. Psychopharmacology, 162:215-217.

Cole JC, Sumnall HR. (2003): Altered states: the clinical effects of ecstasy. Pharmacology & Therapeutics, 98: 35-98.

Commonwealth Department of Health and Family Services (1996): National Drug Strategy Household Survey, Survey Report 1995 (Canberra, Australian Government Publishing Service). Cited in Lenton S, Boys A, Norcross K. (1997).

Cooper GA, Allen DL, Scott KS, Oliver JS, Ditton J, Smith ID. (2000): Hair analysis: self-reported use of 'speed' and 'ecstasy' compared with laboratory findings. Journal Forensic Science, 45(2): 400-406.

Creighton FJ, Black DL, Hyde CE. (1991): 'Ecstasy' psychosis and flashbacks. British Journal of Psychiatry, 159: 713-715.

Croft RJ, Kulgman A, Baldeweg T, Gruzelier JH. (2001): Electrophysiological evidence of serotonergic impairment in long-term MDMA ("ecstasy") users. American Journal of Psychiatry, 158: 1687-1692.

Croft RJ, Mackay AJ, Mills ATD, Gruzelier GH. (2001): The relative contributions of ecstasy and cannabis to cognitive impairment. Psychopharmacology, 153: 373-379.

Curran VH. (2000) Is MDMA ('Ecstasy') Neurotoxic in Humans? An overview of evidence and of methodological problems in research. Neuropsychobiology, 42 (1): 34-41.

Curran VH. (2002) Psychopharmacological Perspectives on Memory. In Tulving E, Craik F I M (eds), The Oxford Handbook of Memory. Oxford University Press.

Curran VH, Rees H, Hoare T, Hoshi R, Bond A. (2004): Empathy and aggression: two faces of ecstasy? A study of interpretative cognitive bias and mood change in ecstasy users. Psychopharmacology (Berl), 173(3-4):425-33

Curran VH, Travill RA. (1997): Mood and cognitive effects of 3,4-methlylenedioxymethamphetamine (MDMA, 'ecstasy') week-end 'high' followed by mid-week 'low'. Addiction, 92: 821-831.

Curran VH, Verheyden SL. (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.

D'Arcy CU, Siddique CM. (1984): Psychological distress among Canadian adolescents. Psychological Medicine, 14(3):615-628.

Dafters RI, Duffy F, O'Donnell PJ, Bouquet C. (1999): Level of use of 3,4-methlylenedioxymethamphetamine (MDMA or Ecstasy) in humans correlates with EEG power and coherence. Psychopharmacology, 145: 82-90.

Daumann J, Pelz S, Becker S, Tuchtenhagen F, Gouzoulis-Mayfrank E. (2001) Psychological profile of abstinent recreationl ecstasy (MDMA) users and significance of concomitant cannabis use. Human Psychopharmacology, 16:627-633.

Davison D & Parrott AC. (1997): Ecstasy (MDMA) in recreational users: self-reported psychological and physiological effects. Human Psychopharmacology, 12: 221-226.

Delgado L, Charney DS, Price LH, Aghajanion GK, Landis H, Heninger GR (1990): Serotonin function and the mechanism of antidepressant action: reversal of anti-depressant-induced remission by rapid depletion of plasma tryptophan. Archives General Psychiatry, 47: 411-418.

Demirkiran M, Jankovic J, Dean JM (1996) Ecstasy Intoxication: An Overlap Between Serotonin Syndrome and Neuroleptic Malignant Syndrome. Clinical Neuropsychology 19(2):157-164.

Demir B, Ulug BD, Ergun EL, Erbas B. (2002): Regional cerebral blood flow and neuropsychological functioning in early and late onset alcoholism. Psychiatry Research Neuroimaging, 115: 115-125.

Derogatis LR, Melisaratos N. (1983) The Brief Symptom Inventory: an introductory report. Psychological Medicine, 13(3): 595-605.

Dornan WA, Katz JL, Ricaurte GA. (1991): The effects of repeated administration of MDMA on the expression of sexual behaviour in the male rat. Pharmacology, Biochemistry & Behaviour, 39:813-816.

Downing J (1986): The Psychological and Physiological Effects of MDMA on normal volunteers. Journal of Psychoactive Drugs, 18(4): 335-340.

Dughiero G, Schifano F, Forza G. (2001): Personality dimensions and psychopathological profiles of Ecstasy users. Human Psychopharmacology, 16: 635-639.

Dyck CH van, Malison RT, Seibyl JP, Laruelle M, Klumpp H, Zoghbi SS, Baldwin RM, Innis RB. (2000): Age-related decline in central serotonin transporter availability with [^{123}I]β-CIT SPECT. Neurobiology of Aging, 21: 497-501.

Ehrenreich H, Rinn T, Kunert HJ, Moeller MR, Poser W, Schilling L, Gigerenzer G, Hoehe MR. (1999): Specific attentional dysfunction in adults following early start of cannabis use. Psychopharmacology, 142(3): 295-301

Eitan N, Levin Y, Ben-Artzi E, Levy A, Neuman M. (1992): Effects of antipsychotic drugs on memory functions of schizophrenic patients. Acta Psychiatr Scand., 85(1):74-6.

Ellis P, Schimmel P. (1989): Ecstasy abuse. New Zealand Medical Journal, 102(871):358.

EMCDDA. (1998): Annual report on the state of the drugs problem in the European Union. European Monitoring Centre for Drugs and Drug Addiction, 18 December 1998.

EMCDDA. (2001): Annual report on EU drugs problem: Special overview of main trends. News release from EU drugs agency in Lisbon, 20 November 2001.

EMCDDA. (2002): Annual report on the state of the drugs problem in the European Union and Norway. European Monitoring Centre for Drugs and Drug Addiction, 2002.

ESPAD. (2001): The 1999 European Survey Project on Alcohol and Drugs. Press release issued by the State university of New York at Albany, 20 February 2001. http://monitoringthefuture.org/pubs/espad_pr.pdf

Eysenck MW. (1982): Attention and arousal: Cognition and performance. Berlin: Springer.

Fernstrom JD. (1987): Food-induced changes in brain serotonin synthesis: is there a relationship to appetite for specific macronutrients? Appetite, 8: 163-182.

Finnegan KT, Ricaurte GA, Ritchie LD, Irwin I, Peroutka SJ, Langston JW. (1988): Orally administered MDMA causes a long-term depletion of serotonin in rat brain. Brain Research, 447(1): 141-144.

Fischer C, Hatzidimitriou G, Wlos J, Katz J, Ricaurte G (1995): Reorganisation of ascending 5-HT axon projections in animals previously exposed to the recreational drug 3,4-methlylenedioxymethamphetamine (MDMA, "ecstasy"). 15(8): 5476-5485.

Frederick DL, Ali SF, Gillam MP, Gossett J, Slikker JR, Paule MG. (1998): Acute effects of dexfenfluramine (d-FEN) and methylenedioxymethamphetamine (MDMA) before and after short-course, high-dose treatment. Annals New York Academy of Sciences, 899:183-190.

Frederick DL, Ali SF, Slikker JR Gillam MP, Allem RR, Paule MG. (1995): Behavioural and neurochemical effects of chronic methylenedioxymethamphetamine (MDMA) treatment in rhesus monkeys. Neurotoxicology and Teratology, 17(5): 531-543.

Friend KB, Malloy PF, Sindelar HA. (2004): The effects of chronic nicotine and alcohol ise on neurocognitive function. Addictive Behaviours, 30(1):193-202.

Forsyth AJM. (1996): Places and patterns of drug use in the Scottish dance scene. Addiction, 91(4): 511-521.

Fox HC. (2002): Cognitive and Neuropsychological Profiles of Recreational Ecstasy Polydrug Users. PhD Thesis. University of East London.

Fox HC, McLean A, Turner JJD, Parrott AC, Roders R, Sahakian BJ. (2002): Neuropsychological evidence of relatively selective profile of temporal dysfunction in drug-free MDMA ('ecstasy') polydrug users. Psychopharmacology, 162(2): 203-214.

Fox HC, Milani MR, Parrott AC, Turner JJD. (2001a): Differences in premorbid adjustment between problematic and non-problematic ecstasy users. Canadian College of Neuropsychopharmacology (CCNP) Annual Meeting: 52 (abstract).

Fox HC, Parrott AC, Turner JJD. (2001b): Ecstasy use: cognitive deficits related to dosage rather than self-reported problematic use of the drug. Journal of Psychopharmacology, 15(4): 273-281.

Fox HC, Toplis AS, Turner JJD, Parrott AC. (2001c) Auditory verbal learning in drug-free Ecstasy polydrug users. Human Psychopharmacology, 16: 613-618.

Gabbard GO, Goodwin FK. (1996): Integrating biological and psychosocial perspectives. American Psychiatric Press Review of Psychiatry, 15: 527-548.

Gamma A, Buck A, Berthold, Vollenweider FX. (2000): 3,4-Methylenedioxymethamphetamine (MDMA) modulates cortical and limbic brain activity as measured by [$H_2{}^{15}O$]-PET in healthy humans. Neuropsychopharmacology, 23(4): 389-395.

Gamma A, Buck A, Berthold, Vollenweider FX. (2001): No difference in brain activation during cognitive performance between ecstasy (3,4-methylenedioxymethamphetamine) users and control subjects: A [$H_2{}^{15}O$] position emission tomograpy study. Journal of Clinical Psychopharmacology, 25(1): 66-71.

Garvey MJ, Noyes R, Woodman C, Lawkes C (1995): Relationship of generalised anxiety symptoms to urinary 5-hydroxyindoleacetic acid and vanillylmandelic acid. Psychiatry Research, 57: 1-5.

Geffen G, Moar KJ, O'Hanlon AP (1990): The Auditory Verbal Learning Test (Rey): performance of 16 to 86 year olds of average intelligence. The Clinical Neuropsychologist, 4: 45-63.

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-methlylenedioxymethamphetamine (ecstasy) on serotonin system function in humans. Biological Psychiatry, 47: 127-136.

Gerra G, Zaimovic A, Giucastro G, Maestri D, Monica C, Sartori R, Caccavari R, Delsignore R. (1998): Serotonergic function after (±)3,4-methlylenedioxymethamphetamine ('ecstasy') in humans. International Clinical Psychopharmacology, 13: 1-9.

Gerra G, Zaimovic A, Moi G, Giusti F, Gardini S, Delsignore R, Laviola G, Macchia T, Brambilla F. (2002): Effects of (±) 3,4-methylene-dioxymethamphetamine (ecstasy) on dopamine system function in humans. Behavioural Brain Research 134: 403-410.

Gillman PK. (1997): Ecstasy, serotonin syndrome and the treatment of hyperpyrexia. Medical Journal Australia, 167:109-111.

Gillman PK (1998) Serotonin Syndrome: history and risk. Fundamental Clinical Pharmacology, 12:482-491.

Greer G, Tolbert R. (1986): Subjective reports of MDMA in a clinical setting. Journal of Psychoactive Drugs, 18(4): 319-327.

Green AR, Cross AJ, Goodwin GM. (1995): Review of the pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy"). Psychopharmacology, 119: 247-260.

Green AR, Mechan AO, Elliott JM, O'Shea E, Colado MI. (2003): The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). Pharmacological Review, 55(3): 463-508.

Grob CS, Poland RE, Chang L, Ernst T (1996): Psychobiologic effects of 3,4-Methylenedioxymethamphetamine in humans: methodological considerations and preliminarily observations. Behavioural Brain Research, 73: 103-107.

Gross SR, Barrett SP, Shestowsky JS, Pihl RO. (2002): Ecstasy and drug consumption patterns: A Canadian rave population study. Canadian Journal Psychiatry, 47(6): 546-551.

Goldstone S, Nurnberg GH, Lhamon WT. (1979): Effects of trifluoperazine, chlorpromazine and haloperidol upon temporal information processing by schizophrenic patients. Psychopharmacology, 65(2):119-124.

Goodwin, GM. (1997): Neuropsychological and neuroimaging evidence for the involvement of the frontal lobes in dementia. Journal of Psychopharmacology, 115-122.

Gough B, Ali SF, Slikker W Jr, Holson RR. (1991): Acute effects of 3,4-methylenedioxymethamphetamine (MDMA) on monoamines in rat caudate. Pharmacology, Biochemistry & Behaviour, 39(3): 619-623.

Gouzoulis-Mayfrank E, Becker S, Pelz S, Tuchtenhagen F, Daumann J. (2002): Neuroendocrine abnormalities in recreational ecstasy (MDMA) users: is it ecstasy or cannabis? Biological Psychiatry, 51: 766-769.

Gouzoulis-Mayfrank E, Daumann J, Tuchtenhagen F, Pelz S, Becker S, Kunert HJ, Fimm B, Sass H. (2000): Impaired cognitive performance in drug free users of recreational ecstasy (MDMA). Journal of Neurological & Neurosurgical Psychiatry, 68: 719-725.

Gunnarsdottir ED, Pingitore RA, Spring BJ, Konopka LM, Crayton JW, Milo T, Shirazi P. (2000): Individual differences among cocaine users. Addictive Behaviours, 25(5):641-652.

Hale WD, Cochran CD. (1987): The relationship between locus of control and self-reported psychopathology. Journal of Social Psychology, 127(1): 31-37.

Hammersley R, Ditton J. Smith I, Short E. (1999): Patterns of ecstasy use by drug users. British Journal of Criminiology 39(4): 625-647.

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. Journal of Neuroscience, 19(12): 5096-5107.

Hawkins JD, Catalano RF, Miller JY. (1992): Risk and protective factors for alcohol and other drug problems in adolescence and early adulthood: implications for substance abuse prevention. Psychological Bulletin, 112(1): 64-105.

Hawkins KA, Trobst KK. (2000): Frontal lobe dysfunction and aggression: conceptual issues and research findings. Aggression and Violent Behaviour, 5(2):147-157.

Hatzitaskos P, Soldatos CR, Kokkeiv A, Stefanis CN. (1999): Substance abuse patterns and their association with psychopathology and type of hostility in male patients with borderline and antisocial personality disorder. Comprehensive Psychiatry, 40(4): 278-282.

Heffernan TM, Jarvis H, Rodgers J, Scholey AB, Ling J. (2001): Prospective memory, everyday cognitive failures and central executive function in recreational users of ecstasy. Human Psychopharmacology, 16(8): 619-626.

Hegerl U, Juckerl G (1993): Intensity dependence of auditory evoked potentials as an indicator of central serotonergic neurotransmission: a new hypothesis. Biological Psychiatry, 33:173-187.

Hernandez-Lopez C, Farre M, Roset PN, Menoyo E, Pizarro N, Ortuno J, Torrens M, Cami J, Torre R De La. (2002): 3,4-methylenedioxymethamphetamine (ecstasy) and alcohol interactions in humans: psychomotor performance, subjective effects and pharmacokinetics. Journal of Pharmacology and Experimental Therapeutics, 300(1): 236-244.

Huether G, Zhou D, Ruther E (1997): Causes and consequences of the loss of serotonergic presynapses elicited by the consumption of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') and its congeners. Journal of Neural Transmission, 104(8-9):771-94

Ho YJ, Pawlak CR, Guo L, Schwarting KW. (2004): Acute and long-term consequences of single MDMA administration in relation to individual anxiety levels in the rat. Behavioural Brain Research, 149:135-144

Holland J. (2001): Ecstasy: the complete guide. Park Street Press. Rochester, Vermont.

Hoff AL, Riordan H, Morris L, Cestaro V, Wieneke M, Alpert R, Wang GJ, Volkow N. (1996): Effects of crack cocaine on neurocognitive function. Psychiatry Research, 60:167-176.

Hoehn-Saric, R McLeod DR. (1985): Locus of control in chronic anxiety disorders. Acta Psychiatrica Scandinavica 72(6):529-535.

Horner MD, Waid LR, Johnson DE, Latham PK, Anton RF. (1999): The relationship of cognitive functioning to amount of recent and lifetime alcohol consumption in outpatient alcoholics. Addictive Behaviours, 24(3): 449-453.

Hunter A (1988): Serotonergic involvement in learning and memory. Biochemical Soc. Trans. 17:79-81.

Iravani M, Asari D, Patel J, Wieczorek WJ, Kruk ZL. (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(4): 275-285.

Jansen KL. (1999): Ecstasy (MDMA) dependence. Drug Alcohol Dependence, 53(2):121-4

Johnston LD, O'Malley PM, Bachman JG. (2002): Monitoring the future national results on adolescent drug use. Overview of key findings 2001. National Institute on Drug Abuse. http://monitoringthefurture.org

Keenan E, Gervin M, Dorman A, O'Connor JJ. (1993). Psychosis and recreational use of MDMA ("Ecstasy"). Irish Journal of Psychological Medicine, 10(3): 162-163.

Keller T, Miki A, Regenscheit P, Dirnhofer R, Schneider A, Tsuchihashi H. (1998): Detection of designer drugs in human hair by ion mobility spectrometry (IMS). Forensic Science International, 94: 55-63.

Kikura R, Nakahara Y, Mieczkowski T, Tagliaro F. (1997): Hair analysis for drug Abuse XV. Disposition of 3,4-methylenedioxymethamphetamine (MDMA) and its related compounds into rat hair and application to hair analysis for MDMA abuse. Forensic Science International, 84: 165-177.

Kish SJ, Furukawa Y, Ang L, Vorce SP, Kalansinsky KS. (2000): Striatal serotonin is depleted in brain of a human MDMA (ecstasy) user. Neurology, 55:294-296.

Kish SJ. (2002): How strong is the evidence that brain serotonin neurons are damaged in human users of ecstasy? Pharmacol. Biochem. Behav, 71(4):845-855

Kopelman MD, Reed LJ, Marsden P, Mayes AR, Jaldow E, Laing H, Isaac C. (2001): Amnesic Syndrome and Severe Ataxia Following the Recreational Use of 3,4-methlylenedioxymethamphetamine (MDMA, 'Ecstasy') and other substances. Neurocase, 7: 423-432.

Kreth KP, Kovar KA, Schwab M, Zanger UM. (2000): Identification of the human cytochromes P450 involved in the oxidative metabolism of "ecstasy" related designer drugs. Biochemical Pharmacology, 59: 1563-1571.

Krystal JH, Price LH, Opsahl C, Ricaurte GA, Heninger GR. (1992): Chronic 3,4-methlylenedioxymethamphetamine (MDMA) use: effects on mood and neuropsychological function? American Journal of Drug Alcohol Abuse, 18(3): 331-41.

Lavik NJ & Onstad S. (1986): Drug use and psychiatric symptoms in adolescence. Acta Psychiatrica Scandinavica, 73(4): 437-440.

Laviola G, Adriani W, Terranova ML, Gerra G. (1999): Psychobiological risk factors for vulnerability to psychostimulants in human adolescents and animal models. Neuroscience and Biobehavioral Reviews, 23:993-1010.

Lenton S, Boys A, Norcross K. (1997): Raves, drugs and experience: drug use by a sample of people who attend raves in Western Australia. Addiction, 92(10): 1327-1337.

Lew R, Sabol KE, Chou C, Vosmer GL, Richards J, Seiden LS. (1996): Methylenedioxymethamphetamine-induced serotonin deficits are followed by partial recovery over a 52-week period. Part II: Radioligand binding and autoradiography studies. J. Pharmacology and Experimental Therapeutics, 276(2): 855-865.

Lezak MD. (1995) Neuropsychological Assessment. 3rd Edition. Oxford University Press.

Lieb R, Schuetz CG, Pfister H, von Sydow K, Wittchen HU. (2002): Mental disorders in ecstasy users: a prospective-longitudinal investigation. Drug and Alcohol Dependence, 65: 195-207.

Liechti ME, Baumann C, Gamma A, Vollenweider FX. (2000a): Acute psychological effects of 3,4-Methylenedioxymethamphethamine (MDMA, "Ecstasy") are attenuated by the serotonin uptake inhibitor citalopram. Neuropsychopharmacology, 22(5):513-521.

Liechti, ME, Gamma A, Vollenweider FX. (2001): Gender differences in the subjective effects of MDMA. Psychopharmacology, 154: 161-168.

Liechti ME, Saur MR, Gamma A, Hell D, Vollenweider FX. (2000b): Psychological and Physiological effects of MDMA ("ecstasy") after pre-treatment with the 5-HT2 antagonist ketanserin in healthy humans. Neuropsychopharmacology, 23(4):396-404.

Liechti ME, Vollenweider FX. (2001): Which neuroreceptors mediate the subjective effects of MDMA in humans? A summary of mechanistic studies. Human Psychopharmacology, 16:589-598.

Linnoila M, Virkkunen M, George T, Higley D (1993): Impulse control disorder. Int. Clinical Psychopharmacology, 8:53-56

Ling J, Heffernan T, Buchanan T, Rodgers J, Scholey AB, Parrott AC. (2003): Effects of alcohol on subjective ratings of perspective and everyday memory deficits. Alcoholism: Clinical and Experimental Research, 27(6): 970-974.

LoCurto MJ (1997) The Serotonin Syndrome. Neurologic Emergencies, 15(3):665-675.

Loubinoux I, Pariente J, Boulanouar K, Carel C, Manelfe C, Rascol O, Celsis P, Chollet F. (2002): A single dose of the serotonin neurotransmission agonist paroxetine enhances motor output: double-blind, placebo-controlled, fMRI study in healthy subjects. NeuroImage, 15(1): 26-36.

McGuire P. (2000) Long term psychiatric and cognitive effects of MDMA use. Toxicology Letters, 112-113: 153-156.

MacInnes N, Handley SL, Harding GFA (2001) Former chronic methylenedioxymethamphetaine (MDMA or ecstasy) users report mild depressive symptoms. Journal of Psychopharmacology, 15(3): 181-186

Malberg JE, Seiden LS. (1980): 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.

Maldonado E & Navarro JF. (2001): MDMA ('Ecstasy') exhibits an anxiogenic-like activity in social encounters between male mice. Pharmacological Research, 44(1):27-31.

Malin LS, Fordham U. (2002): Attitudes about seeking professional psychological help, self-efficacy and locus of control among individuals with a dual diagnosis. Dissertation Abstracts International: Section B: The Sciences and Engineering, 63(3-B):1567.

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, 144: 67-76.

Mass R, Bardong C, Kindl K, Dahome B. (2001): Relationship between cannabis use, schizotypal traits, and cognitive function in healthy subjects. Psychopathology, 34(4):209-214.

McCann UD, Eligulashvili V, Merti M, Murphy DL, Ricaurte G. (1999): Altered neuroendocrine and behavioural responses to m-chlorophenylpiperazine in 3,4-methlylenedioxymethamphetamine (MDMA) users. Psychopharmacology, 147: 56-65.

McCann UD, Mertl M, Eligulashvili V, Ricaurte GA. (1999): Cognitive performance in (±)3,4-methlylenedioxymethamphetamine (MDMA, 'ecstasy') users: a controlled study. Psychopharmacology, 143:417-425.

McCann UD, Ricaurte GA. (1992): MDMA ("ecstasy") and panic disorder: induction by a single dose. Biological Psychiatry, 32: 950-953.

McCann UD, Ridenour Am Shaham Y, Ricuarte GA. (1994): Serotonin neurotoxicity after (±)3,4-methlylenedioxymethamphetamine (MDMA; "ecstasy"): a controlled study in humans. Neuropsychopharmacology, 10(2): 129-138.

McCann UD, Szabo Z, Scheffel U, Dannals RF, Ricaurte GA. (1998): Position emission tomographic evidence of toxic effect of MDMA ("ecstasy") on brain serotonin neurons in human beings. The Lancet, 352: 1433-1437.

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 dose not predict long-term outcomes. Psychopharmacology, Published (Online): http://www.erowid.org/references/refs_view.php?A=ShowDoc1&ID=6105

McGuire PK, Cope H, Fahy TA. (1994): Diversity of psychopathology associated with use of 3,4-methylenedioxymethamphetamine ('ecstasy'). British Journal of Psychiatry, 165(3): 391-395.

McGuire P, Fahy T. (1991): Chronic paranoid psychosis after misuse of MDMA ('ecstasy'). British Medical Journal, 203(6778):697.

McNamara MG, Kelly JP, Leonard BE. (1995): Some behavioural and neurochemical aspects of subacute (±)3,4-methylenedioxymethamphetamine (MDMA) administration in rats. Pharmacology, Biochemistry and Behaviour, 52(3):479-484.

Measham F, Parker H, Aldridge J. (1998): The teenage transition: from adolescent recreational drug use to the young adult dance culture in Britain in the mid-1990s. Journal of Drug Issues, 29(1): 9-32.

Mechan AC, Esteban B, O'Shea E, Elliott JM, Colado MI, Green AR. (2002): The pharmacology of the acute hyperthermic response that follows administration of 3,4-

methylenedioxymethamphetamine (MDMA, 'ecstasy') to rats. British Journal of Pharmacology, 135(1): 170-180.

Medalia A, Gold J, Merriam A. (1988): The effects of neuroleptics on neuropsychological test results of schizophrenics. Archives of Clinical Neuropsychology, 3(3):249-271.

Merck E. (1914): Merch MDMA Patent. German Patent Office. http://www.erowid.org/references/refs_view.php?A=ShowDoc1&ID=1127

Messing RB, Lythe LD. (1977): Serotonin containing neurons: their possible role in pain and analgesia. Pain, 4:1-22.

Milas M. (2000): Acute psychosis with aggressive behaviour as a consequence of MDMA (ecstasy) consumption. Lijec Vjsen, 122(1-2): 27-30.

Milani R (1997): Disturbi neuropsicologici associate all'uso di ecstasy. Dissertation, Faculty of Psychology, University of Padova (I).

Milani RM, Parrott AC, Turner JJD. (2001): Self reported 'problematic' and non-problematic' ecstasy/MDMA users in relation to a psychiatric symptom profile and patterns of drug use. 5th Endo-Neuro Meeting, Doorweth, Netherlands, 5-7 June 2001, 86:156 (abstract).

Milani R & Schifano F. (2000): Neuropsychological problems associated with ecstasy use. Journal of Psychopharmacology, 14(3): PA17.

Milani R, Turner JJD, Parrott AC, Parmar R. (2000): Recreational drug use and psychobiological problems, collaborative UK/Italy study (5): ecstasy (MDMA) polydrug user findings. Journal of Psychopharmacology, 14(3): PA22 (abstract).

Miller DB, O'Callaghan JP. (1994): Environment-, drug- and stress-induced alterations in body temperature affect the neurotoxicity of substituted amphetamines in the C57BL/6J mouse. Journal of Pharmacology and Experimental Therapeutics, 270:752-760.

Minnes S. (1998): Executive function, psychological distress and psychobehavioural deficits in post-partum cocaine-using women. Dissertation Abstracts International Section A: Humanities & Social Sciences, 59(5-A): 1777.

Mishara AL, Goldberg TE. (2004): A meta-analysis and critical review of the effects of conventional neuroleptic treatment on cognition in schizophrenia: opening a closed book. Biological Psychiatry, 55:1013-1022.

Mitushina MN, Kyle BB, D'Elia LF. (1999): Handbook of normative data for neuropsychological assessment. Oxford University Press: Oxford.

Montgomery AMJ & Butler G. (2001a): Ecstasy (MDMA) use is associated with risk-taking and increased self-report scores for impulsiveness and novelty seeking. CCNP 2001 Annual Meeting June17th-20th, 2001, pg. 63.

Montgomery AMJ & Butler G. (2001b): Evidence for increased impulsivity in recreational ecstasy (MDMA) users. CCNP 2001 Annual Meeting, June17th-20th, 2001, pg. 63.

Morgan MJ. (1998): Recreational use of 'ecstasy' (MDMA) is associated with elevated impulsivity. Neuropsychopharmacology, 19(4): 252-264.

Morgan MJ. (1999): Memory deficits associated with recreational use of 'ecstasy' (MDMA). Psychopharmacology, 141: 30-36.

Morgan MJ, McFie L, Fleetwood LH, Robinson JA. (2002): Ecstasy (MDMA): are the psychological problems associated with its use reversed by prolonged abstinence? Psychopharmacology, 159: 592-303.

Morley-Fletcher S, Puopolo M, Gentili S, Gerra G, Macchia T, Laviola G. (2004): Prenatal stress affects 3,4-methylenedioxymethamphetamine pharmacokinetics and drug-induced motor alterations in adolescent female rats. European Journal of Pharmacology, 489: 89-92.

Mueller PD, Korey WS (1998) Death by "ecstasy": the serotonin syndrome? Annuals of Emergency Medicine, 32:377-380.

Navarro JF, Riveria A, Maldonado E, Cavas M, Calle de la A. (2004): Anxiogenic-like activity of 3,4-methylenedioxy-methamphetamine ("Ecstasy") in the social interaction test is accompanied by an increase of c-*fos* expression in mice amygdala. Progress in Neuro-Psychopharmacology & Biological Psychiatry 28: 249-254.

Nelson HE. (1982): The National Adult Reading Test (NART): Test Manual. NFER-Nelson. Windsor, Berks, UK.

Newcomb MD & Bentler PM. (1986): Cocaine use among adolescents: longitudinal associations with social context, psychopathology, and use of other substances. Addictive Behaviours, 11(3): 263-273.

Newcomb MD, Scheier LM, Bentler PM. (1993): Effects of adolescent drug use on adult mental health: a prospective study of a community sample. Experimental and Clinical Psychopharmacology, 1(1-4): 215-241.

Nixdorf WL, Burrows KB, Gudelsky GA, Yamamoto BK. (2001): Enhancement of 3,4-methylenedioxymethamphetamine neurotoxicity by the energy inhibitor malonate. Journal of Neurochemistry, 77: 647-654.

Obergreisser T, Ende E, Braus DF, Henn FA. (2001): Hippocampal ^{1}H-MRSI in ecstasy users. Eur Arch Psychiatry Clinical Neuroscience, 251: 114-116.

Obrocki J, Buchert R, Vaterlwin O, Thomasius R, Beyer W, Schiemann T. (1999): Ecstasy – long-term effects on the human central nervous system revealed by position emission tomography. The British journal of Psychiatry, 175(8): 186-188.

O'Connell D, Heffron JJA. (2000): Rapid analysis of illicit drugs by mass spectrometry: results from seizures in Ireland. Analyst, 125: 119-121.

O'Leary MR, Donovan DM, Freeman CW, Chaney EF. (1976): Relationship between psychopathology, experienced control and perceived locus of control: in search of alcoholic subtypes. Journal of Clinical Psychology, 32(4): 899-904.

O'Loinsigh ED, Kelly JP, O'Boyle KM. (2000): Co-administration of d-amphetamine alters the acute and long-term effects of 3,4-methylenedioxymethamphetamine in rats. British Journal of Pharmacology, 131: 154P.

O'Shea E, Esteban B, Camarero J, Green AR, Colabo MI. (2001): Effect of GBR 12909 and fluoxetine on the acute and long term changes induced by MDMA ('ecstasy') on the 5-HT and dopamine concentrations in mouse brain. Neuropharmacology, 40(1):65-74

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.

Oswald I, Berger RJ, Evans JI, Thacore VR. (1964): Effects of l-tryptophan upon human sleep. British Journal Psychiatry, 109: 66-78.

Palenicek T, Fiserova M, Kubu P. (2002): Testing of ecstasy tablets in Czech Republic – quantitative analysis. Psychopharmacology of Cannabis and Ecstasy, BAP and CNPS Joint Workshop, April 18th-21st 2002 p.52.

Pallanti S, Mazzi D. (1992): MDMA (ecstasy) precipitation of panic disorder. Biological Psychiatry, 32: 91-95.

Panagopoulos I, Ricciardelli LA. (2005): Harm reduction and decision making among recreational ecstasy users. International Journal of Drug Policy, 16: 54-64.

Parrott AC. (2000): Human research on MDMA (3,4-methylene-dioxymethamphetamine) neurotoxicity: cognitive and behavioural indices of change. Neuropsychobiology, 42: 17-24.

Parrott AC. (2001) Human psychopharmacology of ecstasy (MDMA): a review of 15 years of empirical research. Human Psychopharmacology, 16: 557-577.

Parrott AC. (2002): Recreational ecstasy/MDMA, the serotonin syndrome and serotonergic neurotoxicity. Pharmacology, Biochemistry and Behaviour, 71: 837-844.

Parrott AC. (2003): Cognitive deficits and cognitive normality in recreational cannabis and Ecstasy/MDMA users. Human Psychopharmacology, 18: 89-90.

Parrott AC (2004): Is ecstasy MDMA? A review of the proportion of Ecstasy tablets containing MDMA, their dosage levels and the changing perceptions of purity. Psychopharmacology, 173: 234-241.

Parrott AC, Fox HC, Milani RM. (2003): Cannabis, ecstasy/MDMA and memory: a commentary on Simon & Mattick's recent study. Letters to the Editor, Addiction, 98: 1003-1005.

Parrott AC & Lasky J. (1998): Ecstasy (MDMA) effects upon mood and cognition: before, during and after a Saturday night dance. Psychopharmacology, 139: 261-268.

Parrrott AC, Lees A, Garnham NJ, Jones M, Wesnes K. (1998): Cognitive performance in recreational users of MDMA or 'ecstasy': evidence for memory deficits. Journal of Psychopharmacology, 12(1): 79-83.

Parrott AC, Milani R, Parmar R, Turner JJD. (2000): Recreational drug use and psychobiological problems, collaborative UK/Italy study (1): overview and main findings. Journal of Psychopharmacology, 14(3): PA18 (abstract).

Parrott AC, Milani RM, Parmar R, Turner JJD. (2001): Recreational ecstasy/MDMA and other drug users from the UK and Italy: psychiatric symptoms and psychobiological problems. Psychopharmacology, 159: 77-82.

Parrott AC, Milani RM, Turner JJD. (2002): Ecstasy and the SCL-90 findings: a reply to Cole et al. Psychopharmacology, 162:218-222.

Parrott AC, Sisk E, Turner JJD. (2000): Psychobiological problems in heavy 'ecstasy' (MDMA) polydrug users. Drug Alcohol Dependence, 60(1):105-110.

Parrott AC & Stuart M. (1997): Ecstasy (MDMA), amphetamine and LSD: comparative mood profiles in recreational polydrug users. Human Psychopharmacology, 12: 501-504.

Pedersen W & Skrondal A. (1999): Ecstasy and new patterns of drug use: a normal population study. Addiction, 94(1), 1695-1706.

Penev PD, Turek FW, Zee PC. (1995): A serotonin neurotoxin attenuates the phase-shifting effects of triazolam on the circadian clock in hamsters. Brain Research, 669(2): 207-216.

Peroutka SJ, Pascos N, Faull KF. (1987): Monoamine metabolites in the cerebrospinal fluid of recreation users of 3,4-methlylenedioxymethamphetamine (MDMA; "ecstasy"). Research Communications in Substances of Abuse, 8(3&4): 125-138.

Petrosky MJ, Birkimer JC. (1991): The relationship among locus of control, coping styles and psychological symptom rating. Journal of Clinical Psychology, 47(3): 336-345.

Piper BJ & Meyer JS. (2004): Memory deficit and reduced anxiety in young adult rats given repeated intermittent MDMA treatment during the periadolescent period. Pharmacology, Biochemistry and Behaviour, 79:723-731

Price LH, Ricaurte GA, Krystal JH, Heninger GR. (1989): Neuroendocrine and mood responses to intravenous L-tryptophan in 3,4-methlylenedioxymethamphetamine (MDMA) users. Arch Gen Psychiatry, 46: 20-22.

Pope HG, Gruber AJ, Hudson JI, Cohane G, Huestus MA, Yurgelun-Todd D. (2001): Neuropsychological performance in long-term cannabis users. Archives General Psychiatry, 58:909-915.

Pope HG, Yurgelun-Todd D. (1996): The residual cognitive effects of heavy marijuana use in college students. Journal of American Medical Association, 275:521-527.

Pope HG, Gruber AJ, Hudson JI, Cohane G, Huestus MA, Yurgelun-Todd D. (2003): Early-onset cannabis use and cognitive deficits: what is the nature of the association? Drug and Alcohol Dependence, 69:303-310.

Pope HG, Ionescu-Pioggia M, Pope KW. (2001): Drug use and life style among college undergraduates: A 30-year longitudinal study. American Journal of Psychiatry, 158(9): 1519-1521.

Purcell R, Maruff P, Kyrios M, Pantelis C. (1997): Neuropsychological function in young patients with unipolar major depression. Psychological Medicine, 27: 1277-1285.

Ramamoorthy Y, Yu A, Suh N, Haining RL, Tyndale RF, Sellers EM. (2002): Reduced (±) 3,4-methylenedioxymethamphetamine ("ecstasy") metabolism with cytochrome P450 2D6 inhibitors and pharmacogenetic variants in vitro. Biochemical Pharmacology, 63: 2111-2119.

Reist C, Helmaste D, Albers L, Chay H, Tang SW. (1996): Serotonin indices and impulsivity in normal volunteers. Psychiatry Research, 60: 177-184.

Reneman L, Booij J, de Burin K, Reitsma JB, de Wolff A, Gunning WB, Heeton den GJ, van den Brink W. (2001): Effects of dose, sex and long-term abstention from use on toxic effects of MDMA (ecstasy) on brain serotonin neurons. The Lancet, 358: 1864-1869.

Reneman L, Booij J, Majoie CBLM, van den Brink,W, den Heeten GJ. (2001): Investigating the potential neurotoxicity of Ecstasy (MDMA): an imaging approach. Hum Psychopharmacology Clinical & Experimental, 16(8):577-588

Reneman L, Booij J, Schmand B, van den Brink W, Gunning B. (2000): Memory disturbances in 'Ecstasy' users are correlated with an altered brain serotonin neurotransmission. Psychopharmacology, 148:322-324.

Reneman L, de Burin K, Reitsma JB, Gunning WB, den Heeton GJ, van den Brink W. (2002): Use of amphetamine by recreational users of ecstasy (MDMA) is associated with reduced striatal dopamine transporter densities: a [^{123}I]-βCIT SPECT study – preliminary report. Psychopharmacology, 159: 335-340.

Reneman L, Endert E, Bruin de K, Lavalaye J, Feenstra MG, Wolff de FA, Booij J. (2002): The acute and chronic effects of MDMA ("Ecstasy") on cortical 5-HT_{2A} receptors in rat and human brain. Neuropsychopharmacology, 26(3): 387-396.

Reneman L, Habraken JBA, Majoie CBL, Booij J, den Heeton GJ. (2000): MDMA ("Ecstasy") and its association with cerebrovascular accidents: preliminary findings. American Journal Neuroradiology, 21: 1001-1007.

Reneman L, Majoie CBLM, Flick H, den Heeton GJ. (2002): Reduced N-Acetylaspartate levels in the frontal cortex of 3,4-methlylenedioxymethamphetamine (ecstasy) users: preliminary results. American Journal Neuroradiology, 23: 231-237.

Reneman L, Majoie CBLM, Habraken JBA, den Heeton GJ. (2002): Effects of ecstasy (MDMA) on the brain in abstinent users: initial observations with diffusion and perfusion MR imaging. Radiology, 220: 611-617.

Reneman L, , Schmand B, de Wolff FA, , van den Brink W, den Heeton GJ, Booij J. (2002): Cortical serotonin transporter density and verbal memory in individuals who stopped using 3,4-methlylenedioxymethamphetamine (MDMA or "Ecstasy"). Archives General Psychiatry, 58: 901-906.

Reneman l, Lavalaye J, Schmand B, de Wolff FA, van den Brink W, den Heeton GJ, Booij J. (2001): Cortical Serotonin Transporter density and Verbal Memory in Individuals Who Stopped Using 3,4-methlylenedioxymethamphetamine (MDMA or "Ecstasy"). Archives General Psychiatry, 58: 901-906.

Rey A. (1964) L'examen clinique en psychologie. Presses Universitaires de France: Paris

Ricaurte GA (1989): Studies of MDMA-induced neurotoxicity in nonhuman primates: a basis for evaluating long-term effects in humans. NIDA Research Monographs, 94: 306-22.

Ricaurte GA, DeLanney LE, Irwin I, Langston JW. (1988): Toxic effects of MDMA on central serotonergic neurons in the primate: importance of route and frequency of drug administration. Brain Research, 446(1): 165-168.

Ricaurte GA, Finnegan KT, Irwin I, Langston JW. (1990): Aminergic metabolites in cerebrospinal fluid of humans previously exposed to MDMA: preliminary observations. Annuals New York Academy of Sciences, 600: 699-710.

Ricaurte GA, Markowska AL, Wenk GL, Hatzidimitriou G, Wlos J, Olton DS. (1993): 3,4-methylenedioxymethamphetamine, serotonin and memory. Journal of Pharmacology and Experimental Therapeutics 256(2):1097-1105.

Ricaurte GA, Martello AL, Katz JL, Martello MB. (1992): Lasting effects of (±)-3,4-methylenedioxymethamphetamine (MDMA) on central serotonergic neurons in nonhuman primates: neurochemical observations. Journal of Pharmacology and Experimental Therapeutics 261(2): 616-622

Ricaurte GA, Yuan J, McCann UD. (2000): (±)3,4-methylenedioxymethamphetamine ('ecstasy')-induced serotonin neurotoxicity: studies in animals. Neuropsychobiology, 42(1): 5-10.

Riley SCE, James C, Gregory D, Dingle H, Cadger M. (2001): Patterns of recreational drug use at dance events in Edinburgh, Scotland. Addiction, 96(7):1035-1048.

Robinson TE, Castaneda E, Whishaw IQ. (1993): Effects of cortical serotonin depletion induced by 3,4-methylenedioxymethamphetamine (MDMA) on behaviour, before and after additional cholinergic blockade. Neuropsychopharmacology, 8(1): 77-85.

Rodgers J. (2000): Cognitive performance amongst recreational users of 'ecstasy'. Psychopharmacology, 151: 19-24.

Rodgers J, Buchanan T, Scholey AB, Heffernan TM, Ling J, Parrott A. (2001): Differential effects of ecstasy and cannabis on self-reports of memory ability: a web-based study. Human Psychopharmacology, 16:619-625.

Rodgers J, Buchanan T, Scholey AB, Heffernan TM, Ling J, Parrott A. (2003): Patterns of drug use and the influence on self-reports of memory ability in ecstasy users: a web-based study. Journal of Psychopharmacology, 17(4):389-396.

Rodgers RD & Robbins TW. (2001) Investigating the neurocognitive deficits associated with chronic drug misuse. Current Opinion in Neurobiology, 11: 250-257.

Rothman RB, Baumann MH, Dersch CM, Romero DV, Rice KC, Carroll FI, Partilla JS. (2001): Amphetamine-type central nervous stimulants release norepinephrine more potently than they release dopamine and serotonin. Synapse, 39(1): 32-41

Rotter JB. (1954): Social Learning and Clinical Psychology. Englewood Cliffs: Prentice Hall.

Rotter JB. (1966): Generalised expectancies for internal and external control of reinforcement. Psychological Monographs, 80 (1): 1-28.

Rotter JB (1975): Some problems and misconceptions related to the construct of internal versus external control of reinforcement. Journal of Consulting and Clinical Psychology, 43(1):56-67.

Sabol KE, Lew R , Richards J, Vosmer GL, Seiden LS. (1996): Methylenedioxymethamphetamine-induced serotonin deficits are followed by partial recovery over a 52-week period. Part I: Synaptosomal uptake and tissue concentrations Journal Pharmacology Experimental Therapeutics, 276(2): 846-54.

Saunders, N. (1997). Ecstasy Reconsidered. Nicholas Saunders: London

Scanzello CR, Hatzidimitriou G, Martello AL, Katz JL, Ricaurte GA. (1993): Serotonergic recovery after (+/-)3,4-(methlylenedioxy)methamphetamine injury: observations in rats. Journal Pharmacology Experimental Therapeutics, 264(3): 1484-91.

Scheffel U, Szabo Z, Matthews WB, Finley PA, Dannals RF, Ravert HT, Szabo K, Yuan J, Ricaurte GA. (1998): In vivo detection of short- and long-term MDMA neurotoxicity – a position emission tomography study in the living baboon brain. Synapse, 29(2): 183-92.

Schifano F. (1991): Chronic atypical psychosis associated with MDMA ("ecstasy") abuse. The Lancet, 338: 1335.

Schifano F. (2000): Potential neurotoxicity of MDMA ('Ecstasy'): Subjective self-reports, evidence from an Italian Drug Addiction Centre and Clinical Case Studies. Neuropsychobiology, 42(1): 25-33.

Schifano F. (2004): A bitter pill. Overview of ecstasy (MDMA, MDA) related fatalities. Psychopharmacology, 173: 242-248.

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 Dependence, 52(1): 85-90.

Schifano F & Magni G. (1994): MDMA ("Ecstasy") abuse: psychopathological features and craving for chocolate: a case series. Biological Psychiatry, 36: 763-767.

Schmidt CJ, Taylor VL. (1988): Direct central effects of acute methylenedioxymethamphetamine on serotonergic neurons. European Journal of Pharmacology, 156(1): 121-131.

Seiden LS, Woolverton WL, Lorens SA, Williams JEG, Corwin RL, Hata N, Ollmski M. (1993): Behavioural consequence of partial monoamine depletion in the CNS after methamphetamine-like drugs: the conflict between pharmacology and toxicology. NIDA Research Monographs, 136:34-46.

Semple DM, Ebmeir KP, Glabus MF, O'Carroll, RE, Johnstone EC. (1999): Reduced in vivo binding to the serotonin transporter in the cerebral cortex of MDMA ('ecstasy') users. British Journal of Psychiatry, 175: 63-69.

Series H, Boeles S, Dorkins E, Peveler R. (1994): Psychiatric complications of 'ecstasy' use. Journal of Psychopharmacology, 8(1): 60-61.

Shallice T. (1982): Specific impairments in planning. Philos Trans R. Soc B. 298: 199-209.

Sharkey J, McBean DE, Kelly PA. (1991): Alterations in hippocampal function following repeated exposure to the amphetamine derivative methylenedioxymethamphetamine ("ecstasy").

Sherlock K, Wolff K, Hay AWM, Conner M. (1999): Analysis of illicit ecstasy tablets: implications for clinical management in the accident and emergency department. Journal Accident Emergency Medicine, 16: 194-197.

Shulgin AT & Nichols DE. (1978) Characterization of three new psychotomimetics. In Stillman RC, Willette RE (Eds), The Psychopharmacology of Hallucinogens. Pergamon, New York.

Simon NG, Mattick RP. (2002). The impact of regular ecstasy use on memory function. Addiction, 97: 1523-1529.

Slikker W , 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

Soar K, Parrott AC. (2002). Problematic ecstasy use: is it due to patterns of ecstasy use? Journal of Psychopharmacology, 16(3): G4, A58.

Soar K, Turner JJD, Parrott A. (2001) Psychiatric disorders in ecstasy (MDMA) users: a literature review focusing on personal predisposition and drug history. Human Psychopharmacology Clinical Experimental, 16:641-645

Solowij N, Hall W, Lee N. (1992): Recreational MDMA use in Sydney: a profile of 'ecstasy' users and their experiences with the drug. British Journal of Addiction, 87(8):1161-72

Spatt J, Glawar B, Mamoli B. (1997): A pure amnesic syndrome after MDMA ("ecstasy") ingestion. Journal of Neurology, Neurosurgery and Psychiatry 62: 418-428.

Stein RA, Strickland TL, Khalsa-Dennison, Andre K. (1997): Gender differences in neuropsychological test performance among cocaine abusers. Archives of Clinical Neuropsychology, 12(4):410-411

Sternbach H. (1991): The Serotonin Syndrome. American Journal of Psychiatry, 148(6):705-713.

Stone DM, Johnson M, Hanson GR, Gibb JW. (1989): Acute inactivation of tryptophan hydroxlyase by amphetamine analogues involves the oxidation of sulfhydryl sites. European Journal of Pharmacology, 172(1): 93-97.

Strote J, Lee JE, Wechsler H. (2002): Increased MDMA use among college students: results of a national survey. Journal of Adolescent Health, 30: 64-72.

Taffe MA, Weed MR, Davis S, Huitron-Resendiz S, Schroeder R, Parsons LH, Henriksen SJ, Gold LH. (2001): Functional consequences of repeated (+) 3, 4-methylenedioxymethamphetamine (MDMA) treatment in rhesus monkeys. Neuropsychopharmacology, 24(3): 230-239.

Taffe MA, Davis S, Yuan J, S, Schroeder R, Hatzidimitriou G, Parsons LH, Ricaurte GA, Gold LH. (2002): Cognitive performance of MDMA-treated rhesus monkeys: sensitivity to serotonergic challenge. Neuropsychopharmacology, 27(6): 993-1005.

Teggin AF. (1992): Ecstasy - a dangerous drug. South African Medical Journal, 81: 431-432.

Thomasius R, Petersen K, Buchert R, Andresen B, Zapletalova P, Wartberg L, Nebeling B, Schmoldt A. (2003): Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users. Psychopharmacology, http://Fireball/Alex/thomasius_2003.html Published on line March 2003.

Topp L, Hando J, Dillon, Roche A, Solowij N. (1999): Ecstasy use in Australia: patterns of use and associated harm. Drug and Alcohol Dependence, 55: 105-115.

Tuchtenhagen F, Daumann J, Norra C, Gobbele R, becker S, Pelz S, Sass H, Buchner H, Gouzoulis-Mayfrank E. (2000): High intensity dependence of auditory evoked dipole source activity indicates decreased serotonergic activity in abstinent ecstasy (MDMA) users. Neuropsychopharmacology, 22(6): 608-615.

Tucker GT, Lennard MS, Ellis SW, Woods HF, Cho AK, Lin LY, Hiratsuka A, Schhmitz DA, Chu TY. (1994): The demethylenation of methylendioxymethamphetamine ("ecstasy") by de-brisoquine hypdroxlase (CYP2D6). Biochemical Pharmacology, 47: 1151-1156.

Turner JJD, Juby K, Parrott AC. (1998): Spatial and object recognition performance of regular MDMA users assess in virtual reality. Journal of Psychopharmacology, 12: A43.

Turner JJD, Parrott AC. (2000): 'Is MDMA a human neurotoxin?' Diverse views from the discussants. Neuropharmacology, 42: 42-48.

Tune LE, Straus ME, Lew MF, Breitlinger E, Coyle JT. (1982): Serum levels of anticholinergic drugs and impaired recent memory in chronic schizophrenic patients. American Journal of Psychiatry, 139(11):1460-1462.

Unterrainer JM, Rahm B, Leonhart R, Ruff CC, Halsband U. (2003): The Tower of London: the impact of instructions, cueing and learning on planning abilities. Cognitive Brain Research, 17(3): 675-683.

Vaiva G, Boss V, Bailly D, Thomas P, Lestavel P, Goudemand M. (2001): An "accidental" acute psychosis with ecstasy use. Journal of Psychoactive Drugs, 33(1): 95-96.

Van Kampen J, Katz M. (2001): Persistent psychosis after a single ingestion of 'ecstasy'. Psychosomatics, 42(6): 525-527.

Velligan DI, Ritch JL, Sui D, DiCocco M, Huntzinger CD. (2002): Frontal systems behaviour scale in schizophrenia: relationshiops with psychiatric, symptomatology, cognition and adaptive function. Psychiatry Research, 113(3): 227-236.

Verbaten MN. (2003): Specific memory deficits in ecstasy users? The results of a meta-analysis. Human Psychopharmacology, 18:281-290.

Verheyden SL, Hadfield J, Calin T, Curran VH. (2002): Sub-acute effects of MDMA (+ 3,4-methylenedioxymethamphetamine, "ecstasy") on mood: evidence of gender differences. Psychopharmacology, 161(1): 23-31

Verheyden SL, Henry JA, Curran VH. (2003): Acute, sub-acute and long-term subjective consequences of 'ecstasy' (MDMA) consumption in 430 regular users. Human Psychopharmacology, 18: 507-517

Verheyden SL, Maidment R, Curran VH. (2003): Journal of Psychopharmacology, 17(4): 371-378.

Verkes RJ, Gilsman HJ, Pieters MSM, Schoemaker RC, Visser SD, Kuilpers M, Pennings EJM, Bruin DD, Wingaart GV, Van Gerven JMA, Cohen AF. (2001): Cognitive performance and serotonergic function in users of ecstasy. Psychopharmacology, 153: 196-202.

Virkkunen MU, Goldman D, Nielsen DA, Linnolia M. (1995): Low brain serotonin turnover rate (low CSF 5-HIAA) and impulsive violence. Journal of Psychiatry & Neuroscience, 20(4): 271-275.

Wall de C, Wilson BA, Baddeley AD (1994): The extended Rivermead Behavioural Memory Test: A measure of everyday memory performance in normal adults. Memory, 2(2): 149-166.

Wallston KA, Wallston BS, DeVellis R (1978): Development of the Multidimensional Health Locus of Control (MHLC) Scale. Health Education Monographs, 6:161-170.

Wareing M, Fisk JE, Murphy PN. (2000): Working memory deficits in current and previous users of MDMA ('ecstasy'). British Journal of Psychology, 91: 181-188.

Webb E, Ashton CH, Kelly P, Kamali F. (1996): Alcohol and drug use in the UK university students. The Lancet, 348:922-925.

Weickert TW, Goldberg TE, Marenco S, Bigelow LB, Egan MF, Weinberger DR. (2003): Comparison of cognitive performances during placebo period and an atypical antipsychotic treatment period in schizophrenia: critical examination of confounds. Neuropsychopharmacology, 28:1491-1500.

Weir E. (2000): Raves: a review of the culture, the drugs and the prevention of harm. Canadian Medical Association Journal, 162(13):1843-8

Whitaker-Azmitia PM, Aronson TA. (1989): "Ecstasy" (MDMA)-induced panic. American Journal of Psychiatry, 146(1): 119.

Williams H, Meagher D, Galligan P. (1993): MDMA ("ecstasy"): a case of possible drug-induced psychosis. Irish Journal of Medical Science, 43-44.

Wills P, Clare L, Shiel A, Wilson BA. (2000): Assessing subtle memory impairments in everyday memory performance of brain injured people: exploring the potential of the Extended Rivermead Behavioural Memory Test. Brain Injury, 14(8): 693-704.

Wilson B, Cockburn J, Baddeley A, Hiorns R. (1989): The development and validation of a test battery for detecting and monitoring everyday memory problems. Journal of Clinical and Experimental Neuropsychology, 11(6): 855-870.

Wilson B, Cockburn J, Baddeley A, Hiorns R. (1991) The Rivermead Behavioural Memory Test. 2nd Edition. Thames Valley Test Company, Bury St Edmunds.

Wilson W, Roy M, Turkington T, Hawk T, Coleman RE, Provenzale J. (2000): Brain morphological changes and early marijuana use: a magnetic resonance and position emission tomography study. Journal of Addictive Diseases, 19(1):1-22.

Windhaber J, Maierhofer D, Dantendorfer K. (1998): Panic disorder induced by large dose of 3,4-methylenedioxymethamphetamine resolved by Paroxetine. Journal of Clinical Psychopharmacology, 18(1): 95-96.

Winsaur PJ, McCann UD, Yuan J, Dleatte MS, Stevenson MW, Ricaurte GA, Moerschbaecher JM. (2002): Effects of fenfluramine, m-CPP and triazolam on repeated-acquisition in squirrel monkeys before and after neurotoxic MDMA administration. Psychopharmacology, 159:388-396.

Winstock AR, Griffiths P, Stewart D. (2001): Drugs and the dance music scene: a survey of current drug is patterns among a sample o dance music enthusiasts in the UK. Drug and Alcohol Dependence, 64: 9-17.

Yamamoto BK, Spanos LJ (1988): The acute effects of methylenedioxymethamphetamine on dopamine release in awake-behaving rat. European Journal of Pharmacology, 148(2): 195-203.

Young SW, Smith SE, Pihl RO, Ervin FR. (1985): Tryptophan depletion causes rapid lowering of mood in normal males. Psychopharmacology, 87:173-177.

Young T & Washburn U. (1992): Locus of control and self-reported psychopathology among Native Americans. Social Behaviour & Personality, 20(4): 235-236.

Zakzanis KK & Young DA. (2001): Executive function in abstinent MDMA ('ecstasy') users. Med Sci Monit, 7(6): 1292-1298.

Zakzanis KK & Young DA. (2001): Memory impairment in abstinent MDMA ('ecstasy') users: a longitudinal investigation. Neurology, 56: 966-969.

Zakzanis KK, Young DA, Radkhoshnoud NF. (2002): Attentional processes in abstinent methylenedioxymethamphetamine (ecstasy) users. Applied Neuropsychology, 9(2):84-91

Zhou D, Schreinert M, Pilz J, Huether G (1996): Rat strain differences in vulnerability of serotonergic nerve endings to neurotoxic damage by p-chlororamphetamine. Journal Neural Transmission, 103:1381-1395.

Zhu BT (2002): Catechol-O-methyltranferase (COMT)-mediated methylation metabolism of endogenous bioactive catechols and modulation by endobiotics and xenobiotics: importance in pathophysiology and pathogenesis. Current Drug Metabolism, 3: 321-349.

Zilberman ML, Tavares H, Blume, el-Guebaly N. (2003): Substance Use Disorders: sex differences and psychiatric comorbidities. Canadian Journal of Psychiatry, 48(10): 5-14

Zuckerman M (1994): Behavioural expressions and biosocial bases of sensation seeking. Cambridge University Press: Cambridge.

Zuckerman & Neeb M. (1979): Sensation seeking and psychopathology. Psychiatry Research, 1(3):255-264.

APPENDIX A

PERSONAL HISTORY

Age_____ **Gender**_____

Age left education _____ **Nationality**_____

	Bad	Moderate	Fine	Good
Current rating of health	1	2	3	4

Have you ever been clinically diagnosed (by a Doctor) with any of the following?

Anxiety	Yes ☐	No ☐
Depression	Yes ☐	No ☐
OCD (Obsessive Compulsive Disorder)	Yes ☐	No ☐
Schizophrenia or Paranoia	Yes ☐	No ☐
Phobia	Yes ☐	No ☐
Panic attacks	Yes ☐	No ☐
Eating disorders	Yes ☐	No ☐
Alcohol or Drug dependency	Yes ☐	No ☐

Have any member of your immediate family ever been diagnosed (by a Doctor) with any of the following?

Anxiety	Yes ☐	No ☐
Depression	Yes ☐	No ☐
OCD (Obsessive Compulsive disorder)	Yes ☐	No ☐
Schizophrenia or Paranoia	Yes ☐	No ☐
Phobia	Yes ☐	No ☐
Panic attacks	Yes ☐	No ☐
Eating disorders	Yes ☐	No ☐
Alcohol or Drug dependency	Yes ☐	No ☐

Have you ever been hospitalised for any brain injury? Yes ☐ No ☐

Are you on any current medication? Yes ☐ No ☐

If yes, what is this medication prescribed for?

_____

_____

_____

DRUG USE QUESTIONNAIRE

Please answer these as accurately as possible:

1. ECSTASY/MDMA AND OTHER DRUGS

Which of the following drugs have you taken, and approximately how many times?

Ecstasy/MDMA	No ☐	Yes ☐	If yes, how many times? _____
Amphetamine	No ☐	Yes ☐	If yes, how many times? _____
Cocaine	No ☐	Yes ☐	If yes, how many times? _____
Crack	No ☐	Yes ☐	If yes, how many times? _____
Opiates (Heroin, morphine)	No ☐	Yes ☐	If yes, how many times? _____
Cannabis	No ☐	Yes ☐	If yes, how many times? _____
Benzodiazepines (e.g. Valium)	No ☐	Yes ☐	If yes, how many times? _____
LSD	No ☐	Yes ☐	If yes, how many times? _____
Magic mushrooms	No ☐	Yes ☐	If yes, how many times? _____
Anabolic steroids	No ☐	Yes ☐	If yes, how many times? _____
Solvents	No ☐	Yes ☐	If yes, how many times? _____
Poppers	No ☐	Yes ☐	If yes, how many times? _____
Ketamine	No ☐	Yes ☐	If yes, how many times? _____
Prozac	No ☐	Yes ☐	If yes, how many times? _____
GHB (liquid ecstasy)	No ☐	Yes ☐	If yes, how many times? _____

Others *(Please specify & indicate how often used, as above):*

_____

_____

2. ALCOHOL, TOBACCO AND CANNABIS USE

Do you smoke tobacco? No ☐ Yes ☐
If yes, how many cigarettes do you smoke per day on average?_____

Do you drink alcohol? No ☐ Yes ☐
If yes, how many units of alcohol do you drink in a typical week?_____

Do you smoke cannabis? No ☐ Yes ☐
If yes, how many times do you smoke per month on average?_____

APPENDIX B

ECSTASY QUESTIONNAIRE

(Only complete if you have taken ecstasy)

1. **When was the first time you took Ecstasy/MDMA?**_____
2. **When did you last take Ecstasy/MDMA?**_____
3. **How many tablets would you normally take in one occasion?**_____
4. **What is the largest number of tablets you have taken in one occasion?**
   _____
5. **How many ecstasy tablets have you taken in your lifetime?**_____
6. **Have you increased the number of ecstasy tablets you take on each occasion?**
   Yes ☐ No ☐
7. **Has the effect of ecstasy changed, the more you have taken it?**
   Yes ☐ No ☐
8. **Do you suffer if you go for sometime without taking ecstasy?**
   Yes ☐ No ☐
9. **Do you *need* to take ecstasy regularly?**
   Yes ☐ No ☐
10. **Do you feel you are dependent or addicted to ecstasy in any way?**
    Yes ☐ No ☐
11. **Do you consider yourself to be a stable user of ecstasy, using approximately the same amount of tablets on each occasion with regular intervals between each occasion?**
    Yes ☐ No ☐
12. **Do you continue to use ecstasy?**
    Yes ☐ No ☐
13. **Do you usually take other drugs together with ecstasy?**
    Yes ☐ No ☐

If yes, please indicate which ones: _____
_____

14. **Do you take any drugs that are supposed to prevent ecstasy side effects?**
    Yes ☐ No ☐

APPENDIX C

15. The following are a list of effects that you may have experienced whilst on ecstasy. Please indicate whether you ever experienced them and if so how much.

	Not at all	Slightly	Moderate	Strongly
Confusion/disorientation	1	2	3	4
Agitation/irritability	1	2	3	4
Anxiety	1	2	3	4
Euphoria/extreme happiness	1	2	3	4
Unresponsiveness	1	2	3	4
Largely reduced body temperature	1	2	3	4
Excessive sweating	1	2	3	4
Large increase in heart rate	1	2	3	4
Dilated pupils	1	2	3	4
Nausea/sickness	1	2	3	4
Unreactive pupils	1	2	3	4
Flushing	1	2	3	4
Tremors	1	2	3	4
Restlessness/hyperactivity	1	2	3	4
Lack of muscle co-ordination	1	2	3	4
Uncontrollable muscle spasms/twitching	1	2	3	4
Muscle stiffness	1	2	3	4

APPENDIX D

16. Has your use of ecstasy led to changes in your experiences of life? Please indicate how much the following changes apply to you, some are positive changes others are negative.

	Not at all	Slightly	Moderate	Strongly
Increased empathy	1	2	3	4
Obsessive Thoughts	1	2	3	4
Aggression	1	2	3	4
Loss of organisational skills	1	2	3	4
Backache	1	2	3	4
Breathlessness	1	2	3	4
Decrease in defensiveness	1	2	3	4
Confidence Loss	1	2	3	4
Less Sociable	1	2	3	4
Mood Swings	1	2	3	4
Improved social/interpersonal functioning	1	2	3	4
Depression	1	2	3	4
Anxiety	1	2	3	4
Paranoia	1	2	3	4
Increased feelings of well being	1	2	3	4
Hallucinations or flashbacks	1	2	3	4
Panic attacks	1	2	3	4
Phobias	1	2	3	4
Enhanced sensations	1	2	3	4
Sex problems	1	2	3	4
General Illness	1	2	3	4
Weight Loss	1	2	3	4
Sleep Problems	1	2	3	4
Spiritual enlightenment	1	2	3	4
Memory Loss	1	2	3	4
Concentration Loss	1	2	3	4
Decrease in fear	1	2	3	4
Motivational Problems	1	2	3	4

17. During which period of your ecstasy use did these changes start occurring?_____

18. Have any of these changes led you to seek help or advice from a professional organisation?

Yes ☐ No ☐

If yes, please indicate which of the following you have approached:

GP (Doctor)	Yes ☐	No ☐
Clinical psychologist	Yes ☐	No ☐
Psychiatrist	Yes ☐	No ☐
Drug services/clinic	Yes ☐	No ☐
Other (please specify)_____	Yes ☐	No ☐

19. Have you been prescribed some form of treatment for these changes?

Yes ☐ No ☐

If yes, please indicate:

_____

_____

APPENDIX E

DRUG USE QUESTIONNAIRE

Please answer these as accurately as possible:

1. PAST DRUG USE

Which of the following drugs have you taken, and approximately how many?

Amphetamine	No ☐	Yes ☐	If yes, how many? _____
Cocaine	No ☐	Yes ☐	If yes, how many? _____
LSD	No ☐	Yes ☐	If yes, how many? _____
Magic mushrooms	No ☐	Yes ☐	If yes, how many? _____
Poppers	No ☐	Yes ☐	If yes, how many? _____
Ketamine	No ☐	Yes ☐	If yes, how many? _____
GHB (liquid ecstasy)	No ☐	Yes ☐	If yes, how many? _____
Prozac (not prescribed)	No ☐	Yes ☐	If yes, how many? _____
Crack	No ☐	Yes ☐	If yes, how many? _____
Opiates (e.g. Heroin, morphine)	No ☐	Yes ☐	If yes, how many? _____
Benzodiazepines (e.g. Valium)	No ☐	Yes ☐	If yes, how many? _____
Anabolic steroids	No ☐	Yes ☐	If yes, how many? _____
Solvents	No ☐	Yes ☐	If yes, how many? _____

Others *(Please specify & indicate how often used, as above):*

_____

2. CANNABIS USE

Do you currently smoke cannabis? No ☐ Yes ☐

If yes, how many times do you smoke per month on average? _____

how many years have you smoked for? _____

Have you smoked cannabis in the past? No ☐ Yes ☐

If yes, how many times did you smoke per month on average? _____

How many years did you smoke for? _____

3. CURRENT ALCOHOL AND TOBACCO USE

Do you smoke tobacco? No ☐ Yes ☐

If yes, how many cigarettes do you smoke per day on average?_____

Do you drink alcohol? No ☐ Yes ☐

If yes, how many units of alcohol do you drink in a typical week?_____

4. PAST ECSTASY USE (only complete if you have taken ecstasy)

When was the first time you took Ecstasy/MDMA (year/month)? _____

When did you last take Ecstasy/MDMA (year/month)? _____

How many ecstasy tablets have you taken in your lifetime? _____

Please indicate by circling the appropriate statement, how often, on average, you use or did use ecstasy?

Weekly Monthly Every 3 months Yearly

On average, how many tablets would you normally take in one occasion?

_____

What is the largest number of tablets you have taken in one occasion?

_____

Do you continue to use ecstasy? No ☐ Yes ☐

If no, please indicate why you stopped:

_____

Have you experienced any problems, which you attribute to your ecstasy use?

No ☐ Yes ☐

Have any of these problems led you to seek help or advice from a professional organisation? No ☐ Yes ☐

If yes, please indicate which of the following you have approached:

GP (Doctor)	Yes ☐
Clinical psychologist	Yes ☐
Psychiatrist	Yes ☐
Drug services/clinic	Yes ☐
Other (please specify)_____	Yes ☐

APPENDIX F

CHANGES IN LIFE EXPERIENCES

Below are a list of positive and negative life experiences, please indicate whether you have experienced any of these and what you attribute this change to the most by circling the appropriate statement. If you have never used drugs, please still indicate whether you have experienced this change.

1. Positive changes in your life (when not under the influence of drugs or alcohol)

Increased empathy attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Decrease in defensiveness attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Improved social/interpersonal functioning attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Increased feelings of well being attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Decrease in fear attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Spiritual enlightenment attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Enhanced sensations attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced

2. Negative changes in your life (when not under the influence of drugs or alcohol)

Obsessive Thoughts attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Aggression attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Mood Swings attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Less Sociable attributed to	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Confidence Loss attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Depression attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Anxiety attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Paranoia attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Hallucinations or flashbacks attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Panic attacks attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Phobias attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Breathlessness attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Backache attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Sex problems attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced

General Illness attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Weight Loss attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Sleep Problems attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Loss of organisational skills attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Motivational Problems attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Memory Loss attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Concentration Loss attributed to:	Other non-drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced

APPENDIX G

Table 31: Percentages of reported positive and negative life changes in drug-naïve controls and whether they attributed this change to alcohol

N=111	Other non-drug factor	Alcohol	No change experienced
Positive life changes			
Increased empathy	19.8	5.4	74.8
Decrease in defensiveness	11.7	6.3	82
Improved social/interpersonal functioning	24.3	18	57.7
Increased feelings of well being	26.1	9.9	64
Decrease in fear	20.7	12.6	66.7
Spiritual enlightenment	18	0.9	81.1
Enhanced sensations	18	9	73
Negative life changes			
Obsessive thoughts	15.3	4.5	80.2
Aggression	20.7	9	70.3
Mood swings	28.8	4.5	66.7
Less sociable	25.2	2.7	72.1
Confidence loss	35.1	1.8	63.1
Depression	25.2	6.3	68.5
Anxiety	17.1	1.8	81.1
Paranoia	9	9	88.3
Hallucinations	4.5	0	95.5
Panic attacks	2.7	0.9	96.4
Phobias	9	0	91
Breathlessness	12.6	1.8	85.6
Backache	28.8	0	71.2
Sex problems	10.8	0	89.2
General illness	27	1.8	71.2
Weight loss	23.4	0.9	75.7
Sleep problems	25.2	6.3	68.5
Loss of organisational skills	12.6	4.5	82.9
Motivational problems	23.4	5.4	71.2
Memory loss	9	5.4	85.6
Concentration loss	21.6	9	69.4

Table 32: Percentages of reported positive and negative life changes in polydrug controls which, if any drug(s) they attributed this change to

N=62	Other non-drug factor	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Positive life changes							
Increased empathy	24.2	0	3.2	0	17.7	11.3	48.4
Decrease in defensiveness	16.1	0		0	21.0	17.7	48.4
Improved social/interpersonal functioning	21	1.6	4.8	0	19.4	45.2	21
Increased feelings of well being	30.6	4.8	3.2	0	24.2	21.0	24.2
Decrease in fear	21	1.6	1.6	0	9.7	32.3	38.7
Spiritual enlightenment	19.4	0	0	1.6	12.9	0	66.1
Enhanced sensations	9.7	1.6	3.2	1.6	22.6	9.7	58.1
Negative life changes							
Obsessive thoughts	21	0	3.2	0	12.9	6.5	59.7
Aggression	24.2	0	3.2	0	14.5	24.2	50
Mood swings	32.3	1.6	3.2	0	8.1	16.1	40.3
Less sociable	24.2	0	1.6	0	12.9	14.5	48.4
Confidence loss	32.3	0	1.6	0	8.1	6.5	53.2
Depression	27.4	1.6	1.6	0	9.7	11.3	53.2
Anxiety	24.2	0	1.6	0	14.5	9.7	53.2
Paranoia	9.7	0	1.6	0	21.0	4.8	66.1
Hallucinations	6.5	1.6	0	1.6	3.2	3.2	87.1
Panic attacks	12.9	0	0	0	8.1	1.6	79
Phobias	9.7	0	0	0	0	0	90.3
Breathlessness	27.4	0	0	0	12.9	0	59.7
Backache	33.9	0	0	0	0	0	66.1
Sex problems	12.9	0	0	0	1.6	4.8	79
General illness	32.3	0	1.6	0	3.2	9.7	56.5
Weight loss	21	1.6	0	0	6.5	0	71
Sleep problems	32.3	1.6	1.6	0	8.1	3.2	54.8
Loss of organisational skills	21	1.6	1.6	0	12.9	4.8	56.5
Motivational problems	29	1.6	0	0	17.7	12.9	46.8
Memory loss	14.5	1.6	0	0	16.2	12.9	3.2
Concentration loss	22.6	3.2	0	0	24.2	19.4	41.9

Table 33: Percentages of reported positive and negative life changes in non-problematic ecstasy users which, if any drug(s), they attributed this change to

N=62	Other non0drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Positive life changes								
Increased empathy	19.4	45.2	6.5	9.7	16.1	21.0	12.9	29
Decrease in defensiveness	12.9	17.7	8.1	6.5	11.3	21.0	22.6	45.2
Improved social/interpersonal functioning	12.9	35.5	17.7	33.9	6.5	19.4	43.5	17.7
Increased feelings of well being	22.6	33.9	9.7	27.4	8.1	17.7	25.8	29
Decrease in fear	9.7	16.1	4.8	21.0	4.8	6.5	32.3	46.8
Spiritual enlightenment	11.3	27.4	3.2	3.2	27.4	22.6	8.1	51.6
Enhanced sensations	1.6	54.8	12.9	25.8	24.2	22.6	11.3	35.5
Negative life changes								
Obsessive thoughts	11.3	3.2	8.1	16.1	8.1	21.0	8.1	43.5
Aggression	4.8	4.8	4.8	11.3	0	0	32.3	53.2
Mood swings	14.5	25.8	19.4	21.0	9.7	12.9	25.8	32.3
Less sociable	8.1	9.7	8.1	8.1	4.8	22.6	16.1	41.9
Confidence loss	16.1	4.8	4.8	4.8	3.2	12.9	9.7	51.6
Depression	12.9	16.1	11.3	6.5	4.8	9.7	16.1	46.8
Anxiety	12.9	14.5	8.1	11.3	6.5	22.6	1.6	35.5
Paranoia	1.6	11.3	9.7	8.1	11.3	25.8	3.2	45.2
Hallucinations	1.6	9.7	1.6	0	21.0	4.8	1.6	66.1
Panic attacks	9.7	9.7	4.8	3.2	4.8	8.1	1.6	77.4
Phobias	8.1	0	0	0	0	0	1.6	88.7
Breathlessness	9.7	3.2	8.1	3.2	0	11.3	1.6	66.1
Backache	16.1	9.7	3.2	1.6	0	0	3.2	71
Sex problems	8.1	6.5	6.5	3.2	0	0	14.5	69.4
General illness	1.6	9.7	1.6	4.8	0	0	9.7	74.2
Weight loss	4.8	19.4	22.6	6.5	0	1.6	0	50
Sleep problems	6.5	14.5	22.6	19.4	4.8	12.9	3.2	40.3
Loss of organisational skills	6.5	1.6	1.6	0	0	16.1	11.3	56.5
Motivational problems	8.1	1.6	1.6	0	0	30.6	6.5	41.9
Memory loss	1.6	4.8	0	0	0	27.4	11.3	40.3
Concentration loss	6.5	3.2	3.2	0	0	19.4	17.7	38.7

Table 34: Percentages of reported positive and negative life changes in problematic ecstasy users which, if any drug(s), they attributed this change to

N=53	Other non0drug factor	Ecstasy	Amphetamine	Cocaine	LSD	Cannabis	Alcohol	No change experienced
Positive life changes								
Increased empathy	7.5	45.3	7.5	15.1	17.0	26.4	13.2	34
Decrease in defensiveness	13.2	35.8	9.4	9.4	13.2	20.8	13.2	32.1
Improved social/interpersonal functioning	22.6	45.3	11.3	18.9	3.8	17.0	28.3	17.0
Increased feelings of well being	22.6	35.8	11.3	15.1	9.4	15.1	20.8	28.3
Decrease in fear	17	20.8	1.9	17.0	7.5	7.5	17.0	47.2
Spiritual enlightenment	9.4	30.2	3.8	3.8	18.9	24.5	1.9	37.7
Enhanced sensations	5.7	56.6	20.8	18.9	20.8	26.4	11.3	24.5
Negative life changes								
Obsessive thoughts	1.9	37.7	18.9	18.9	20.8	30.2	13.2	32.1
Aggression	11.3	11.3	18.9	17.0	3.8	3.8	26.4	45.3
Mood swings	7.5	54.7	28.3	28.3	9.4	24.5	24.5	15.1
Less sociable	5.7	17.0	13.2	9.4	5.7	39.6	9.4	35.8
Confidence loss	11.3	22.6	24.5	15.1	5.7	24.5	9.4	37.7
Depression	5.7	62.3	28.3	18.9	7.5	17.0	22.6	17.0
Anxiety	9.4	37.7	24.5	22.6	9.4	24.5	9.4	26.4
Paranoia	3.8	34.0	30.2	20.8	17.0	49.1	9.4	20.8
Hallucinations	1.9	24.5	3.8	3.8	24.5	3.8	3.8	52.8
Panic attacks	7.5	34.0	17.0	11.3	5.7	17.0	5.7	47.2
Phobias	9.4	9.4	3.8	3.8	3.8	3.8	3.8	75.5
Breathlessness	7.5	17.0	17.0	7.5	1.9	11.3	0	52.8
Backache	15.1	28.3	15.1	1.9	0	0	1.9	47.2
Sex problems	13.2	13.2	3.8	11.3	1.9	5.7	5.7	60.4
General illness	7.5	39.6	20.8	15.1	9.4	22.6	3.8	43.4
Weight loss	7.5	49.1	32.1	15.1	1.9	5.7	1.9	28.3
Sleep problems	3.8	35.8	35.8	20.8	9.4	20.8	15.1	28.3
Loss of organisational skills	1.9	18.9	5.7	1.9	0	13.2	5.7	41.5
Motivational problems	5.7	13.2	11.3	3.8	0	32.1	5.7	30.2
Memory loss	3.8	13.2	3.8	1.9	0	7.5	1.9	24.5
Concentration loss	7.5	17.0	9.4	3.8	1.9	24.5	3.8	17.0

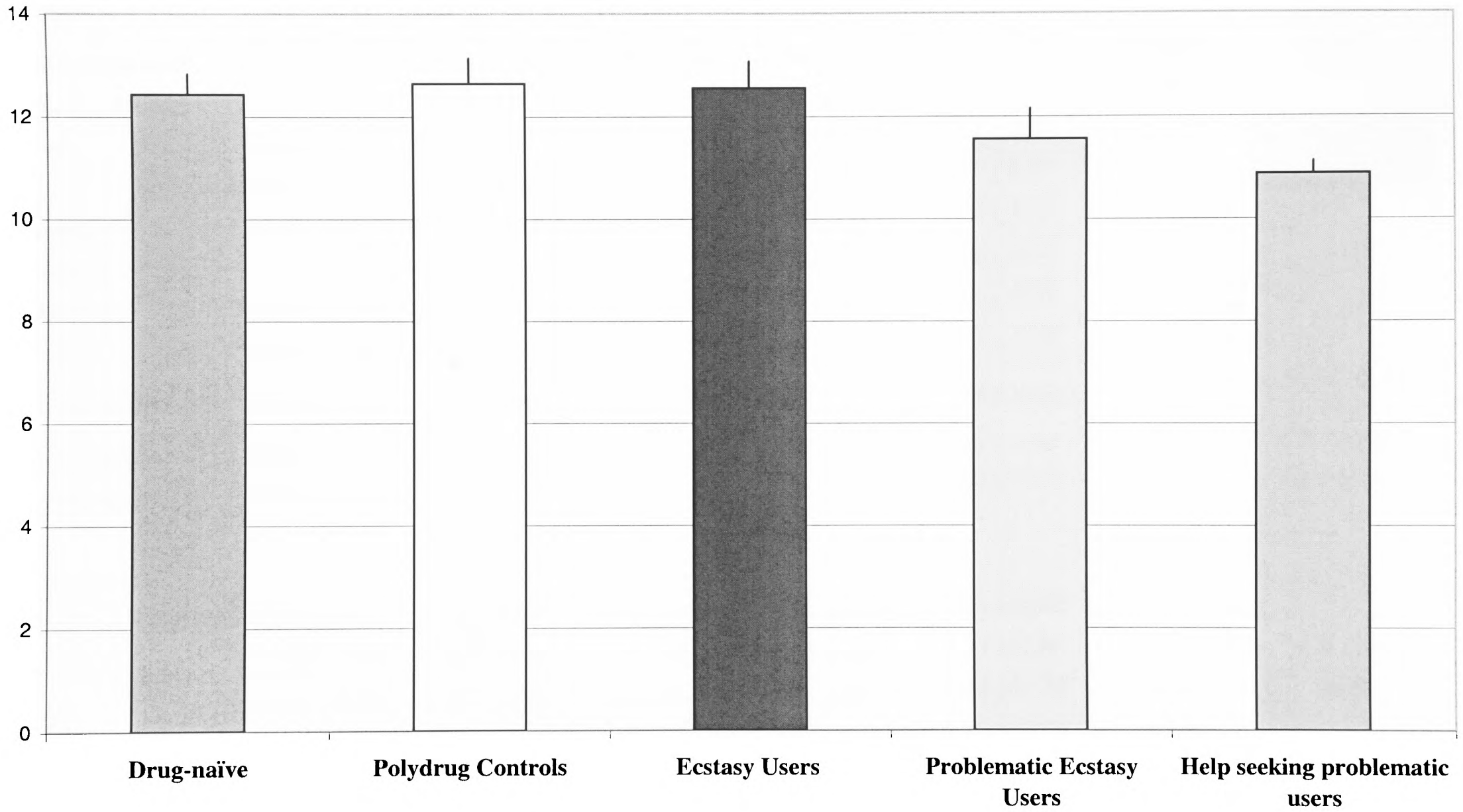
APPENDIX H

Table 40: Locus of Control mean scores (SD) for drug-naïve, polydrug controls, non-problematic ecstasy, problematic ecstasy users and problematic ecstasy users who reported seeking help.

	N	LOC
Drug Naïve (N)	111	12.44 ± 4.19
Non-ecstasy Polydrug Users (C)	62	12.65 ± 3.87
Non-problematic Ecstasy users (E)	62	12.56 ± 4.08
Problematic ecstasy users (P)	36	11.56 ± 4.19
Problematic ecstasy users, seeking help (PE)	17	10.88 ± 4.79
Group effect (sig.)	-	0.411

APPENDIX I

Figure 33: Mean LOC Scores for drug-naive, polydrug controls, ecstasy users, problematic ecstasy users and problematic ecstasy users seeking help (Bars indicate 1 standard errror)



APPENDIX J: Table 41: Mean BSI scores for all groups, including assessment of problematic ecstasy users and 'help-seeking' problematic ecstasy users.

Symptom	Drug Naïve [N] n = 111	Polydrug Controls [C] n = 62	Non-problematic Ecstasy users [E] n=62	Problematic ecstasy users [P] n=36	Help seeking Users [H] =17	Group Effect	Post Hoc Comparisons
Negative Symptoms							
Somatisation	0.46 ± 0.53	0.48 ± 0.56	0.45 ± 0.49	0.78 ± 0.57	0.73 ± 0.77	0.012	N & E < P: E<P
Obsessive-compulsive	1.05 ± 0.77	1.41 ± 0.92	1.21 ± 0.74	1.44± 0.68	1.55 ± 0.91	0.008	N < C
Interpersonal sensitivity	0.98 ± 0.89	1.14 ± 0.96	1.04 ± 0.88	1.31 ± 0.89	1.53 ± 0.98	0.092	
Depression	0.69 ± 0.78	0.83 ± 0.82	0.74 ± 0.69	1.03 ± 0.86	1.27 ± 0.94	0.020	N < H
Anxiety	0.63 ± 0.65	0.83 ± 0.87	0.63 ± 0.65	0.99 ± 0.68	1.37 ± 1.03	<0.001	N & E < H
Anger/hostility	0.65 ± 0.69	0.95 ± 0.89	0.81 ± 0.83	0.89 ± 0.81	1.12 ± 1.11	0.064	
Phobic anxiety	0.37 ± 0.56	0.47 ± 0.71	0.36 ± 0.55	0.46 ± 0.49	0.71 ± 0.98	0.232	
Paranoid ideation	0.88 ± 0.78	1.03 ± 0.86	0.85 ± 0.75	1.03 ± 0.68	1.12 ± 0.89	0.442	
Psychoticism	0.58 ± 0.68	0.65 ± 0.74	0.66 ± 0.70	0.77 ± 0.71	0.95 ± 0.89	0.273	
Negative psychobiology	0.86 ± 0.70	1.05 ± 0.84	0.99 ± 0.67	1.30 ± 0.82	1.59 ± 0.86	0.001	N < P & H: E<H
Sexual functioning	0.47 ± 0.41	0.73 ± 0.55	0.76 ± 0.44	0.76 ± 0.54	0.98 ± 0.61	<0.001	N<C,E,P& H
Cognitive failures	1.18 ± 0.98	1.66 ± 1.04	1.45 ± 1.00	1.76 ± 1.01	1.68 ± 0.82	0.005	N < C & P
Positive Symptoms							
Feeling content with life	2.33 ± 0.91	2.22 ± 0.75	2.47 ± 0.71	2.16 ± 0.78	2.40 ± 0.69	0.326	
Positive Mood state	1.92 ± 0.79	1.94 ± 0.73	2.34 ± 0.63	1.99 ± 0.82	2.24 ± 0.86	0.006	N & C < E
Sociability	2.12 ± 0.80	2.28 ± 0.96	2.47 ± 0.72	2.25 ± 0.70	2.36 ± 0.74	0.056	N<E
Positive psychobiology	2.17 ± 0.82	2.07 ± 0.66	2.37 ± 0.70	2.17 ± 0.73	2.18 ± 0.75	0.278	

APPENDIX K

Table 42: Ethnic diversity in drug naïve, polydrug controls, non-problematic and problematic ecstasy users

	Drug naïve	Polydrug users	Non-problematic Ecstasy users	Problematic Ecstasy users
Caucasian	67	47	59	50
Asian	13	7	2	2
Afro-Caribbean	9	4	1	1
Chinese	1	1	0	0
Other	21	3	0	0

APPENDIX L

THE MODIFIED BRIEF SYMPTOM INVENTORY

Below is a list of problems and complaints that people sometimes have. Please read each one carefully. After you have done so please circle one of the numbers to the right that best describes HOW MUCH YOU HAVE EXPERIENCED THAT FEELING OR COMPLAINT, WHEN NOT UNDER THE EFFECT OF DRUGS, IN THE PAST FOUR WEEKS.

WE ARE VERY INTERESTED IN YOUR QUESTIONNAIRE EVEN IF YOU HAVE NEVER TAKEN DRUGS.

Circle only ONE number for each problem and do not skip any items.

Please see example below before beginning.

EXAMPLE:

IN THE PAST MONTH, WHEN FREE OF DRUGS, HAVE YOU EVER EXPERIENED:

1. Backaches

Not at all	A little Bit	Moderately	Quite a bit	Extremely
0	1	(2)	3	4

The "2" has been circled, this means that the person had been Moderately bothered by backache in the past 4 weeks, **IN A DRUG FREE SITUATION.**

APPENDIX L

IN THE PAST MONTH, WHEN NOT UNDER THE EFFECT OF DRUGS, HAVE YOU EVER EXPERIENCED:

	Not at all	A Little Bit	Moderately	Quite a bit	Extremely
1. Nervous or shakiness inside	0	1	2	3	4
2. Faintness or dizziness	0	1	2	3	4
3. Feeling interested in things	0	1	2	3	4
4. Feeling comfortable with others	0	1	2	3	4
5. The idea that someone else can control your thoughts	0	1	2	3	4
6. Feeling others are to blame for most of your troubles	0	1	2	3	4
7. Feeling quick witted	0	1	2	3	4
8. Trouble remembering things	0	1	2	3	4
9. Increased sexual desire	0	1	2	3	4
10. Sleeping well	0	1	2	3	4
11. Feeling easily annoyed or irritated	0	1	2	3	4
12. Feeling rash or impulsive	0	1	2	3	4
13. Pains in heart or chest	0	1	2	3	4
14. Feeling afraid of open spaces	0	1	2	3	4
15. Thoughts of ending your life	0	1	2	3	4
16. Feeling alert and attentive	0	1	2	3	4
17. Feeling that most people cannot be trusted	0	1	2	3	4
18. Poor appetite	0	1	2	3	4

APPENDIX L

IN THE PAST MONTH, WHEN NOT UNDER THE EFFECT OF DRUGS, HAVE YOU EVER EXPERIENCED:

	Not at all	A Little Bit	Moderately	Quite a bit	Extremely
19. Having sexual interest and/or pleasure	0	1	2	3	4
20. Craving for chocolate	0	1	2	3	4
21. Suddenly scared for no reason	0	1	2	3	4
22. Temper out bursts that you could not control	0	1	2	3	4
23. Feeling satisfied with life	0	1	2	3	4
24. Feeling lonely even when you are with other people	0	1	2	3	4
25. Feeling blocked in getting things done	0	1	2	3	4
26. Having good times with friends	0	1	2	3	4
27. Decreased sexual desire	0	1	2	3	4
28. Feeling lonely	0	1	2	3	4
29. Feeling blue	0	1	2	3	4
30. Having good appetite	0	1	2	3	4
31. Feeling no interest in things	0	1	2	3	4
32. Feeling fearful	0	1	2	3	4
33. Feeling clear-headed	0	1	2	3	4
34. Your feelings being easily hurt	0	1	2	3	4
35. Difficulties in planning things	0	1	2	3	4
36. Feeling that people are unfriendly or dislike you	0	1	2	3	4
37. Feeling in good spirits	0	1	2	3	4

APPENDIX L

IN THE PAST MONTH, WHEN NOT UNDER THE EFFECT OF DRUGS, HAVE YOU EVER EXPERIENCED:

	Not at all	A Little Bit	Moderately	Quite a bit	Extremely
38. Feeling inferior to others	0	1	2	3	4
39. Nausea or upset stomach	0	1	2	3	4
40. Feeling that you are watched or talked about by others	0	1	2	3	4
41. Trouble falling asleep	0	1	2	3	4
42. Feeling non-judgemental of others	0	1	2	3	4
43. Having to check and double check what you do	0	1	2	3	4
44. Feeling healthy and proficient	0	1	2	3	4
45. Difficulty making decisions	0	1	2	3	4
46. Feeling afraid to travel on buses, subways or trains	0	1	2	3	4
47. Premature orgasm (premature ejaculation in males)	0	1	2	3	4
48. Trouble getting your breath	0	1	2	3	4
49. Feeling happy	0	1	2	3	4
50. Hot or cold spells	0	1	2	3	4
51. Having to avoid certain things, places or activities because they frighten you	0	1	2	3	4
52. Your mind going blank	0	1	2	3	4
53. Feeling creative	0	1	2	3	4
54. Numbness or tingling in parts of your body	0	1	2	3	4
55. Mid-week blues	0	1	2	3	4

APPENDIX L

IN THE PAST MONTH, WHEN NOT UNDER THE EFFECT OF DRUGS, HAVE YOU EVER EXPERIENCED:

	Not at all	A Little Bit	Moderately	Quite a bit	Extremely
56. The idea that you should be punished for your sins	0	1	2	3	4
57. Delayed orgasm (difficulty in achieving orgasm for females)	0	1	2	3	4
58. Feeling hopeless about the future	0	1	2	3	4
59. Trouble concentrating	0	1	2	3	4
60. Feeling close to others	0	1	2	3	4
61. Feeling weak in parts of your body	0	1	2	3	4
62. Feeling tense or keyed up	0	1	2	3	4
63. Enjoying dancing and/or music	0	1	2	3	4
64. Overeating	0	1	2	3	4
65. Feeling confident about the future	0	1	2	3	4
66. Having urges to beat, injure or harm someone	0	1	2	3	4
67. Having mood swings	0	1	2	3	4
68. Feeling good about your body	0	1	2	3	4
69. Having urges to break or smash things	0	1	2	3	4
70. Feeling very self conscious with others	0	1	2	3	4
71. Feeling liked by others	0	1	2	3	4
72. Physical problems with sex (impotence, genital pain)	0	1	2	3	4
73. Feeling uneasy in crowds	0	1	2	3	4

APPENDIX L

IN THE PAST MONTH, WHEN NOT UNDER THE EFFECT OF DRUGS, HAVE YOU EVER EXPERIENCED:

	Not at all	A Little Bit	Moderately	Quite a bit	Extremely
74. Feeling tranquil	0	1	2	3	4
75. Never feeling close to another person	0	1	2	3	4
76. Spells of terror or panic	0	1	2	3	4
77. Getting into frequent arguments	0	1	2	3	4
78. Having trust in other people	0	1	2	3	4
79. Feeling nervous when you are left alone	0	1	2	3	4
80. Others not giving you proper credit for your achievements	0	1	2	3	4
81. Feeling so restless you couldn't sit still	0	1	2	3	4
82. Feelings of worthlessness	0	1	2	3	4
83. Feeling its wonderful to be alive	0	1	2	3	4
84. Feeling that people will take advantage of you if you let them	0	1	2	3	4
85. Feeling full of energy	0	1	2	3	4
86. Feelings of guilt	0	1	2	3	4
87. The idea that something serious is wrong with your mind	0	1	2	3	4
88. Feeling relaxed	0	1	2	3	4
89. Forgetting to do something	0	1	2	3	4
90. Feeling easily distracted	0	1	2	3	4
91.Trouble making up your mind	0	1	2	3	4
92. Forgetting where you had left something	0	1	2	3	4
93. Feeling confused	0	1	2	3	4

APPENDIX L

Modified Brief Symptom Inventory Subscale Definitions

Somatisation

Distress arising from perceptions of bodily dysfunction e.g. faintness or dizziness, pains in heart or chest, hot or cold spells, feeling weak in parts of your body.

Obsessive-compulsive

Thoughts, impulses and actions that are experienced as unremitting and irresistible by the individual but ego-alien or unwanted in nature e.g. feeling blocked in getting things done, having to check and double check what you do, difficulty making decisions, your mind going blank.

Interpersonal sensitiveness

Focuses on feelings of personal inadequacy and inferiority, particularly in comparison to other individuals e.g. your feelings being easily hurt, feeling that people are unfriendly or dislike you, and feeling very self conscious with others.

Depression

Feelings of hopelessness and other cognitive somatic correlates of depression e.g. thoughts of ending your life, feeling lonely, having no interest in things, feeling worthlessness and hopeless about the future.

Anxiety

Behaviours usually associated with high manifest anxiety e.g. nervous or shakiness inside, suddenly scared for no reason, feeling tense or keyed up and spells of terror or panic.

Anger/hostility

Anger and hostile behaviour act under the 3 categories; thoughts, feelings and action. E.g. feeling easily annoyed or irritated, temper outbursts are uncontrollable, having urges to beat, injure or harm someone, and to break or smash things and getting into frequent arguments.

Phobic Anxiety

Consists of fears of a phobic nature orientated towards travel in open spaces, crowds or public places and conveyances represented by this dimension. E.g. feeling afraid of open spaces or on the street, feeling afraid to travel on buses, subways or trains, having to avoid certain things, places or activities because they frighten you, feeling uneasy in crowds and feeling nervous when left alone.

Paranoid ideation

Paranoid phenomena are most effectively conceived as thinking, primary characteristics of paranoid thought e.g. feeling others are to blame for most of your troubles, feeling that most people cannot be trusted and feeling that you are watched or talked about by others.

Psychoticism

APPENDIX L

Behaviours and thoughts which form broad spectrum psychotic behaviour including, the idea that someone else can control your thoughts, feeling lonely even when you are with people, the idea that you should be punished for your sins, the idea that something is wrong with your mind.

Negative psychophysiology

Include items such as poor appetite, trouble falling asleep and overeating.

MDMA side effects

Consists of subjective side effects repeatedly reported by ecstasy users e.g. feeling rash or impulsive, craving for chocolate, difficulties in planning things, mid-week blues, having mood swings.

Sexual functioning

Focuses on changes in sexual desire and performance e.g. decreased sexual desire, premature orgasm, delayed orgasm, and other physical problems with sex (impotence, genital problems).

Cognitive failures

Allows for subjective assessment of everyday cognitive performance e.g. forgetting to do something, feeling easily distracted, forgetting where something had been left.

Feeling content with life

Feeling interested in things
Feeling satisfied with my life
Feeling in good spirits
Feeling creative
Feeling confident about the future
Feeling it's wonderful to be alive

Mood State

Feelings associated with positive and elevated mood e.g. quick wittedness, attentiveness, feeling happy, tranquil and relaxed.

Sociability

Behaviour and feelings associated with the ability to socialise effectively with others e.g. feeling comfortable with others, having a good time with friends, having trust in other people, and feeling liked and being close to others.

Psychobiology

Includes positive psychobiological behaviours, thoughts and feelings e.g. sleeping well, having a good appetite, feeling healthy and proficient, feeling good about your body and feeling full of energy.

APPENDIX M

PUBLICATIONS

Journal Papers

Soar K, Parrott AC, Turner JJD, Fox HC, Milani RM. (2004). Psychobiological problems in a former heavy ecstasy (MDMA) polydrug user after seven years of abstinence: a case study. *Psychological Reports Perceptual and Motor Skills* 95:192-196

Soar K, Turner JJD, Parrott AC. (2001). Psychiatric Disorders in ecstasy (MDMA) users: a literature review focusing on personal predisposition and drug history. *Human Psychopharmacology Clinical and Experimental*, 16(8): 641-645.

Conference Poster Presentations

Soar K, Fox, HC, Turner JJD, Parrott AC. (2003). The relationship between problematic ecstasy use, dosage and the serotonin syndrome. *Journal of Psychopharmacology* 17(3): C18, A35.

Soar K, Parrott AC. (2002). Problematic ecstasy use: is it due to patterns of ecstasy use? *Journal of Psychopharmacology* 16(3): G4, A58.

Soar K, Parrott AC, Turner JJD. (2002). Prolonged cognitive and psychological problems from chronic-repeated ecstasy (MDMA) exposure: a case study. *Journal of Prevention, Treatment and Research of Addictions*, Supplement No. 1: 73-74

Soar K, Turner JJD, Parrott AC. (2001). A review of the psychiatric effects of ecstasy (MDMA), from research conducted in the last ten years. 5th Dutch Endo-Neuro Meeting, Doorweth. 5-7 June 2001. Abstract.

Soar K, Turner JJD, Parrott AC. (2001). A review of the psychiatric effects of ecstasy (MDMA), from research conducted in the last ten years. 24th Annual Meeting June 14-20, 2001. Abstract.

HUMAN PSYCHOPHARMACOLOGY
Hum Psychopharmacol Clin Exp 2001; **16**: 641–645.
DOI: 10.1002/hup.350

Psychiatric disorders in Ecstasy (MDMA) users: a literature review focusing on personal predisposition and drug history

K. Soar*, J. J. D. Turner and A. C. Parrott

Department of Psychology, University of East London, London, UK

3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) has been implicated in the onset of a number of psychological disorders and associated with a number of psychiatric symptoms that have persisted after cessation of the drug. This paper is a review of the published psychiatric case studies from the last 10 years involving MDMA. Only 24% of patients had a previous psychiatric history and 34% had a psychiatric illness amongst first degree relatives. The percentage of patients not having had a personal or family history of psychiatric illness and the temporal relationship between MDMA ingestion and the experience of recurring symptoms strongly suggest a causal relationship between the drug and neuropsychiatric manifestations. Further supporting evidence comes from several studies using non-clinical samples. Ecstasy users that don't present themselves in healthcare settings as having clinical symptoms have significantly higher scores on certain subscales of the SCL-90 compared with Ecstasy-naive controls, with higher pathology scores in heavier Ecstasy users. The full-blown psychiatric cases may represent the broad end of this problematic spectrum.

KEY WORDS — Ecstasy; psychopathology; problematic; recreational; polydrug

INTRODUCTION

3,4-methylenedioxymethampethamine (MDMA or Ecstasy) is a popular recreational drug, due to the easily controllable emotional state it gives. MDMA has been associated with a number of psychological disorders and psychiatric symptoms, which often persist after cessation of the drug; these include panic attacks (Whitaker-Azmitia and Aronson, 1989), depression (Cohen, 1996), flashbacks (Creighton *et al.*, 1991), psychosis (Vaiva *et al.*, 2001), paranoid ideation (McGuire and Fahy, 1991) and suicidal ideation (Benazzi and Mazzoli, 1991). The fact that MDMA is a prominent feature in many reported adverse psychiatric cases suggests that MDMA's pharmacological properties play a role in the development of such disorders. The question arises whether there is a causal link between Ecstasy use and the development of psychiatric disorders or whether MDMA exacerbates a predisposed neurological condition in individuals. This paper attempts to address this question by reviewing all published psychiatric cases from the last 10 years where MDMA has been the prominent feature and looking at further new evidence of clinical symptoms in a non-psychiatric population.

PSYCHIATRIC CASES

Numerous case studies where psychiatric symptoms have developed where MDMA use has been a prominent feature are summarised in Table 1. The adverse symptoms, which vary in nature and intensity, are most in behavioural domains that are putatively influenced by brain serotonin. Of these cases 29% involve psychotic symptoms, 26% anxiety and panic attacks, 26% delusions, hallucinations or visual illusions and a further 16% involve some form of depression. The varying persistency of the psychiatric disorders suggests that Ecstasy can cause long-term neurotoxicity, with symptoms evident long after Ecstasy use has been

* Correspondence to: K. Soar, Department of Psychology, University of East London, Romford Road, London E15 4LZ, UK. Tel: +44-20-82234556. Fax: +44-20-82234937.
E-mail: k.soar@uel.ac.uk

Accepted 3 October 2001

Table 1. Summary of 38 case studies from a clinical sample in the last 10 years where Ecstasy appears to have been a prominent feature

Reference	Symptom or disorder	Age, Sex	Psychiatric history	Psychiatric illness among first degree relatives	Duration of MDMA use
Teggin (1992)	Hysterical dissociative state followed by mild expressive aphasia	32, F	?	?	1 occasion
Cohen & Cocores (1997)	Perpetual neuropsychotic symptomatology	17, M	None	?	1 occasion
Cohen (1996)	Adverse symptomatology incl. persistent depressive episodes	22, F	None	?	6 years
McGuire and Fahy (1991)	Paranoid symptoms	28, M	Amphetamine psychosis	Schizophrenia	2–10 per night for 18 months
	Paranoid delusions	22, M	None	Unknown (adopted)	2 years
Cassidy and Ballard (1994)	Paranoid psychosis	21, M	None	None	1–2 per week for 6 months
Series *et al.* (1994)	Paranoid psychosis	24, M	None	None	2 in 1 month
Keenan *et al.* (1993)	Paranoid psychosis	17, M	None	None	1–2 per week for 5 months
Bone *et al.* (2000)	Paranoid psychosis	24, M	Bad manners & violent conduct	?	5 every weekend
Williams *et al.* (1993)	Psychosis	18, M	None	Psychotic depression & paranoid delusions	1/4 tablet on occasions
Creighton *et al.* (1991)	Psychosis	22, M	None	None	4–7 per week for 4 months
Vaiva *et al.* (2001)	Acute psychosis	26, M	Moderate anxiety disorder	?	1 tablet
Schifano (1991)	Chronic atypical psychosis	24, M	None	None	150 over 4 years
Milas (2000)	Acute psychosis with aggressive behaviour	26, ?	?	?	?
Spatt *et al.* (1997)	Psychotic episode with ongoing pure amnesic syndrome	20, F	None	None	1/2 tablet
Cassidy & Ballard (1994)	Hallucinogenic delusional disorder	17, M	None	None	2–3 per week for 4–6 months
McGuire *et al.* (1994)	Depersonalisation/hallucinations	19, M	Cannabis & LSD-induced hallucinations	Drug abuse	Less than 1 week
	Delusions/hallucinations	26, M	None	Alcohol abuse	2 years
	Delusions	24, M	Paranoid ideation	None	7 months
	Delusions	30, M	None	Personality disorder & drug abuse	13 months
	Delusions/illusions	21, M	Transient paranoid psychosis	Depression	1 year
	Delusions/hallucinations	20, M	Paranoid ideation	None	2 years
	Illusions/hallucinations	18, F	None	None	6 months
Creighton *et al.* (1991)	Flashbacks & anxiety symptoms	22, F	None	None	2 in 1 week
	Flashbacks & anxiety symptoms	17, M	None	None	
McGuire *et al.* (1994)	Delusions/panic attacks	32, M	Paranoid ideation	Depression	3 months
	Panic attacks/flashbacks	18, F	None	None	4 months
	Panic attacks/depersonalisation	22, F	None	Panic disorder	3 years
Pallanti & Mazzi (1992)	Panic disorder & agoraphobic avoidance	27, M	None	None	20 in 10 months
	Panic disorder & agoraphobic avoidance	21, M	None	None	3 in 6 months
	Panic disorder & agoraphobic avoidance	28, M	None	None	1 per 2 months for 2 years
McCann & Ricaurte (1992)	Panic disorder	23, M	None	None	?
Windhaber *et al.* (1998)	Panic disorder	23, M	None	None	?
Series *et al.* (1994)	Anxiety & depression	23, F	None	Depression	1–2 for 2 months
Teggin (1992)	Major depressive disorder	48, M	?	?	6 occasions
McGuire *et al.* (1994)	Depression	38, M	None	Depression & drug and alcohol abuse	1 year
Benazzi & Mazzoli (1991)	Depression with suicidal ideation	23, M	None	None	1 on 4 occasions
Cohen (1996)	Depression & suicide	17, M	?	?	1 tablet

discontinued (Cohen, 1996; McCann and Ricaurte, 1992; Schifano, 1991; Windhaber, *et al.*, 1998).

It is difficult to draw any conclusions comparing Ecstasy use amongst these individuals, due to lack of documentation, but the amounts recorded vary greatly from 0.25 tablets (Williams *et al.*, 1993) up to 10 tablets per night (McGuire and Fahy, 1991). The duration of usage also varies extensively, from just the one occasion (Cohen, 1996; Teggin, 1992; Cohen and Cocores 1997; Vaiva *et al.*, 2001; Spatt *et al.*, 1997) to 6 years (McGuire and Fahy, 1991). The majority of patients appear to be male (75%), yet this may reflect the general pattern of drug usage.

Attention should be drawn to the interpretative difficulties of these case studies. The anecdotal nature of case reports makes it difficult to determine the risk to the average recreational user. There is the suggestion that the basis of the disorder already existed before Ecstasy use occurred, since poor premorbid adjustment is associated with increased drug use. The mean age of the sample (24 years) is in the age range when the first episode of psychiatric illness is likely to occur. It could also be possible that a genetic predisposition for a neuropsychiatric illness may exist in these individuals or that a personal history of psychiatric problems increases their likelihood of the development of Ecstasy-induced disorders. A review of 13 case reports by McGuire *et al.* (1994) reported that a psychiatric illness had occurred among first-degree relatives of approximately 50% of patients. However, the current review found that only 24% of patients had a previously diagnosed psychiatric illness and that only 34% had a family psychiatric history.

Additional evidence suggesting a relationship between Ecstasy use per se and psychiatric problems are the studies by Series *et al.* (1994), McGuire *et al.* (1994) and Milas (2000). They present cases where a reoccurrence of symptoms occurred after further Ecstasy use. In addition, Creighton *et al.* (1991) reported a patient who was free of psychiatric symptoms for 8 months, but after taking a further 4 doses of Ecstasy the psychological symptoms returned. The individual reported by Cassidy and Ballard (1994) stated that there was a close relationship between symptom improvement and Ecstasy cessation. Additional support comes from a large-scale clinical survey (Schifano *et al.*, 1998), where the longer-term polydrug users, who had consumed an average of 43 Ecstasy tablets, were found to be at a considerably higher risk of developing a psychopathological disorder than the patients who took smaller amounts (average = 3). Most importantly, these patients specifically denied the presence of these psychiatric disturbances prior to MDMA use. The high percentage of patients who do not have a personal and family history of mental illness and the temporal relationship between MDMA ingestion and the experience of recurring symptoms after additional Ecstasy consumption strongly suggest a cause and effect relation in most of the reported cases.

NON-PSYCHIATRIC CASES

Ecstasy-related psychopathology has not only been shown in a clinical population. Recent research suggests that there may be other Ecstasy users who experience milder psychiatric disturbances but who do not contact health professionals. There is a growing body of evidence for this in studies of recreational users who don't present themselves to clinicians, general practitioners or drug services with clinical symptoms, yet who have significantly higher scores on a revised version of the SCL-90 (self-rating clinical symptom questionnaire) than Ecstasy-naive controls. The revised version of the SCL-90 includes 30 extra questions on various positive moods and life experiences, together with an 'Ecstasy side effects' factor.

Parrott *et al.* (2000b) surveyed a group of young people from a small town near Cork, Ireland. All volunteers completed a questionnaire on past drug use and the SCL-90. Heavy Ecstasy users reported significantly higher scores on several dimensions of the SCL-90 than the non-Ecstasy users. These included somatisation, obsessionality, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism and appetite. Similar results were found in a large-scale survey of 768 volunteers from Italy and the UK (Parrott *et al.*, 2000a). Using the UEL drug questionnaire, the researchers placed participants in one of six groups, depending on their past drug use: non-drug users; alcohol and tobacco users; cannabis, alcohol and tobacco users; illicit polydrug users, but not of Ecstasy; light Ecstasy polydrug users; and heavy Ecstasy (20 + tablets) polydrug users. All participants completed the modified version of the SCL-90. There were significant differences between non-drug users and Ecstacy polydrug users on the somatisation, obsessive-compulsive, anxiety, anger/hostility, phobic anxiety, psychoticism and MDMA side effect scales. The highest pathology scores were found in the heavy Ecstasy polydrug users and to a lesser extent in the light Ecstasy polydrug users.

It should be emphasised that in these studies polydrug use was a general characteristic of Ecstasy use. The heavier the Ecstasy use, the heavier the polydrug use. Symptom profiles were similar among the

polydrug users who hadn't taken Ecstasy, thus the high pathology scores for the heavy Ecstasy users could simply be a profile of polydrug use in general. Support for this comes from a study by Fox *et al.* (2001), which reported that psychological symptoms in such individuals were unrelated to Ecstasy use. This study examined the differences between 'self-reported problem' (psychological, emotional and somatic problems) and 'non-problem' Ecstasy users in relation to both consumption and premorbid life adjustment variables. The problem Ecstasy group had significantly higher scores on all scales of the SCL-90, yet their self-perceived problematic use was related not to their drug use but to negative interpersonal relationships prior to taking the drug and less socially orientated motivations for using the drug. However, this study used a relatively small sample of Ecstasy users. Milani *et al.* (2000) showed there was a significant positive correlation between the amount of Ecstasy pills consumed by polydrug users and their scores on the anxiety, phobic anxiety and psychoticism scales. Furthermore, in a study by Milani *et al.* (2001) of 234 Ecstasy polydrug users, 'problematic' users had higher pathology scores on several subscales of the SCL-90, compared with the 'non-problematic' users. But their perceived problems were related to the greater lifetime consumption of Ecstasy and the number of pills taken in a single occasion. This suggests that there may certainly be an association between Ecstasy use and psychopathological symptoms. What needs to be addressed is whether the SCL-90 scores of these individuals lie within the clinical range.

Caution should be taken when interpreting the results of these studies, because a number of methodological issues need to be addressed. These include inadequate sampling techniques through self-referral. The different sample sizes of the studies also leads to inconsistencies, with small sample sizes having lesser statistical power, which is the case in most MDMA-related research. Data were reliant on subjective reports in both the drug use and SCL-90 responses, which may contain inaccuracies. There is also the uncertainty of the pharmacological constituents of the Ecstasy tablets: numerous reports suggest varying levels of MDMA or related compounds in Ecstasy tablets, with some tablets containing other active ingredients (caffeine, amphetamine) and some containing none at all (Curran, 2000). Chemical analysis of street Ecstasy has shown that tablets are unlikely to be pure MDMA. Baggott *et al.* (2000) identified the most common drug other than MDMA in street-bought Ecstasy tablets as the antitussive dextromethorpan (DXM), which in high doses can cause serious adverse reactions, including phencyclidine-like psychosis (Dodds and Reval, 1967). Finally, as already mentioned, it is difficult to determine which, if any, of the previously used drugs are responsible for the manifestation of the symptoms, since Ecstasy users are almost always polydrug users.

Despite the discrepancies in the research non-clinical populations, there is still evidence that MDMA use is significantly related to psychiatric symptoms. Many of the reported symptoms are parallel to the disorders presented in the case studies. It may be that in the individual clinical cases the patients' symptoms developed to such an extent that they sought professional help, and thus they are at the broad end of the problematic spectrum.

CONCLUSION

Given that the total number of people in Britain who have tried Ecstasy is approximately 5 million, if Ecstasy were directly responsible for causing psychiatric symptoms a greater number of reported psychiatric cases would be expected. With adverse individual cases it is more likely that the individual has a pre-existing vulnerability to psychiatric disturbances or low serotonin levels prior to Ecstasy consumption. However, this review shows that there is some evidence that MDMA may cause psychopathology in recreational users. This evidence comes from the reports of psychiatric disorders among individuals who have consumed large quantities of Ecstasy (McGuire and Fahy, 1991; Creighton *et al.*, 1991) and from reports of psychological symptoms in Ecstasy users that have not manifested to such a degree that they seek professional help.

The suggestion that the intensity of dosing of Ecstasy is crucial in the development of psychopathology has also been made. Individuals who have taken a larger number of MDMA tablets have a higher risk of developing psychiatric disorders (Milani *et al.*, 2000; Schifano *et al.*, 1998) and are more likely to report having been inpatients (Hammersley *et al.*, 1999).

Attention should be drawn to the fact that more often than not recreational Ecstasy users take other drugs, such as cannabis, psychostimulants and hallucinogens. Polydrug use itself may lead to different types of psychobiological problems. Milani *et al.* (2000) found a correlation between other drug use and pathology scores, and Parrott *et al.* (2000a) showed that heavy Ecstasy polydrug users have the highest pathology scores. Because of these constraints it may be beneficial to assess the consequences of

Ecstasy use within the wider context of recreational drug use as a whole.

Ideally a prospective study should be done that combines detailed psychiatric and psychological assessments with functional neuroimaging techniques, to clarify the relationship between the intensity of Ecstasy dosing and the resulting psychological effects. However, the illegality of Ecstasy use and ethical constraints mean that such a study is unlikely.

REFERENCES

Baggott M, Heifets B, Jones RT, Mendelson J, Sferios E, Zehnder J. 2000. Chemical analysis of ecstasy pills. *JAMA* **284**: 2190.

Benazzi F, Mazzoli M. 1991. Psychiatric illness associated with 'Ecstasy'. *Lancet* **338**: 1520.

Bone PI, Ramos GP, Villalba YP, Valle FJ. 2000. Persisting and late onset psychotic disorder due to consumption of ecstasy (MDMA). *Nota Clinica* **25**: 61–65.

Cassidy G, Ballard CG. 1994. Psychiatric sequelae of MDMA (ecstasy) and related drugs. *Ir J Psychol Med* **11**: 132–133.

Cohen RS. 1996. Adverse symptomatology and suicide associated with the use of methylenedioxymethamphetamine (MDMA; 'ecstasy'). *Biol Psychiatry* **39**: 816–818.

Cohen RS, Cocores J. 1997. Neuropsychiatric manifestations following use of 3,4-methylenedioxymethampehetamine (MDMA; ecstasy). *Prog Neuropsychopharmacol Biol Psychiatry* **21**: 727–734.

Creighton FJ, Black DL, Hyde CE. 1991. 'Ecstasy' psychosis and flashbacks. *Br J Psychiatry* **159**: 713–715.

Curran HV. 2000. Is MDMA (ecstasy) neurotoxic in humans? An overview of evidence and of methodological problems in research. *Neuropsychobiology* **42**: 34–41.

Dodds A, Reval E. 1967. Toxic psychosis due to dextromethorphan. *Med J Aust* **2**: 231.

Fox HC, Milani MR, Parrott AC, Turner JJD. 2001. Differences in premorbid adjustment between problematic and non-problematic ecstasy users. Annual meeting of the Canadian College of Neuropscyhopharmacol (CCNP) **52** [abstract].

Hammersley R, Ditton J, Smith I, Short E. 1999. Patterns of ecstasy use by drug users. *Br J Criminology* **39**: 625–647.

Keenan E, Gervin M, Dorman A, O'Connor JJ. 1993. Psychosis and recreational use of MDMA (ecstasy). *Ir J Psychol Med* **10**: 162–163.

McCann UD, Ricaurte GA. 1992. MDMA (ecstasy) and panic disorder: induction by a single dose. *Biol Psychiatry* **32**: 950–953.

McGuire P, Fahy T. 1991. Chronic paranoid psychosis after misuse of MDMA (ecstasy). *BMJ* **203**: 697.

McGuire PK, Cope H, Fahy TA. 1994. Diversity of psyhopathology associated with use of 3,4-methylenedioxymethamphetamine (ecstasy). *Br J Psychiatry* **165**: 391–395.

Milani R, Turner JJD, Parrott AC, Parmar R. 2000. Recreational drug use and psychobiological problems. Collaborative UK/Italy study (5): ecstasy (MDMA) polydrug user findings. *J Psychopharmacol* **14**: PA22 [abstract].

Milani RM, Parrott AC, Turner JJD. 2001. Self reported 'problematic' and non-problematic' ecstasy/MDMA users in relative to a psychiatric symptom profile and patterns of drug use. 5th Endo-Neuro Meeting **86**: 156 [abstract].

Milas M. 2000. Acute psychosis with aggressive behaviour as a consequence of MDMA (ecstasy) consumption. *Lijec Vjesn* **122**: 27–30.

Pallanti S, Mazzi D. 1992. MDMA (ecstasy) precipitation of panic disorder. *Biol Psychiatry* **32**: 91–95.

Parrott AC, Milani R, Parmar R, Turner JJD. 2000a. Recreational drug use and psychobiological problems. Collaborative UK/Italy study (1): overview and main findings. *J Psychopharmacol* **14**: PA18 [abstract].

Parrott AC, Sisk E, Turner JJD. 2000b. Psychobiological problems in heavy 'ecstasy' (MDMA) polydrug users. *Drug Alcohol Depend* **60**: 105–110.

Schifano F. 1991. Chronic atypical psychosis associated with MDMA (ecstasy) abuse. *Lancet* **338**: 1335.

Schifano F, 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**: 85–90.

Series H, Boeles S, Dorkins E, Peveler R. 1994. Psychiatric complications of 'ecstasy' use. *J Psychopharmacol* **8**: 60–61.

Spatt J, Glawar B, Mamoli B. 1997. A pure amnesic syndrome after MDMA (ecstasy) ingestion. *J Neurol Neurosurg Psychiatry* **62**: 418–428.

Teggin AF. 1992. Ecstasy–a dangerous drug. *S Afr Med J* **81**: 431–432.

Vaiva G, Boss V, Bailly D, Thomas P, Lestavel P, Goudemand M. 2001. An 'accidental' acute psychosis with ecstasy use. *J Psychoactive Drugs* **33**: 95–96.

Whitaker-Azmitia PM, Aronson TA. 1989. 'ecstasy' (MDMA)-induced panic. *Am J Psychiatry* **146**: 119.

Williams H, Meagher D, Galligan P. 1993. MDMA (ecstasy); a case of possible drug-induced psychosis. *Ir J Med Sci* **162**: 43–44.

Windhaber J, Maierhofer D, Dantendorfer K. 1998. Panic disorder induced by large dose of 3,4-methylenedioxymethamphetamine resolved by paroxetine. *J Clin Psychopharmacol* **18**: 95–96.

PERSISTENT NEUROPSYCHOLOGICAL PROBLEMS AFTER 7 YEARS OF ABSTINENCE FROM RECREATIONAL ECSTASY (MDMA): A CASE STUDY

K. SOAR
School of Psychology
University of East London

A. C. PARROTT
Department of Psychology
University of Wales Swansea

H. C. FOX
Psychiatry Department
Yale University

Psychological Reports, 2004, 95, 192-196.

PERSISTENT NEUROPSYCHOLOGICAL PROBLEMS AFTER 7 YEARS OF ABSTINENCE FROM RECREATIONAL ECSTASY (MDMA): A CASE STUDY[1]

K. SOAR
School of Psychology
University of East London

A. C. PARROTT
Department of Psychology
University of Wales Swansea

H. C. FOX
Psychiatry Department
Yale University

Summary.—This case study concerns a 26-yr.-old male who had consumed large amounts of Ecstasy seven years previously. He stated that his increasingly intensive use of ecstasy over a 4-yr. period had led to the emergence of multiple psychiatric and psychological problems. Given these problems, he stopped using Ecstasy, but the problems had not resolved despite seven years of abstinence. The neurocognitive profile was very similar to that shown by current heavy Ecstasy users, with deficits in immediate and delayed verbal recall, moderately impaired memory function, but normal expressive language ability and perceptual functioning. Extremely high pathology was evident, including depression and phobic anxiety. Severe problems with sleep and sex were also reported. Further studies involving larger groups of abstinent former users are needed; adverse sequelae associated with intensive Ecstasy use may sometimes be enduring.

The recreational use of Ecstasy (MDMA, 3,4-Methylenedioxymethamphetamine) is associated with a range of psychobiological deficits, including phobic anxiety, impulsivity, depression, psychosis, hostility/aggression, and disorders of sleep (Morgan, 1998; Schifano, De Furia, Forza, Minicuci, & Bricolc, 1998; McGuire, 2000; Parrott, Sisk, & Turner, 2000; Parrott, Milani, Parmar, & Turner, 2001; Soar, Turner, & Parrott, 2001). In neurocognitive terms, deficits in working memory (Wareing, Fisk, & Murphy, 2000; Verkes, Gilsman, Pieters, Schoemaker, Visser, Kuilpers, Pennings, Bruin, Wijngaart, Van Gerven, & Cohen, 2001), episodic memory (Morgan, 1999; Rodgers, 2000), prospective memory (Heffernan, Jarvis, Rodgers, Scholey, & Ling, 2001), and higher executive functioning (Fox, Parrott, & Turner, 2001b; Morgan, McFie, Fleetwood, & Robinson, 2002), have all been reported.

Despite the empirical evidence for neuropsychological problems in recreational users, there has been very little research into whether these deficits remain after abstinence from Ecstasy. Tentative evidence for the persistence of deficits on some aspects of central executive functioning and measures of anxiety has been shown by Wareing, *et al.* (2000). Morgan, *et al.* (2002) found that selective cognitive impairments remained after an average of two

[1]Address correspondence to Kirstie Soar, Department of Psychology, University of East London, Romford Road, London E15 4LZ, UK or e-mail (k.soar@uel.ac.uk).

years of abstinence. Evidence for the persistence of depression after an average of 6 mo. of abstinence has also been shown (MacInnes, Handley, & Harding, 2001). However, we are not aware of any published studies involving a longer period of cessation.

Case Study

This paper describes an individual case study (RW) who contacted the Recreational Drugs Research Group at the University of East London. He described himself as having severe psychobiological problems, which he attributed to past Ecstasy use. RW was a 26-yr.-old Caucasian male, who stated that he had no history of a closed head injury or psychiatric illness prior to his Ecstasy use, although there was a history of anxiety and depression amongst first-degree relatives. Between 1991 and 1994, RW reported that he had taken around 750 Ecstasy tablets. Initially he took 1–2 tablets on each occasion, but this increased to an average of 10 per night, whilst on some evenings he would take 25 tablets, stating "*. . . they were like sweeties* (candy), *I just kept popping them in my mouth one after the other. . . .*" He stated that he felt he needed to take Ecstasy and reported being dependent (Jansen, 1999) and addicted to the drug despite not suffering if he went some time without taking it. During this 3-yr. period he also reported taking amphetamine (10 occasions), cocaine (25), crack cocaine (6), d-lysergic acid diethylamide (35), solvents (20), nitrates/poppers (20) and cannabis on a daily basis and for a year after the onset of these psychological symptoms.

Over the three years of increasingly intensive Ecstasy use he developed escalating problems including depression, suicidal thoughts, visual illusions, panic attacks, social phobia, sexual impotence, and severe sleeping problems, which he directly attributed to Ecstasy. Their increasing severity led him to cease taking Ecstasy but with no alleviation of these symptoms. He therefore approached his local physician, sought advice from a drug clinic, and was assessed by a clinical psychologist and a psychiatrist. He was diagnosed with a constellation of psychiatric disorders including anxiety, depression, phobia disorder, and panic attacks, which were related to his drug dependency. Various medications were tried, including fluoxetine, tripfluoperazine (still a current daily medication of 15 mg) and diazepam (used intermittently); these latter drugs partially relieved some symptoms, although mostly they have remained. Currently, he consumed 18 units[2] of alcohol per week and smoked on average 30 cigarettes a day.

Findings

RW exhibited elevated psychopathological scores on all dimensions of

[2]A unit of alcohol is 8 grams by weight or 1cl/10 ml by volume, of pure alcohol.

the Brief Symptom Inventory compared to normal controls, psychiatric inpatients, and psychiatric outpatients (Derogatis & Melisaratos, 1983). RW's psychopathology is consistent with his self-reported depression, suicidal thoughts, panic attacks, social phobia, sexual impotence, and sleeping problems (and also apparently with his previous psychiatric reports; however, we have no record of these). These high scores were also consistent with previous empirical research findings of elevated psychiatric symptoms on the SCL-90, an outpatient psychiatric symptom checklist (Parrott, *et al.*, 2000, 2001; Dughiero, Schifano, & Forza, 2001; Morgan, *et al.*, 2002).

Cognitively, RW demonstrated poor immediate recall on the Auditory Verbal Learning Task compared to normative data (Rey, 1964) and impairments on the Rivermead Behavioural Memory Test on which his total memory score (16) indicated moderately impaired memory function, specifically, poor face recognition and borderline performances on immediate article recall and message delivery (Wilson, Cockburn, Baddeley, & Hiorns, 1991). Executive functioning was also assessed using a manual version of the Tower of London (Shallice, 1982). The Tower of London planning and solution times were compared with data from an earlier study, which used an identical testing procedure. RW exhibited longer planning and solution times for all 12 trials, compared to non-Ecstasy controls, a profile of deficits similar to those displayed by current heavy Ecstasy users (Fox, *et al.*, 2001b).

Discussion

The neurocognitive profile, in this case, mirrors the pattern of selective impairments exhibited by current Ecstasy-polydrug users, where significant deficits in immediate and delayed verbal recall and executive functioning are often demonstrated (Fox, Parrott, & Turner, 2001a; Fox, *et al.*, 2001b; Parrott, 2001; Morgan, *et al.*, 2002). Furthermore, RW's neuropsychological profile is very similar to that of a group of former Ecstasy users who had been abstinent on average two years but still exhibited significantly impaired recall on the Rivermead Behavioural Memory test and committed significantly more errors in executive functioning, compared to polydrug-using controls (Morgan, *et al.*, 2002). The elevated psychopatholgy demonstrated by RW was also consistent with raised psychiatric profiles demonstrated by current Ecstasy-polydrug users (Parrott, *et al.*, 2001) and the heightened depression scores of former Ecstasy users (MacInnes, *et al.*, 2001). These similar patterns of neurocognitive deficits and psychobiological problems lend support to the notion that RW's problems are a reflection of intensive past Ecstasy use. Three similar case studies of severe psychobiological problems in very intensive Ecstasy users have been described by Jansen (1999).

Causality between RW's past Ecstasy use and his current neuropsychological status cannot be directly determined, given the design limitation of

this case study. There is reliance on self-reported data. Also, there are no objective measures of neuropsychological status, either prior to, during or directly after the crucial period of intensive Ecstasy usage. RW may also have had some premorbid neuropsychological deficits or personality dispositions which led him to heavy drug use, or there was some form of comorbidity. Self-reported drug history is also unverifiable, both in quantity consumed and the length of abstinence from drugs, if at all. There is also the potentially confounding factor of other psychoactive drug use, both of illicit recreational drugs and of psychotherapeutic medications. These may have contributed to the neurocognitive and psychiatric symptom profiles (Parrott, *et al.*, 2001; Curran, 2002; Morgan, *et al.*, 2002).

In light of preliminary observations made in this case study, we argue the need for studies where better methodological control could be obtained. Larger groups of former users would allow the influence of other psychoactive drug use to be statistically assessed. Prospective studies should also be undertaken among drug users, when Ecstasy and other drug use could be recorded using detailed drug diaries and verified using hair analysis, along with objective psychiatric and personality assessment. Such studies could answer not only questions about psychoactive drug effects, but also the longevity of neuropsychological effects, independent of premorbid psychiatric or personality dispositions.

Important topics for research are the intensity of Ecstasy use and the patterns of neurocognitive recovery of time. These factors may all be related. Thus, light or intermittent Ecstasy use may lead to minimal drug-related problems (Fox, *et al.*, 2001b; Parrott, 2001), whereas intensive Ecstasy usage may lead to the most severe problems while on the drug (Jansen, 1999), followed by minimal recovery afterwards—as illustrated by this case study.

REFERENCES

Curran, V. H. (2002) Psychopharmacological perspectives on memory. In E. Tulving & F. I. M. Craik (Eds.), *The Oxford handbook of memory*. Oxford, UK: Oxford Univer. Press. Pp. 539-544.

Derogatis, L. R., & Melisaratos, N. (1983) The Brief Symptom Inventory: an introductory report. *Psychological Medicine*, 13, 595-605.

Dughiero, G., Scheeano, E. & Forza, G. (2001) Personality dimensions and psychopathological profiles of Ecstasy users. *Human Psychopharmacology*, 16, 635-639.

Fox, H. C., Parrott, A. C., & Turner, J. J. D. (2001a) Auditory verbal learning in drug-free Ecstasy polydrug users. *Human Psychopharmacology*, 16, 613-618.

Fox, H. C., Parrott, A. C., & Turner, J. J. D. (2001b) Ecstasy use: cognitive deficits related to dosage rather than self-reported problematic use of the drug. *Journal of Psychopharmacology*, 15, 273-281.

Heffernan, T. M., Jarvis, H., Rodgers, J., Scholey, A. B., & Ling, J. (2001) Prospective memory, everyday cognitive failure and central executive function in recreational use of Ecstasy. *Human Psychopharmacology*, 16, 607-612.

Jansen, K. L. R. (1999) Ecstasy (MDMA) dependence. *Drug and Alcohol Dependence*, 53, 121-124.

MacInnes, N., Handley, S. L., & Harding, G. F. A. (2001) Former chronic methylene-

dioxymethamphetamine (MDMA or Ecstasy) users report mild depressive symptoms. *Journal of Psychopharmacology*, 15, 181-187.

McGuire, P. (2000) Long-term psychiatric and cognitive effects of MDMA use. *Toxicology Letters*, 112-113, 153-156.

Morgan, M. (1998) Recreational use of 'Ecstasy' (MDMA) is associated with elevated impulsivity. *Neuropsychopharmacology*, 19, 252-264.

Morgan, M. (1999) Memory deficits associated with recreational use of 'Ecstasy' (MDMA). *Psychopharmacology (Berlin)*, 141, 30-36.

Morgan, M. J., McFie, L., Fleetwood, L. H., & Robinson, J. A. (2002) Ecstasy (MDMA): are the psychological problems associated with its use reversed by prolonged abstinence? *Psychopharmacology*, 159, 294-303.

Parrott, A. C. (2001) Human psychopharmacology of Ecstasy (MDMA): a review of 15 years of empirical research. *Human Psychopharmacology*, 16, 557-577.

Parrott, A. C., Milani, R. M., Parmar, R., & Turner, J. J. D. (2001) Recreational Ecstasy/MDMA and other drug users from the UK and Italy: psychiatric symptoms and psychobiological problems. *Psychopharmacology*, 159, 77-82.

Parrott, A. C., Sisk, E., & Turner, J. J. D. (2000) Psychobiological problems in heavy 'Ecstasy' (MDMA) polydrug users. *Drug and Alcohol Dependence*, 60, 105-110.

Rey, A. (1964) *L'examen clinique en psychologie*. Paris: Presses Universitaires de France.

Rodgers, J. (2000) Cognitive performance amongst recreational users of 'Ecstasy'. *Psychopharmacology*, 151, 19-24.

Schifano, F., Di Furia, L., Forza, G., Minicuci, N., & Bricolo, R. (1998) MDMA ('Ecstasy') consumption in the context of polydrug abuse: a report of 150 patients. *Drug and Alcohol Dependence*, 52, 85-90.

Shallice, T. (1982) Specific impairments in planning. *Philosophical Transactions: Biological Sciences*, 298, 199-209.

Soar, K., Turner, J. J. D., & Parrott, A. C. (2001) Psychiatric disorders in Ecstasy (MDMA) users: a literature review focusing on personal predisposition and drug history. *Human Psychopharmacology*, 16, 641-645.

Verkes, R. J., Gilsman, H. J., Pieters, M. S. M., Schoemaker, R. C., Visser, S. D., Kuilpers, M., Pennings, E. J. M., Bruin, D. D., Wijngaart, G. V., Van Gerven, J. M. A., & Cohen, A. F. (2001) Cognitive performance and serotonergic function in users of Ecstasy. *Psychopharmacology*, 153, 196-202.

Wareing, M., Fisk, J. E., & Murphy, P. N. (2000) Working memory deficits in current and previous users of MDMA ('Ecstasy'). *British Journal of Psychology*, 91, 181-188.

Wilson, B., Cockburn, J., Baddeley, A., & Hiorns, R. (1991) *The Rivermead Behavioural Memory Test*. (2nd ed.) Bury St. Edmunds, UK: Thames Valley Trust Co.

Accepted June 17, 2004

UEL ECSTASY RESEARCH
participants required

Psychological research into long-term effects.

- have you suffered problems from ecstasy use, or
- previously used but have stopped for over a year

Please contact Kirstie at k.soar@uel.ac.uk or

0208 2234556

Confidentiality is ensured.

UEL ECSTASY RESEARCH
participants required

Psychological research into long-term effects.

- have you suffered problems from ecstasy use, or
- previously used but have stopped for over a year

Please contact Kirstie at k.soar@uel.ac.uk or

0208 2234556

Confidentiality is ensured.

University of East London

University of East London

Contribute to ECSTASY and POLYDRUG RESEARCH

http://homepages.uel.ac.uk/K.Soar/ecstasy_qa.htm

or **contact Kirstie on 020 8223 4556**

University of East London

University of Sussex at Brighton

ECSTASY RESEARCH

HAVE YOU HAD PROBLEMS WITH ECSTASY USE?
OR HAVE YOU USED OVER 20 TIMES OUTSIDE THE LAST YEAR?
ARE YOU PREPARED TO TAKE PART IN AN ONGOING STUDY WITH UEL AND UNIVERSITY OF SUSSEX?

CALL KIRSTIE AT THE PSYCHOLOGY DEPARTMENT ON 020 8223 4556
OR EMAIL K.SOAR@UEL.AC.UK
SUCCESSFUL APPLICANTS WILL BE REIMBURSED FOR THEIR TIME.....

APPENDIX R

University of East London

Participate in Research

complete a psychological questionnaire

Contact: Kirstie Soar

GN107

k.soar@uel.ac.uk

x4082

APPENDIX S

UNIVERSITY OF EAST LONDON

APPLICATION FOR APPROVAL OF AN EXPERIMENTAL PROGRAMME INVOLVING HUMAN SUBJECTS

Please read the Notes for Guidance before completing this form. If necessary, please continue your answers on a separate sheet of paper: indicate clearly which question the continuation sheet relates to and ensure that it is securely fastened to the application form.

1. Title of the programme:

Long term psychological effects of recreational ecstasy/MDMA use

2. Name of person responsible for the programme: Prof. Andy Parrott

Status: Reader in Psychology

3. Faculty: Science & Health **Department/Unit:** Psychology

4. Level of the programme (delete as appropriate):

(a) undergraduate basic
(b) undergraduate project
(c) postgraduate
(d) post-doctoral or staff

5. Number of:

(a) experimenters (approximately): One

(b) subjects (approximately): Sixty

6. Nature of experimenters (delete as appropriate):

(a) staff **(b) students** **(c) others**

If "others" please give full details:

Post graduate Researcher

7. Nature of subjects (general characteristics, e.g. University students, primary school children, etc):

Young people aged 18+ years.

8. Probable duration of the programme: 1 year

from (starting date): April 2001 **to (finishing date):** April 2002

APPENDIX S

9. Aims of the programme including any hypothesis to be tested:

The study attempts to assess the psychobiological functioning of recreational ecstasy users who complain of problems, which that attribute to ecstasy use. There have been numerous reports of individuals that have developed chronic problems after the consumption of ecstasy. However, these papers only look at individual cases and don't assess the subjects psychiatric history, drug use history and cognitive abilities compared to heavy MDMA users who don't complain of problems. This study aims to assess these factors and try's to establish why certain individuals develop these problems whilst other heavy MDMA users seem to be void of them. Deficits on selective memory and executive functioning tests have been shown in MDMA users. Similar tests will be used to assess whether those that report problems have greater deficits in these tasks compared to heavy users with no reported problems. This may help to establish whether potential deficits occur as a function of problematic ecstasy use. Psychiatric histories and SCL-90 scores will also be compared to assess whether there are certain vulnerability factors in developing problems from ecstasy use or whether there a just certain individuals that seek help rather than others who are presented with problems but just 'suffer in silence'.

10. Description of the procedures to be used (give sufficient detail for the Committee to be clear about what is involved in the programme). Please append to the application form copies of any instructional leaflets, letters, questionnaires, forms or other documents which will be issued to the subjects:

All participants will be tested individually in a room within the psychology department in the Science and Health faculty or in a counselling room at local drug advice centres. Prior to the investigation, all participants will be informed of the aims and ethical considerations of the research and requested to sign a consent form (see appendix 1). The participant will then be seated at a table in order to fill out a personal history questionnaire and a drug portfolio questionnaire (see appendix 2); the NART will then be administered as a general measure of intellectual ability and to ensure participants have an adequate knowledge of English. All responses will be taped. The participant will then be administered the SCL-90 followed by number of cognitive tasks to complete:

Adult Verbal Learning Test (AVLT): which involves several lists of words being read aloud in order for each participant to recall them both immediately and following a period of delay. Again all response will be recorded.

Rivermead Behavioural Memory Test Battery: a highly standardised neurological assessment battery that involves a series of short sub-tests used to measure participants` everyday memory. Comprises of paper and pencil tasks.

Tower of London Test (TOL): This task assesses participants planning ability. Participants are requested to move a number of coloured balls from a start position to a goal position in a *minimal* number of moves.

Reaction Time test (RT): A measure of participants processing speed.

Following the completion of these tasks, participants will be asked to expand on three or four answers given in the drug history questionnaire. All responses will be recorded. On completion, participants will be debriefed and time is given for participants to answer any questions.

APPENDIX S

11. **Are there potential hazards to the subject(s) in these procedures?** **YES/*NO***

If yes: (a) what is the nature of the hazard(s)?

(b) what precautions will be taken?

12. **Is medical care or after care necessary?** **YES/*NO***

If yes, what provision has been made for this?

13. **May these procedures cause discomfort or distress?** **YES/*NO***

If yes, give details including likely duration:

14. **(a)** **Will there be administration of drugs (including alcohol)?** **YES/*NO***

If yes, give details:

(b) **Where the procedures involve potential hazards and/or discomfort or distress, please state what previous experience you have had in conducting this type of research:**

15. **(a)** **How will the subjects' consent be obtained?**

Prior to the investigation, the aims and objectives of the study will be explained verbally and in writing. An assigned consent form will then be required before procedures are to continue.

(b) **What will the subjects be told as to the nature of the experiment?**

The nature of the investigation will be fully described, prior to administration.

APPENDIX S

16. (a) Will the subjects be paid? *YES*/NO

(b) If yes, please give the amount: **£ 10.00**

(c) If yes, please give full details of the reason for the payment and how the amount given in 16 (a) above has been calculated (i.e. what expenses and time lost is it intended to cover):

Payment is given to reimburse participants for their time and to cover any travel expenses.

17. Are the services of the University Health Service likely to be required during or after the programme? YES/*NO*

If yes, give details:

18. (a) Where will the experiments take place?

In a counselling room/psychology laboratory at the Science and Health faculty, The Green

(b) What equipment (if any) will be used?

A laptop computer containing the Reaction time test, a stopwatch and a small tape recorder.

(c) If equipment is being used is there any risk of accident or injury? If so, what precautions are being taken to ensure that should any untoward event happen adequate aid can be given

N/A

APPENDIX S

19. Are personal data to be obtained from any of the subjects? *YES*/NO

If yes, (a) give details:

Detailed personal history and portfolio of drug use will be obtained. This will include family history of psychiatric conditions; subjective reports of any drug induced problems participants feel they have encountered and when these occurred. It will also include details of types of drugs taken, quantity of drugs taken and patterns of usage.

(b) state what steps will be taken to protect the confidentiality of the data?

Participants will be allotted a drug sub-code, which will be placed on any paper work containing sensitive data. Confidentiality will be ensured to participants and they will be informed that they are under no obligation to give their name. They are informed, that the signing of the consent form in no way defines them as either a drug user or non-drug user and they are also informed that drug status will not be accessible.

(c) state what will happen to the data once the experimental programme has been completed and the results written-up. If the data is to be destroyed how will this be done? How will you ensure that the data will be disposed of in such a way that there is no risk of its confidentiality being compromised?

All detailed questionnaires and result data will be shredded. Tape recordings will be destroyed. Any other personal information will be kept on a computer system with restricted access; by the experimenter only.

20. Will any part of the experimental programme take place in premises outside the University or will any members of the experimental team be external to the University? *YES*/NO

If yes, please give full details of the extent to which the participating institution will indemnify the experimenters against the consequences of any untoward event:

21. Are there any other matters or details which you consider relevant to the consideration of this proposal? If so, please elaborate below:

APPENDIX S

22. DECLARATION

I undertake to abide by accepted ethical principles and appropriate code(s) of practice in carrying out this programme.

Personal data will be treated in the strictest confidence and not passed on to others without the written consent of the subject.

The nature of the investigation and any possible risks will be fully explained to intending subjects, and they will be informed that:

(a) they are in no way obliged to volunteer if there is any personal reason (which they are under no obligation to divulge) why they should not participate in the programme; and

(b) they may withdraw from the programme at any time, without disadvantage to themselves and without being obliged to give any reason.

NAME OF APPLICANT:
(Person responsible) **Signed:** _____

_____ **Date:** _____

NAME OF HEAD OF DEPARTMENT: **Signed:** _____

_____ **Date:** _____

UNIVERSITY OF EAST LONDON

MEMORANDUM

QUALITY ASSURANCE

From: Mrs Sue Green

Dept: Quality Assurance, Barking Campus

Email: BKSTAFF1/GREEN2

To: Professor A C Parrott

Dept: Psychology
The Green

Date: 16 February 2001 **Ref:** SLG/ETH/99/83/Soar

Subject: **University Ethics Committee: Approval of an experimental programme involving human subjects: Long term effects of recreational ecstasy/MDMA use**

---

cc:

I advise that Members of the University Ethics Committee have now approved the above application on the terms previously advised to you, so I now write to give formal confirmation of this approval.

Sue Green

Sue Green

full'app.mem

APPENDIX T

UNIVERSITY OF EAST LONDON

APPLICATION FOR APPROVAL OF AN EXPERIMENTAL PROGRAMME INVOLVING HUMAN SUBJECTS

Please read the Notes for Guidance before completing this form. If necessary, please continue your answers on a separate sheet of paper: indicate clearly which question the continuation sheet relates to and ensure that it is securely fastened to the application form.

1. Title of the programme:

Persistent Neuropsychological effects of 'ecstasy' (MDMA), in recreational users.

2. Name of person responsible for the programme: Prof. Andy Parrott

Status: Reader in Psychology

3. Faculty: Science & Health **Department/Unit:** Psychology

4. Level of the programme (delete as appropriate):

(a) undergraduate basic
(b) undergraduate project
(c) postgraduate
(d) post-doctoral or staff

5. Number of:

(a) experimenters (approximately): one

(b) subjects (approximately): 45

6. Nature of experimenters (delete as appropriate):

(a) staff **(b) students** **(c) *others***

If "others" please give full details:

Post graduate Researcher

7. Nature of subjects (general characteristics, e.g. University students, primary school children, etc):

Young people over the age of 18

8. Probable duration of the programme: 3 months

from (starting date): May 2001 **(finishing date):** Sept 2001

9. Aims of the programme including any hypothesis to be tested:

This study attempts to assess the persistent effects of MDMA neurotoxicity and its functional sequel in recreational ecstasy users and ex-users. It has been repeatedly shown in animals and now documented in human studies that MDMA is a highly selective serotonin neurotoxin. These neurodegenerative effects are long lasting, however recovery has been shown in brain areas of some animals. The functional consequence of serotonin neurotoxicity in humans is thought to be associated with subtle but significant cognitive deficits, as measured by neuropsychological tests and possible psychiatric symptoms. Deficits on selective memory and executive functioning tests have been shown in MDMA users along with significant scores on a clinical symptom self-reporting questionnaire. This study aims to test whether serotonin recovery occurs in humans as shown in animals, by assessing participant's abilities on certain neuropsychological tests. Selective memory tests and executive planning tests will be used to assess whether ex-users of ecstasy have a recovery in their ability to complete these tasks compared to current users. SCL-90 scores will also be recorded to assess whether ecstasy users exhibit psychiatric symptoms compared to ecstasy naïve subjects and whether these are persistent symptoms by comparing them with ex-users SCL-90 scores.

10. Description of the procedures to be used (give sufficient detail for the Committee to be clear about what is involved in the programme). Please append to the application form copies of any instructional leaflets, letters, questionnaires, forms or other documents which will be issued to the subjects:

The participant will be tested within the Psychology department in the Science and Health faculty. Prior to the investigation, the participants will be informed of the aims and ethical considerations of the study and requested to sign a consent form (see appendix 1). The participant will then be seated at a table in order to fill out a personal history questionnaire and drug portfolio questionnaire (appendix 2); the NART will then be administered as a general measure of intellectual ability. The participant will then be administered the SCL-90 followed by a number of cognitive tasks to complete:

Prospective memory tasks: taken from the Rivermead Behavioural Memory test. It involves the participant remembering a previously hidden belonging and also to remember to ask for an appointment on the cue of an alarm.

Immediate and delayed memory task: taken from the Rivermead Behavioural Memory Test, which involves a story being read aloud in order for the participant to recall it both immediately and following a period of delay.

Reaction Time test (RT): A measure of participants processing speed.

Tower of London Test (TOL): This task assesses the participants planning ability. The participant is requested to move a number of coloured balls from a start position to a goal position in a *minimal* number of moves.

All responses to the NART and cognitive tasks will be tape-recorded. All responses will be recorded. On completion, the participants will be debriefed and time is given for him/her to ask any questions.

11. **Are there potential hazards to the subject(s) in these procedures?** **YES/*NO***

If yes: (a) what is the nature of the hazard(s)?

(b) what precautions will be taken?

12. **Is medical care or after care necessary?** **YES/*NO***

If yes, what provision has been made for this?

13. **May these procedures cause discomfort or distress?** **YES/*NO***

If yes, give details including likely duration:

14. **(a)** **Will there be administration of drugs (including alcohol)?** **YES/*NO***

If yes, give details:

(b) **Where the procedures involve potential hazards and/or discomfort or distress, please state what previous experience you have had in conducting this type of research:**

15. **(a)** **How will the subjects' consent be obtained?**

Prior to the investigation, the aims and objectives of the study will be explained verbally and in writing. An assigned consent form will then be required before procedures are to continue.

(b) **What will the subjects be told as to the nature of the experiment?**

The nature of the investigation will be fully described, prior to administration.

16. (a) Will the subjects be paid? YES/*NO*

(b) If yes, please give the amount: £

(c) If yes, please give full details of the reason for the payment and how the amount given in 16 (a) above has been calculated (i.e. what expenses and time lost is it intended to cover):

17. Are the services of the University Health Service likely to be required during or after the programme? YES/*NO*

If yes, give details:

18. (a) Where will the experiments take place?

In a counselling room/psychology laboratory at the Science and Health faculty, The Green

(b) What equipment (if any) will be used?

A laptop computer containing the Reaction time test, a stopwatch and a small tape recorder.

(c) If equipment is being used is there any risk of accident or injury? If so, what precautions are being taken to ensure that should any untoward event happen adequate aid can be given

N/A

19. Are personal data to be obtained from any of the subjects? *YES*/NO

If yes, (a) give details:

Detailed personal history and portfolio of drug use will be obtained. This will include family history of psychiatric conditions; subjective reports of any drug induced problems participants feel they have encountered and when these occurred. It will also include details of types of drugs taken, quantity of drugs taken and patterns of usage.

(b) state what steps will be taken to protect the confidentiality of the data?

Confidentiality will be ensured and the participant will be informed that they are under no obligation to give their name. They are informed that the signing of the consent form in no way defines them as either a drug user or non-drug user.

(c) state what will happen to the data once the experimental programme has been completed and the results written-up. If the data is to be destroyed how will this be done? How will you ensure that the data will be disposed of in such a way that there is no risk of its confidentiality being compromised?

All detailed questionnaires and result data will be shredded. Tape recordings will be destroyed. Any other personal information will be kept on a computer system with restricted access; by the experimenter only.

20. Will any part of the experimental programme take place in premises outside the University or will any members of the experimental team be external to the University? *YES*/NO

If yes, please give full details of the extent to which the participating institution will indemnify the experimenters against the consequences of any untoward event:

21. Are there any other matters or details which you consider relevant to the consideration of this proposal? If so, please elaborate below:

22. DECLARATION

I undertake to abide by accepted ethical principles and appropriate code(s) of practice in carrying out this programme.

Personal data will be treated in the strictest confidence and not passed on to others without the written consent of the subject.

The nature of the investigation and any possible risks will be fully explained to intending subjects, and they will be informed that:

(a) they are in no way obliged to volunteer if there is any personal reason (which they are under no obligation to divulge) why they should not participate in the programme; and

(b) they may withdraw from the programme at any time, without disadvantage to themselves and without being obliged to give any reason.

NAME OF APPLICANT:
(Person responsible) **Signed:** _____

_____ **Date:** _____

NAME OF HEAD OF DEPARTMENT: **Signed:** _____

_____ **Date:** _____

UNIVERSITY OF EAST LONDON

MEMORANDUM

From: Ms Maryam J Kermani

Dept: Graduate School, Stratford

Email: maryam@uel.ac.uk

To: Ms Sue Meade

Dept: School of Psychology

Date: 02 November 2001 **Ref:** SLG/ETH/00/62/0

Subject: **University Ethics Committee: Approval of an experimental programme involving human subjects: Persistent Neuropsychological effects of recreational 'ecstasy' (MDMA), in recreational users. (K Soar) (Professor Andy Parrott)**

---

cc:

I advise that Members of the University Ethics Committee have now approved the above application on the terms previously advised to you, so I now write to give formal confirmation of this approval.

Mr Woodhouse would write again in approximately six months time to monitor progress of the project.

Maryam J Kertmani

Kermani

full'app.mem

APPENDIX U

UNIVERSITY OF EAST LONDON

APPLICATION FOR APPROVAL OF AN EXPERIMENTAL PROGRAMME INVOLVING HUMAN SUBJECTS

Please read the Notes for Guidance before completing this form. If necessary, please continue your answers on a separate sheet of paper: indicate clearly which question the continuation sheet relates to and ensure that it is securely fastened to the application form.

1. Title of the programme:

Personality characteristics of problem versus non-problem ecstasy (MDMA) users.

2. Name of person responsible for the programme: Prof. Andy Parrott

Status: Reader in Psychology

3. Faculty: Psychology **Department/Unit:** Psychology

4. Level of the programme (delete as appropriate):

(a) undergraduate basic
(b) undergraduate project
(c) *postgraduate*
(d) post-doctoral or staff

5. Number of:

(a) experimenters (approximately): One

(b) subjects (approximately): Two hundred

6. Nature of experimenters (delete as appropriate):

(a) staff **(b) students** **(c) others**

If "others" please give full details:

Post graduate Researcher

7. Nature of subjects (general characteristics, e.g. University students, primary school children, etc):

Young people aged 18+ years.

8. Probable duration of the programme: 4 months

from (starting date): July 2002 **to (finishing date):** Oct 2002

APPENDIX U

9. Aims of the programme including any hypothesis to be tested:

There are currently a number of empirical reports demonstrating higher psychological symptoms in ecstasy polydrug users compared to polydrug controls (non-ecstasy users) along with a large number of individual case studies highlighting the association of ecstasy use and behavioural and psychological disorders. Together this research strongly suggests that ecstasy use may contribute or cause psychological problems in the recreational user. However recent literature indicates that there are two distinct groups of ecstasy users, those that develop problems attributable to ecstasy use and those that don't despite similar patterns of ecstasy use and other drug consumption profiles. It is thought that premorbid personality dimensions may play an important role in ecstasy related problems, bearing this is mind, this study attempts to establish whether certain personality factors (in this case, locus of control) are important in determining whether ecstasy users have problems which they attribute to past ecstasy use. This will be achieved by assessing the problems reported by recreational drug users, in particular, which drug they attribute the problems to and whether those that report problems have a greater external locus of control compared to those individuals that don't reported any problems.

10. Description of the procedures to be used (give sufficient detail for the Committee to be clear about what is involved in the programme). Please append to the application form copies of any instructional leaflets, letters, questionnaires, forms or other documents which will be issued to the subjects:

Participants will be informed of the aims and ethical considerations of the research and requested to sign a consent form [see appendix 1], which is attached to the front of a series of questionnaires, which they are then asked to complete. These questionnaires include:

- A personal history questionnaire [appendix 2]
- A drug use questionnaire [appendix 3]
- The Locus of Control Scale (Rotter, 1966) [appendix 4]
- A modified version of the Brief symptom Inventory (BSI), which includes items on sexual dysfunction, positive mood, positive psychobiology and cognitive failures [appendix 5]

On completion of these questionnaires, participants are asked to either hand them back to the experimenter or where necessary post them to the experimenter in the stamped addressed envelope.

11. **Are there potential hazards to the subject(s) in these procedures?** **YES/*NO***

If yes: (a) what is the nature of the hazard(s)?

(b) what precautions will be taken?

12. **Is medical care or after care necessary?** **YES/*NO***

If yes, what provision has been made for this?

13. **May these procedures cause discomfort or distress?** **YES/*NO***

If yes, give details including likely duration:

14. **(a)** **Will there be administration of drugs (including alcohol)?** **YES/*NO***

If yes, give details:

(b) **Where the procedures involve potential hazards and/or discomfort or distress, please state what previous experience you have had in conducting this type of research:**

15. **(a)** **How will the subjects' consent be obtained?**

Prior to the investigation, the aims and objectives of the study will be explained in writing. An assigned consent form will then be required before completion of the questionnaires.

(b) **What will the subjects be told as to the nature of the experiment?**

The nature of the investigation will be fully described in writing, prior to the completion of the questionnaire

APPENDIX U

16. (a) Will the subjects be paid? YES/*NO*

(b) If yes, please give the amount:

(c) If yes, please give full details of the reason for the payment and how the amount given in 16 (a) above has been calculated (i.e. what expenses and time lost is it intended to cover):

17. Are the services of the University Health Service likely to be required during or after the programme? YES/*NO*

If yes, give details:

18. (a) Where will the experiments take place?

The programme is solely based on a series of questionnaires, which can be completed wherever the participant chooses.

(b) What equipment (if any) will be used?

(c) If equipment is being used is there any risk of accident or injury? If so, what precautions are being taken to ensure that should any untoward event happen adequate aid can be given

N/A

19. Are personal data to be obtained from any of the subjects? *YES*/NO

If yes, (a) give details:

Detailed personal history and portfolio of drug use will be obtained. This will include family history of psychiatric conditions; subjective reports of any drug induced problems participants feel they have encountered and when these occurred. It will also include details of types of drugs taken, quantity of drugs taken and patterns of usage. Subjects will also be asked to leave a contact e-mail or telephone if they wish to take part in any future studies of this nature.

(b) state what steps will be taken to protect the confidentiality of the data?

Participants will be allotted a drug sub-code, which will be placed on any paper work containing sensitive data. Confidentiality will be ensured to participants and they will be informed that they are under no obligation to give their name. They are informed that the signing of the consent form in no way defines them as either a drug user or non-drug user.

(c) state what will happen to the data once the experimental programme has been completed and the results written-up. If the data is to be destroyed how will this be done? How will you ensure that the data will be disposed of in such a way that there is no risk of its confidentiality being compromised?

All detailed questionnaires and result data will be shredded. Any other personal information will be kept on a computer system with restricted access; by the experimenter only.

20. Will any part of the experimental programme take place in premises outside the University or will any members of the experimental team be external to the University? YES/*NO*

If yes, please give full details of the extent to which the participating institution will indemnify the experimenters against the consequences of any untoward event:

21. Are there any other matters or details which you consider relevant to the consideration of this proposal? If so, please elaborate below:

APPENDIX U

22. **DECLARATION**

I undertake to abide by accepted ethical principles and appropriate code(s) of practice in carrying out this programme.

Personal data will be treated in the strictest confidence and not passed on to others without the written consent of the subject.

The nature of the investigation and any possible risks will be fully explained to intending subjects, and they will be informed that:

(a) they are in no way obliged to volunteer if there is any personal reason (which they are under no obligation to divulge) why they should not participate in the programme; and

(b) they may withdraw from the programme at any time, without disadvantage to themselves and without being obliged to give any reason.

NAME OF APPLICANT:
(Person responsible) **Signed:** _____

_____ **Date:** _____

NAME OF HEAD OF DEPARTMENT: **Signed:** _____

_____ **Date:** _____

UNIVERSITY OF EAST LONDON

MEMORANDUM

From: Ms Maryam J Kermani

Dept: Graduate School, Stratford

Email: maryam@uel.ac.uk

To: Ms Sue Meade

Dept: School of Psychology

Date: 02 November 2001 **Ref:** SLG/ETH/00/62/0

Subject: **University Ethics Committee: Approval of an experimental programme involving human subjects: Persistent Neuropsychological effects of recreational 'ecstasy' (MDMA), in recreational users. (K Soar) (Professor Andy Parrott)**

---

cc:

I advise that Members of the University Ethics Committee have now approved the above application on the terms previously advised to you, so I now write to give formal confirmation of this approval.

Mr Woodhouse would write again in approximately six months time to monitor progress of the project.

Maryam J Kertmani

Kermani

full'app.mem

APPENDIX V

Table 43: Chapter 3 - Modified BSI subscale ANCOVA statistics, with age as covariant

BSI Subscale	Main effect	Co-variance of age
Somatisation	F(2,52) = 6.714, p = 0.003	F(1,53) = 0.178, = 0.254
Interpersonal Sensitivity	F(2,52) = 6.82, p = 0.002	F(1,53) = 1.33, p=0.624
Depression	F(2,52) = 5.66, p = 0.006	F(1,53) = 0.036, p = 0.850
Anxiety	F(2,52) = 5.58, p = 0.006	F(1,53) = 0.942, p = 0.336
Phobic Anxiety	F(2,52) = 7.781, p = 0.001	F(1,53) = 0.208, p = 0.650
Psychoticism	F(2,52) = 7.737, p = 0.001	F(1,54) = 0.222, p = 0.64

Table 44: Chapter 6 - Modified BSI subscale ANCOVA statistics, with age as covariant

BSI Subscale	Main effect	Co-variance of age
Somatisation	F(3,70) = 9.53, p = <0.001	F(1,73) = 1.54, p = 0.219
Interpersonal Sensitivity	F(3,70) = 5.77, p = 0.001	F(1,73) = 0.75, p = 0.39
Depression	F(3,70) = 5.77, p =0.001	F(1,73) = 0.15, p = 0.701
Anxiety	F(3,70) = 6.14, p= 0.001	F(1,73) = 1.15, p = 0.286
Phobic Anxiety	F(3,70) = 9.56, p < 0.001	F(1,73) = 0.007, p = 0.934
Psychoticism	F(1,73) = 8.515, p <0.001	F(1,73) = 0.79, p = 0.779
MDMA side effects	F(3,70) = 4.09, p = 0.01	F(1,73) = 0.012, p = 0.914
Cognitive failures	F(3,70) = 5.80, p = 0.001	F(1,73) = 1.45, p = 0.705

APPENDIX X

UNIVERISTY OF EAST LONDON
STRATFORD CAMPUS

The Principal Investigator

Kirstie Soar
Psychology Department
(0208 2234556, k.soar@uel.ac.uk)

Project Title

Long term effects of recreational ecstasy/MDMA use.

Project Description

This study is to assessing the long-term effects of to recreational ecstasy use. You will be required to complete in a number of questionnaires covering your personal history and recreational drug use. You will be administered a self-rating questionnaire for positive and negative life experiences and clinical symptoms and some cognitive tests which measure memory ability, planning ability and also reaction times. Following completion of these tasks you will be asked to expand on answers given in the questionnaires and given the opportunity to ask any questions.

Confidentiality of the Data

Confidentiality will be ensured and you are under no obligation to give your name. Signing the consent form does not define you as a drug user or non-drug user.

Disclaimer

You are not obliged to take part in this study and are free to withdraw at any time during the tests. Should you choose to withdraw from the programme you may do so without disadvantage to yourself and without any obligation to give a reason

University Research Ethics Committee

If you have any queries regarding the conduct of the programme in which you are being asked to participate please contact the Secretary of the University Research Ethics Committee: Mr DG Woodhouse, Principal Administrative Officer for Research, Research Unit, University of East London, Longbridge Road, Dagenham, Essex, RM8 2AS (telephone 0208 590 7000 ext. 3006, fax 0208 590 7799, e-mail wdhouse@uel.ac.uk).

APPENDIX X

UNIVERSITY OF EAST LONDON

Consent to Participate in an Experimental Programme

I have read the information leaflet relating to the above programme of research in which I have volunteered to participate in. The nature and purposes of the research have been explained to me, and I have had an opportunity to discuss and ask questions about this. I understand I have been asked to fill in a complete personal and drug history questionnaire, a clinical symptom inventory and complete a number of cognitive tasks.

I understand that my involvement in this study, and particular data from this research, will remain strictly confidential. I am not asked to give my name or address rather my details will be distinguished from others by an allotted drug sub-code, in order to maintain complete anonymity. Only the researchers involved in the study will have access to the data. It has been explained to me what will happen to the data once the experimental programme has been completed.

I hereby fully and freely consent to participate in this study which has been fully explained to me.

Having given this consent I understand that I have the right to withdraw from the programme at any time without disadvantage to myself and without being obliged to give any reason.

Participant's drug subcode .....

Participant's signature.....

Date.....

APPENDIX Y

UNIVERISTY OF EAST LONDON
STRATFORD CAMPUS

Kirstie Soar
Psychology Department
(0208 2234556, k.soar@uel.ac.uk)

Project Title

Persistent neuropsychological effects of 'ecstasy' (MDMA), in recreational users.

Project Description

This study is to assess the persistent long-term effects of recreational ecstasy use. It will involve the completion of a number of questionnaires covering your personal history and recreational drug use. Followed by the administration of a self-rating questionnaire for positive and negative life experiences and clinical symptoms and some cognitive tests, which measure memory ability and planning ability. There will also be an opportunity to ask any questions regarding the study.

Confidentiality of the Data

Confidentiality will be ensured and you are under no obligation to give your name. Signing the consent form does not define you as a drug user or non-drug user and will be detached from any other collated data.

Disclaimer

You are not obliged to take part in this study and are free to withdraw at any time during the tests.

University Research Ethics Committee

If you have any queries regarding the conduct of the programme in which you are being asked to participate please contact the Secretary of the University Research Ethics Committee: Mr DG Woodhouse, (telephone 0208 590 7000 ext. 3006, fax 0208 590 7799, e-mail wdhouse@uel.ac.uk).

APPENDIX Y

UNIVERSITY OF EAST LONDON

Consent to Participate in an Experimental Programme

I have read the information leaflet relating to the above programme of research in which I have volunteered to participate in. The nature and purposes of the research have been explained to me, and I have had an opportunity to discuss and ask questions about this.

I understand that my involvement in this study, and particular data from this research, will remain strictly confidential. I am not asked to give my name or address, in order to maintain complete anonymity.

I hereby fully and freely consent to participate in this study which has been fully explained to me.

Having given this consent I understand that I have the right to withdraw from the programme at any time without disadvantage to myself and without being obliged to give any reason.

Participant's initials.....

Date.....

APPENDIX Z

UNIVERISTY OF EAST LONDON

Kirstie Soar
Psychology Department
(0208 2234556, k.soar@uel.ac.uk)

Project Title

Personality characteristics of problem versus non-problem Ecstasy (MDMA) users.

Project Description

This study is to assess whether there are certain personality factors, which are important in determining whether recreational ecstasy users develop long-term psychological problems. It will involve the completion of a number of questionnaires covering your personal history and recreational drug use; problems attributable to certain drug use; clinical symptoms and a personality questionnaire which determines whether you attribute control to yourselves or to external factors.

Confidentiality of the Data

Confidentiality will be ensured and you are under no obligation to give your name. Signing the consent form does not define you as a drug user or non-drug user and will be detached from any other collated data.

Disclaimer

You are not obliged to take part in this study and are free to withdraw at any time during the tests.

University Research Ethics Committee

If you have any queries regarding the conduct of the programme in which you are being asked to participate please contact the Secretary of the University Research Ethics Committee: Telephone 0208 590 7000 ext. 3006, fax 0208 590 7799.

APPENDIX Z

Consent to Participate

- The study has been fully explained to me
- I have volunteered to participate
- I understand data from this research, will remain strictly confidential.
- I fully and freely consent to participate in this study
- I understand that I have the right to withdraw at any time

Participant's initials.....

Date.....