REVIEW

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Ecstasy (MDMA): a review of its possible persistent psychological effects

Abstract *Rationale:* Recreational use of "ecstasy" (3,4-methylenedioxymethamphetamine; MDMA) has become increasingly widespread. Until recently, however, little was known about the possible persistent psychological effects of extensive use of this drug. *Objective:* The aim of the present review is to evaluate recent empirical evidence concerning the persistent psychological sequelae of recreational ecstasy use. *Methods:* The methodologies of open trial studies of recreational ecstasy users are evaluated and reports of the presence or absence of persistent psychological problems are related to the extent of past exposure to ecstasy. *Results:* There is growing evidence that chronic, heavy, recreational use of ecstasy is associated with sleep disorders, depressed mood, persistent elevation of anxiety, impulsiveness and hostility, and selective impairment of episodic memory, working memory and attention. There is tentative evidence that these cognitive deficits persist for at least 6 months after abstinence, whereas anxiety and hostility remit after a year of abstinence. The possibility that some of these psychological problems are caused by ecstasy-induced neurotoxicity is supported by preclinical evidence of MDMA-induced neurotoxicity and behavioural deficits, evidence of depleted serotonin in heavy ecstasy users, and by dose-response relationships between the extent of exposure to ecstasy and the severity of cognitive impairments. *Conclusions:* An increasing number of young, heavy ecstasy users are at significant risk of persistent cognitive impairments and disturbances of affect and personality. Some of these problems may remit after abstinence, but residual neurotoxicity and decline of serotonergic function with age may result in recurrent psychopathology and premature cognitive decline.

Introduction

The popular recreational drug, "ecstasy" (3,4-methylenedioxymethamphetamine; MDMA), is a phenethylamine with structural similarities to both amphetamine and mescaline. It has been tentatively classified into a novel pharmacological class termed "entactogens", however, because it has a characteristic psychoactive profile that distinguishes it from classic hallucinogens and stimulants. The acute psychological effects of MDMA include feelings of euphoria, elevated self-confidence and heightened sensory awareness (see, for example, Downing 1986; Greer and Tolbert 1986; Vollenweider et al. 1998; Liechti et al. 2000). Acute adverse effects include moderate derealisation and depersonalisation, cognitive disturbances, elevated anxiety, decreased appetite and trismus (jaw-clenching) (Leister et al. 1992; Vollenweider et al. 1998; Liechti et al. 2000). These effects last for 3–5 h after a single recreational dose and can be attenuated by pretreatment with the selective serotonin (5-HT) reuptake inhibitor "Citalopram" (Liechti et al. 2000).

MDMA is generally accepted to be a potent indirect monoaminergic agonist producing both carrier-mediated release and reuptake inhibition of 5-HT (see, for example, Nichols et al. 1982; Schmidt 1987) and to a lesser extent dopamine (see, for example, Yamamoto and Spanos 1988). However, some recent reports have raised the question of the relative importance of 5-HT release (Liechti et al. 2000) versus reuptake inhibition (Iravani et al. 2000). There is also evidence of a less-pronounced direct agonist effect on 5-HT_2, 5-HT_1 and D_2 receptors (Battaglia et al. 1988), which might be of importance for understanding the different psychological profiles of MDMA, hallucinogens, amphetamine and cocaine.

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Epidemiology

The use of ecstasy appears to be spreading in many parts of the western world. In the US, there have been reports of marked increases in association with the "rave" scene in San Francisco, Dallas, Houston, Miami and Denver (Miller 1997). Between 1998 and 1999, a significant increase in the prevalence of twelfth-grade students who had ever used ecstasy from 5.8% to 8.0% was recorded (Johnston et al. 2000). Australian surveys indicate that 1–3% of the general population had used ecstasy between 1990 and 1995 (see, for example, Commonwealth Department of Health and Family Services 1996). The "Annual report on the state of the drug problems in the European Union" also indicates that 0.5–3% of the adult population of the EU has used ecstasy (European Monitoring Centre for Drugs and Drug Addiction 1998). The highest frequencies of use among 15- to 16-year-old school students were reported for Ireland (9%), the Netherlands (8.1%) and the UK (8%). By the mid-1990s, it was estimated that 750,000 ecstasy tablets were consumed by young people attending "raves" and parties every weekend in the UK (Cook 1995). A British Crime Survey indicated that 9% of 16- to 19-year-olds, 13% of 20- to 24-year-olds and 5% of 25- to 29-year-olds had tried ecstasy by 1996 (Ramsey and Spiller 1997). These findings are corroborated by another report that 7% of all 11- to 35-year-olds had tried the drug by 1996 (Tasker et al. 1999). Taken together, these data suggest that more than a million young people aged 16–29 years had tried ecstasy in the UK by 1996, of whom about 240,000, or 18% of ever users, had taken it in the previous month. Thus, it would appear that there were hundreds of thousands of regular ecstasy users in the UK by the mid-1990s and perhaps millions world wide. There is also evidence that these numbers have increased significantly in the last few years (see for example, Abraham et al. 1998; Johnston et al. 2000).

Acute subjective effects of ecstasy

The average recreational dose of ecstasy is between one and two tablets, each containing approximately 60–120 mg MDMA, a standard oral dose of 0.75–4 mg/kg in 60- to 80-kg individuals. Most individuals use the drug at weekends once a week or less because tolerance to its positive effects develops rapidly (Peroutka et al. 1988; Solowij et al. 1992; Davison and Parrott 1997; Hammersley et al. 1999). Subjective reports of the acute effects of street ecstasy are sufficiently similar to those of the acute effects of pharmaceutical MDMA that they suggest that, in most cases, the active drug is MDMA or the related compounds 3,4-methylenedioxyethamphetamine (MDEA) and 3,4-methylenedioxyamphetamine (MDA). Users report that after about 20 min ecstasy begins to produce euphoria, feelings of intimacy and closeness to others, heightened arousal, self-confidence, increased sensory sensitivity, openness to new ideas, increased depth of emotion and decreased appetite (Peroutka et al. 1988; Solowij 1992; Cohen 1995; Davison and Parrott 1997). Other commonly reported acute adverse physiological side effects include tachycardia, bruxism, trismus, pupillary dilation, gait instability and nausea (Downing 1986; Peroutka et al. 1988; Cohen 1995; Davison and Parrott 1997).

Subacute subjective effects of ecstasy

Following the acute subjective effects, ecstasy users generally report a 24- to 48-h period characterised by the persistence of the acute effects and the onset of additional effects that are reminiscent of the "crash" phenomenon reported after psychostimulant administration. The most common subacute symptoms are muscle aches, fatigue, depression, irritability, difficulty in concentrating and headache (Peroutka et al. 1988; Solowji et al. 1992; Cohen 1995; Davison and Parrott 1997; Parrott and Lasky 1998; Topp et al. 1999). The latter reports from surveys of recreational users are corroborated by the results of a controlled comparison of the acute effects of ecstasy and alcohol on mood and cognitive performance. The subacute effects of ecstasy were evident in increased ratings for "discontented", "sad" and "bored" over 4 days after self-administration of the drug. Ecstasy users exhibited lower mood than alcohol users the day after taking the drug, but were even more depressed 4 days later, at which point the scores of some users were within the range for clinical depression (Curran and Travill 1997).

Preclinical evidence of the neurotoxic effects of MDMA

A single dose of MDMA (10 mg/kg) in rats produces a biphasic effect, with acute depletion of 5-HT most prominent 3–6 h after administration and recovery by 24 h, followed by a second phase of depletion of 5-HT depletion a week after drug treatment (Schmidt 1987). The second phase of 5-HT depletion in laboratory animals is accompanied by reductions of 5-hydroxyindoleacetic acid (5-HIAA) concentrations, tryptophan hydroxylase activity and in the density of 5-HT reuptake sites. There is also histological evidence that MDMA produces morphological changes to 5-HT neurones that arise from the dorsal raphe magnus (for reviews see McKenna and Peroutka 1990; Seiden et al. 1993; Steele et al. 1994; Green et al. 1995; Seiden and Sabol 1996; Hegadoren et al. 1999). This has led many investigators to conclude that MDMA is a potent and selective 5-HT neurotoxin in a variety of mammalian species, including non-human primates (see, for example, Commins et al. 1987; O'Hearn et al. 1988; Ricaurte et al. 1988).

Long-term neurotoxic effects of MDMA require either a large single dose (20 mg/kg or more) or several more moderate doses, typically 5 mg/kg twice daily for

4 consecutive days (Battaglia et al. 1988; Ricaurte et al. 1988; Colado et al. 1993; O'Shea et al. 1998). The neurotoxic effects are evident up to a year after drug administration in rats (Battaglia et al. 1987), and have been observed up to 7 years after drug administration in non-human primates (Hatzidimitriou et al. 1999). The lowest MDMA dose that elicited long-term structural damage in non-human primates was 5 mg/kg twice daily for 4 consecutive days (Ricaurte et al. 1992). This is higher and more frequent dosing than is typical in human recreational users. However, principles of interspecies scaling suggest that a dose of 5 mg/kg MDMA in a squirrel monkey is equivalent to 1.4 mg/kg in humans (Ricaurte et al. 2000). Furthermore, it has been reported that up to a third of recreational users "binge" by taking several tablets at once or over a period of hours to days (see, for example, Hammersley et al. 1999; Topp et al. 1999).

There is also preclinical evidence of regional differences in sensitivity to the neurotoxic effects of MDMA. Areas rich in 5-HT terminals, such as the cerebral cortex, show more severe deficits than brain regions containing fibres of passage (for example, hypothalamus) or cell bodies (brain stem) (Commins et al. 1987; O'Hearn et al. 1988; Steele et al. 1994). In particular, repeated administration of MDMA has been found to produce especially long-lasting degeneration of serotonergic axons, and decreases in brain 5-HT and 5-HIAA concentrations, in many regions of the forebrain. These include the neocortex, hippocampus, caudate nucleus, putamen and many thalamic nuclei (Kleven et al. 1989; Ricaurte et al. 1992; Fischer et al. 1995; Frederick et al. 1995; Lew et al. 1996; Sabol et al. 1996; Aguirre et al. 1997; Hatzidimitriou et al. 1999).

Following MDMA injury there is evidence of a lasting reorganisation of ascending 5-HT axon projections, with projections to distant forebrain sites (for example, dorsal neocortex) exhibiting little or no evidence of recovery, while projections to some more proximal targets (for example, hypothalamus) recover fully or in excess (Fischer et al. 1995). The authors of the latter study also reported that altered reinnervation patterns develop much more frequently in MDMA-treated primates than in MDMA-treated rodents. Other investigators employed positron emission tomography (PET) with a radioligand (McN-5652), which selectively labels the 5-HT transporter, to investigate the long-term neurotoxic effects of MDMA in a baboon that had been administered 5 mg/kg MDMA, twice daily for 4 consecutive days (Scheffel et al. 1998). In agreement with the results of Fischer et al. (1995), PET scans 9 and 13 months post-MDMA showed regional differences in the apparent recovery of 5-HT transporters, with increases in some brain regions (for example, hypothalamus) and persistent decreases in others (for example, neocortex). Thus, the available preclinical evidence suggests that a repeated administration of high oral doses of MDMA may produce long-term reductions in serotonergic activity and degeneration of 5-HT neurones in humans. This inference is strengthened by the heightened sensitivity to such effects, and the lesser tendency for reinnervation to occur in cortical 5-HT systems, in primates.

Clinical evidence of selective neurotoxic effects

The neurotoxic potential of MDMA in humans has been evaluated indirectly by measuring the concentration of 5-HIAA in cerebrospinal fluid (CSF) in recreational ecstasy users. The earliest study to employ this technique failed to find evidence of reduced levels of 5-HIAA in recreational users (Peroutka et al. 1987). Subsequently, however, Ricaurte et al. (Ricaurte et al. 1990; McCann et al. 1994, 1999a; Bolla et al. 1998), reported significantly lower levels of CSF 5-HIAA in recreational ecstasy users compared to polydrug users who had never used ecstasy (see Table 1).

Another technique that has been employed to indirectly evaluate the neurotoxic potential of ecstasy is to challenge users with 5-HT agonists (see Table 1). Price et al. (1989) reported that L-tryptophan induced an increase in serum prolactin concentrations in healthy controls, but not in recreational ecstasy users. Peak change and the area under curve (AUC) of the prolactin response appeared to be blunted in ecstasy users, but the difference from controls did not reach statistical significance. McCann et al. (1994) also used L-tryptophan challenge to compare central 5-HT function in ecstasy users and polydrug-using controls, but found no difference in prolactin levels between groups. More recently, both prolactin and cortisol responses to D-fenfluramine challenge were reported to be significantly blunted in exclusive ecstasy users in comparison with control participants after abstinence from ecstasy for 3 weeks (Gerra et al. 1998). Furthermore, after a year of abstinence, although cortisol responses were restored, prolactin responses to D-fenfluramine challenge remained significantly blunted (Gerra et al. 2000). In contrast, Verkes et al. (2000) reported significantly reduced release of cortisol, but not of prolactin, after D-fenfluramine challenge in heavy ecstasy users and moderate users, compared to non-users. Finally, McCann et al. (1999b) reported that both prolactin and cortisol responses to m-chlorophenylpiperazine challenge were significantly blunted in heavy ecstasy users compared to non-users.

The methodology employed by some of the latter studies is questionable with respect to the extent that investigators controlled for other drug use among ecstasy users. This is an issue because recreational ecstasy users are almost always polydrug users (i.e. they tend to also use many other illicit drugs; see, for example, Jansen 1997; Morgan 1998a,b, 1999; Schifano et al. 1998; Hammersley et al. 1999; Topp et al. 1999). Thus, any differences between ecstasy users and control participants who have never used illicit drugs may be attributable to any of the other illicit drugs that the ecstasy users have also used. Most of the latter investigators employed control participants who had less exposure to other illicit drugs, in addition to never having used ecstasy (see, for

Table 1 Clinical evidence of selective neurotoxic effects of ecstasy in recreational users. (*CSF* Cerebrospinal fluid, *5-HIAA* 5-hydroxyindoleacetic acid, *m-CPP* m-chlorophenylpiperazine, *PET* positron emission tomography, *EP* evoked potential, *5-HT* serotonin, – indicates that the variable was not reported)

Authors	Date	Assay	Number in ecstasy group(s)	Mean total number of times used	Mean duration of use in years	Mean weeks drug free pretest	Significant relative reduction?
Peroutka et al.	1987	CSF 5-HIAA	5	18	<1.6	>6	No
Ricaurte et al.	1990	CSF 5-HIAA	33	52	3.5	17	Yes
McCann et al.	1994	CSF 5-HIAA	30	95	5.0	18	Yes
Bolla et al.	1998	CSF 5-HIAA	24	60	4.8	4	Yes
McCann et al.	1999a	CSF 5-HIAA	22	215	4.5	14	Yes
Price et al.	1989	L-tryptophan challenge	9	120[b]	5.1	9	No effect on prolactin response
McCann et al.	1994	L-tryptophan challenge	30	94	5.0	18	No effect on prolactin response
Gerra et al.	1998	D-fenfluramine challenge	15	63	1.2	3	Reduced prolactin and cortisol responses
Gerra et al.	2000	D-fenfluramine challenge	15	69	1.3	52	No effect on cortisol response Reduced prolactin response
Verkes et al.[a]	2000	D-fenfluramine challenge	21	84 and 240[b]	4.4 and 4.5	4 and 3	No effect on prolactin responses Reduced cortisol responses
McCann et al.	1999b	m-CPP challenge	25	196	5.0	14	Reduced prolactin and cortisol responses
McCann et al.	1998	PET	14	228	4.6	19	Decreased 5-HT transporter binding
Semple et al.	1999	SPECT	10	300[b]	–	3	Decreased 5-HT transporter binding
Reneman et al.	2000	SPECT	5	100[b]	–	19	Increased cortical 5-HT$_{2A}$ binding
Tuchtenhagen et al.	2000	Auditory EPs	28	65[b]	2.2	6	Increased amplitude of N1/P2 source activity

[a] Two groups from the same study
[b] Estimated from lifetime dose in tablets or from frequency and duration of use

example, Peroutka et al. 1987; Ricaurte et al. 1990; McCann et al. 1994, 1999a,b; Bolla et al. 1998; Verkes et al. 2000). However, the authors of two of these reports avoided this potential confound by comparing *exclusive* ecstasy users to control participants who had never used any illicit drugs (Gerra et al. 1998, 2000; see Table 1).

Recently, more direct evidence that MDMA produces long-term neurotoxic effects on brain 5-HT systems has emerged from neuroimaging studies. In a PET study with the selective 5-HT transporter McN-5652, heavy ecstasy users (who had remained abstinent for 3–147 weeks) showed decreased brain 5-HT transporter binding compared with ecstasy-na controls and this decrease correlated with the extent of previous ecstasy use (McCann et al. 1998). Other investigators used single photon emission computed tomography (SPECT) with the 5-HT transporter radioligand ([^{123}I] β-CIT) to investigate heavy ecstasy users (who had remained abstinent for an average of 3 weeks) and ecstasy-na controls who were well matched for alcohol, tobacco and cannabis use. The ecstasy users showed a widespread reduction of cortical 5-HT transporter binding, with normal dopamine recep-

tor binding (Semple et al. 1999). However, regional differences in 5-HT receptor density were less marked than in the study by McCann et al. (1998). There was also a suggestion that at least some of the loss of transporter density might be temporary and related to last use of ecstasy (Semple et al. 1999). In another recent SPECT study, [^{123}I]-5-I-R91150 was used to study cortical 5-HT$_{2A}$ receptor densities in five heavy ecstasy users (who had remained abstinent for an average of 4.6 months) and nine healthy controls. 5-HT$_{2A}$ receptor densities appeared to be significantly upregulated in the occipital cortex of ecstasy users compared to controls, possibly as a compensatory response to 5-HT depletion (Reneman et al. 2000). There are some interpretative difficulties with the findings of McCann et al. (1998) and Reneman et al. (2000), however, because these investigators failed to completely control for variations in the use of other illicit drugs.

Other evidence for persistent ecstasy-induced depletion of central 5-HT activity is provided by a comparison of the auditory evoked potentials of heavy ecstasy users with those of two matched control groups, a non-user and a cannabis-user group (Tuchtenhagen et al.

2000). The ecstasy users (who had been drug free for 7 days to a year) exhibited an increase in the amplitude of the tangential N1/P2 source activity with higher stimulus intensities, whereas both control groups failed to show this feature. High intensity dependence of the tangential N1/P2 source activity has been associated with low levels of serotonergic neurotransmission in humans (Hergerl and Juckel 1993).

Finally, there is also evidence that brain atrophy might occur in association with chronic ecstasy use. Proton magnetic resonance spectroscopy has been used to investigate myo-inosital (MI) concentrations, a tentative glial marker (Chang et al. 1999). These investigators reported that MI concentrations were elevated in the parietal white matter of heavy ecstasy users compared to that of drug-na control subjects. There was a significant effect of the logarithm of the cumulative lifetime ecstasy dose on in the parietal white matter and in the occipital cortex, and the duration of ecstasy use was also related to MI in the parietal white matter and in the frontal cortex. Chang et al. (2000) also reported decreased global brain volume and increased percentage of CSF in ecstasy users with longer duration of use. Thus the neuroimaging evidence supports the earlier findings and provides additional clinical evidence that heavy ecstasy users exhibit persistent reductions in brain 5-HT (see Table 1).

The role of serotonin in regulating behaviour

Serotonin has been implicated in the regulation of mood, anxiety, aggression, impulsiveness, sexual activity, appetite, sleep, pain, circadian and seasonal rhythms, motor activity and body temperature. Transient reductions in 5-HT activity, induced by tryptophan depletion, have been reported to produce a rapid lowering of mood in normal males (Young et al. 1985; Smith et al. 1987) and relapse in recently remitted depressed patients (Delgado et al. 1990). Furthermore, there is evidence that disorders of central serotonergic neurotransmission, as reflected by low levels of 5-HIAA, are associated with anxiety disorders (see, for example, Garvey et al. 1995) and impulsive and aggressive personality traits (see, for example, Brown et al. 1979; Coccaro 1989; Linnoila et al. 1993). The place of 5-HT in cognition is poorly understood (McEntee and Crook 1991), but it has been proposed that it may play an orchestrating role in cognition, and that extreme deviations of 5-HT activity can result in biases in cognitive processing (Spoont 1992). There is also evidence that suggests that 5-HT is particularly likely to be involved in learning (see, for example, Hunter 1988), visuospatial memory (Wenk et al. 1987), visual discrimination, associative functions and aspects of planning (Park et al. 1994), and general memory consolidation and retrieval (Meneses and Hong 1994).

Evidence for chronic neuropsychiatric effects

The evidence that recreational ecstasy users have persistently reduced levels of brain serotonergic activity, and that such reductions are associated with neuropsychiatric disorders, suggests that recreational ecstasy users should be more likely to suffer from such disorders. There is a growing body of evidence to suggest that this might, indeed, be the case. There are a number of case reports of chronic psychiatric symptoms following regular use of the drug including reports of depersonalisation (McGuire et al. 1994), obsessive-compulsive symptoms (Cassidy and Ballard 1994), flashbacks (Creighton et al. 1991; McGuire and Fahy 1992; Schifano and Magni 1994), panic attacks (McCann and Ricaurte 1991; Pallantini and Mazzi 1992; McGuire et al. 1994; Schifano and Magni 1994; Series et al. 1994; Cohen 1996; Windhaber et al. 1998), psychosis (Creighton et al. 1991; McCann and Ricaurte 1991; McGuire and Fahy 1991; Schifano 1991; Keenan et al. 1993; Cassidy and Ballard 1994; McGuire et al. 1994) and depression (Benazzi and Mazzoli 1991; McCann and Ricaurte 1991; McGuire et al. 1994; Schifano and Magni 1994). These symptoms appear to differ from the more common acute psychiatric effects of ecstasy (Solowji et al. 1992; Curran and Travill 1997), in that they were often not associated with the timing of each dose, and were chronic, persisting long after ecstasy use had been discontinued (McGuire 1999).

Unfortunately, however, there are a number of interpretative difficulties with such evidence. First, the anecdotal nature of case report evidence makes it difficult to determine the risk to the average recreational ecstasy user of such disorders. The epidemiological evidence suggests that all of these disorders occur with fairly high frequency in the normal population. Thus, the occurrence of such disorders, although suggestive, could simply be attributed to coincidence. Secondly, there is the problem that ecstasy users are almost exclusively polydrug users who tend also to use many other illicit drugs (see, for example, Jansen 1997; Morgan 1998a,b, 1999; Schifano et al. 1998). Therefore, even if the disorder is associated with previous illicit drug use, it is difficult to determine which, if any, of these drugs was responsible. Finally, there is the problem of interpretation of causality. Does chronic ecstasy use cause the disorder or does the basis of the disorder already exist before the individual begins to take ecstasy? There is considerable evidence to support the latter possibility. It is well recognised that poor premorbid adjustment is associated with increased drug use. Some authors of the earlier case reports suggest that either a genetic predisposition for neuropsychiatric illness or a personal history of previous psychiatric problems might increase the likelihood of the development of a chronic ecstasy-related disorder (McCann and Ricaurte 1991; McGuire et al. 1994). In such cases, drug use may be an attempt to "self-medicate" the distress associated with premorbid psychiatric disorders.

An alternative to the case report approach is to conduct a large-scale survey of a representative sample of

recreational users. For example, Cohen (1995) studied the subjective reports of a sample of 500 young ecstasy users. The most frequently reported residual psychiatric effects were depression, depersonalisation and flashbacks. Investigations of this type tend to have their own shortcomings, however. Most have not employed objective psychiatric assessment and have relied instead on self-report measures derived from retrospective responses to anonymous questionnaires administered in nonclinical settings (see, for example, Peroutka 1987; Cohen 1995; Forsyth 1996). In a recent, more highly controlled study, an outpatient psychiatric symptom checklist, the SCL-90 (Derogatis 1997) was used to compare 12 heavy ecstasy users with 16 light users and 22 control participants who had never taken ecstasy. The heavy users reported significantly higher scores than controls on the following SCL-90 factors: paranoid ideation, psychoticism, somatisation, obsessionality, anxiety, hostility, phobic anxiety, altered appetite and restless sleep. Light users generally produced intermediate scores (Parrott et al. 2000).

To date, however, only one large-scale survey of heavy recreational users has employed an objective psychiatric evaluation. Schifano et al. (1998) conducted a psychiatric evaluation of 150 polydrug users who had taken ecstasy on at least one occasion. More than half (53%) of the total sample were affected by one or more psychopathological problems, the most frequent of which were depression, psychotic disorders, cognitive disturbances, bulimic episodes, impulse control disorders, panic disorders and social phobia. Longer-term polydrug users, who had consumed an average of 50 ecstasy tablets in their lives, were found to be at considerably higher risk of developing psychopathological disturbances. Those who were free from psychopathological problems had taken a smaller number of ecstasy tablets in their lifetime, for a shorter duration and with a lower frequency, compared to the others. Ninety-five percent of the patients had experimented with another drug of abuse at least once in their lifetime but the use of other drugs was not statistically related to the occurrence of psychiatric problems. However, most of the ecstasy users had referred themselves for psychiatric evaluation of psychological problems that they attributed to their chronic use of ecstasy, and many were disturbed.

Persistent psychological sequelae of ecstasy use

Until recently, the possible long-term psychological consequences of reduced 5-HT function in recreational ecstasy users was largely a matter of conjecture based upon the evidence concerning the role of 5-HT in the regulation of behaviour. Thus, it could be hypothesised that the long-term effects of recreational ecstasy might include sleep disturbances, depressed mood, elevated anxiety, heightened impulsivity, aggression and hostility, and changes in cognitive processing in general, and learning and memory, in particular. The fact that most controlled laboratory studies of the effects of repeated administration of ecstasy are precluded for legal and ethical reasons has tended to deter attempts to investigate the possible long-term psychological effects of recreational ecstasy use. Nevertheless, evidence is beginning to emerge from open trial studies of recreational ecstasy users (see Table 2).

Table 2 Persistent affective and personality sequelae of recreational ecstasy use in relation to measures of consumption. (– Indicates that the variable was not reported, *?* indicates that these effects were not significant after confounding variables including education level and hyperactivity in youth were considered)

Authors	Date	Number in ecstasy group	Mean lifetime number of tablets used	Mean duration of use in years	Mean weeks drug free pretest	Relative depression of mood?	Relative elevation of anxiety?	Relative elevation of impulsiveness?	Relative elevation of anger/hostility?
Parrott and Lasky[a]	1998	15	7[b]	–	–	N	–	–	–
Parrott et al.[a]	2000	16	7	–	–	N	N	N	N
Parrott and Lasky[a]	1998	15	>18	–	–	N	–	–	–
Morgan[a]	1998b	16	36	2.1	3.0	N	N	N	N
Morgan[a]	1998b	25	50	4.1	9.3	Y	–	Y	–
Gerra et al.	1998	15	89[b]	1.2	3.0	Y	–	Y	Y
Gerra et al.	2000	15	98[b]	1.3	56.0	Y	–	Y	N
Tuchtenhagen et al.	2000	28	93	2.3	5.9	–	–	Y	–
McCann et al.	1994	30	160[b]	5.0	18.0	–	–	N	N
Verkes et al.[a]	2000	21	169	4.4	2.2	N	N	–	–
Gamma et al.	2000	15	222	–	1.0	Y	N	–	–
Parrott et al.[a]	2000	12	371	–	–	N	Y	Y	Y
Verkes et al.[a]	2000	21	741	4.5	1.3	Y?	Y?	Y?	–
Wareing et al.[a]	2000	10	1200[b]	4.1	1.2	–	Y	–	–
Wareing et al.[a]	2000	10	1200[b]	3.9	46.0	–	N	–	–

[a] Different groups from same study
[b] Estimated from lifetime dose in tablets or from frequency and duration of use

Sleep, affect and personality

Sleep

Allen et al. (1993) compared the all night polysomno-grams of recreational ecstasy users (who had used the drug on more than 25 separate occasions) with those of age- and gender-matched control participants who had not taken ecstasy. On average, the ecstasy users had less total sleep and less non-REM sleep. These statistically significant differences were primarily attributable to an average of 37 min less stage 2 sleep, with no significant differences noted in stages 1, 3 or 4. Heavy ecstasy users (who had used the drug on 30–1,000 occasions) also ex-hibited higher scores than control participants on the restless sleep factor of the SCL-90 (Parrott et al. 2000).

Mood

There is little evidence that light ecstasy use is associat-ed with persistent depression of mood (see Table 2). For example, there were no significant differences in visual analogue measures of affective state between novice ec-stasy users (who had taken ecstasy on less than 10 occa-sions), regular users (who had taken ecstasy on 10 or more occasions) and non-using controls (Parrott and Lasky 1998). There were also no significant differences in scores on the depression factor of the SCL-90 between light users (who had taken ecstasy on 1–20 occasions) and non-using controls (Parrott et al. 2000). Finally, Likert scale measures of affective state were not signifi-cantly different between light ecstasy users (who had used a lifetime average of 36 tablets), polydrug users who had never taken ecstasy and control participants who had not used illicit drugs (Morgan 1998a,b).

There is some evidence that a pattern of heavier con-sumption of ecstasy is associated with persistent depres-sion of mood. For example, ecstasy users (who had con-sumed an average of 50 tablets in their lifetime) pro-duced General Health Questionnaire (Goldberg 1978) scores that suggested that they were more psychologi-cally disturbed than non-drug controls (Morgan 1998b). The scores of exclusive ecstasy users (who had con-sumed an average of 63 tablets in their lifetime) on the Hamilton Depression Rating Scale (Hamilton 1976) were elevated compared to drug-na control participants, after abstinence from ecstasy for 3 weeks (Gerra et al. 1998) and 1 year (Gerra et al. 2000). Heavy ecstasy users (who had consumed an average of 222 tablets in their lifetime and had abstained from all psychoactive drug use for a week before testing) had significantly elevated scores for depression, inactivation and emotional excit-ability compared to ecstasy-na controls (Gamma et al. 2000). Finally, heavy ecstasy users (who had consumed an average of 741 tablets in their lifetime and had ab-stained from psychoactive drug use for a week before testing) had elevated scores on the Beck Depression In-ventory (Beck 1978) compared to moderate users and control participants (Verkes et al. 2000). Although the latter results suggest that heavy ecstasy use is associated with persistent depression of mood there is also evidence against such a straightforward interpretation of the litera-ture. First, the findings of Verkes et al. (2000) were not statistically significant after controlling for possible con-founding variables, including education level and hyper-activity in youth. Second, although Parrott et al. (2000) reported that heavy ecstasy users (who had used the drug on 30–1,000 occasions) exhibited higher scores than control participants on other factors of the SCL-90, they did not find a group difference on the depression factor.

Anxiety

The majority of open trial studies of recreational ecstasy users provide no evidence that light to moderate ecstasy use is associated with persistent elevation of anxiety (see Table 2). There were no significant differences in scores on the anxiety factor of the SCL-90 between light users (who had taken ecstasy on 1–20 occasions) and non-us-ing controls (Parrott et al. 2000). Furthermore, there were no significant differences in State/Trait Anxiety In-ventory (STAI; Spielberger et al. 1983) scores between light ecstasy users (who had used a lifetime average of 36 tablets), polydrug users who had never taken ecstasy and control participants who had not used illicit drugs (Morgan 1998a,b). Finally, there were no significant dif-ferences in STAI scores between moderate ecstasy users (who had used it on 73 occasions on average) and con-trol participants (Verkes et al. 2000).

As in the case of mood, however, there is evidence that a pattern of heavier consumption of ecstasy is asso-ciated with persistent elevation of anxiety. Heavy ecstasy users (who had consumed an average of 222 tablets in their lifetime and had abstained from all psychoactive drug use for a week before testing) had elevated anxiety scores compared to ecstasy-na controls that just missed statistical significance (Gamma et al. 2000). Further-more, heavy ecstasy users (who had consumed an aver-age of 741 tablets and had abstained from psychoactive drug use for a week before testing) had elevated STAI trait anxiety scores compared to moderate users and con-trol participants (Verkes et al. 2000). However, the latter effect was not significant after controlling for possible confounding variables, including education level and hy-peractivity in youth.

Parrott et al. (2000) provide more compelling evi-dence that heavier consumption of ecstasy is associated with persistent elevation of anxiety. Heavy ecstasy users (who had used the drug on 30–1,000 occasions) had sig-nificantly higher scores than control participants on the anxiety, phobic anxiety, somatisation and obsessionality factors of the SCL-90. There is also tentative evidence that the anxiety associated with heavy ecstasy use may ameliorate after a prolonged period of abstinence. Wareing et al. (2000) reported that both current and ex-ecstasy users (who had been abstinent for almost a year)

scored higher on an anxiety scale. However, only the difference between current heavy users (who claimed to use the drug more than 100 times a year) and non-users achieved statistical significance.

Impulsiveness, sensation seeking and novelty-seeking

The first evidence to suggest that recreational ecstasy use was associated with persistent differences in impulsiveness was a report by McCann et al. (1994). These investigators reported that heavy ecstasy users exhibited *lower* scores than control participants on a Multidimensional Personality Questionnaire (Tellegen 1982) measure of impulsivity. The same ecstasy users were also reported to exhibit lower levels of CSF 5-HIAA. This finding is surprising in view of the consensus that low levels of CSF 5-HIAA are normally associated with elevated impulsiveness (see, for example, Linnoila et al. 1993). Furthermore, most subsequent investigations of impulsiveness, or related personality traits such as venturesomeness, sensation seeking and novelty seeking, have found heavy ecstasy use to be associated with elevated levels of these traits compared to non-drug controls (see Table 2).

Parrott et al. (2000) reported that there were no significant differences in scores on the impulsiveness or venturesomeness factors of the Impulsiveness, Venturesomeness and Empathy Questionnaire (IVE; Eysenck and Eysenck 1991) between light users (who had taken ecstasy on 1–20 occasions) and non-using controls. Furthermore, there were no significant differences in IVE impulsiveness scores between light ecstasy users, polydrug users who had never taken ecstasy and control participants who had not used illicit drugs (Morgan 1998a,b). However, in the latter study, both drug-using groups were found to score higher than non-drug controls on IVE venturesomeness (Morgan 1998a,b).

With the exception of the findings of McCann et al. (1994), however, heavier exposure to ecstasy has consistently been found to be associated with elevated impulsiveness. In a follow-up study, Morgan (1998b) observed that heavier ecstasy users had elevated IVE trait impulsiveness, as well as venturesomeness, compared to controls. The combined IVE data from the latter two studies revealed an association between ecstasy use and trait impulsiveness; the recreational users who had consumed the most ecstasy in their lives had the most elevated trait impulsiveness scores. Parrott et al. (2000) also reported that heavy ecstasy users had elevated IVE impulsiveness compared to non-drug controls. Other investigators have reported that heavy ecstasy use is associated with elevated sensation seeking as well as impulsiveness. Heavy users had higher scores on the experience seeking subscale of the Sensation Seeking Scale (Zuckerman et al. 1978) and the non-planning impulsivity subscale of the Barratt Impulsiveness Scale (Barratt 1985) than a matched control group who only smoked cannabis (Tuchtenhagen et al. 2000).

Finally, heavy ecstasy use has been reported to be associated with persistent elevations of novelty seeking. Gerra et al. (1998) reported that a group of male, exclusive, heavy ecstasy users who had remained abstinent for 3 weeks had elevated novelty-seeking scores on a subscale of the Tridimensional Personality Questionnaire (TPQ; Cloninger 1987), and 12 of these participants exhibited novelty-seeking behaviour as a characteristic of their lifestyle. After 12 months of abstinence from ecstasy, these ecstasy users maintained significantly higher scores on the novelty seeking TPQ subscale than non-drug controls (Gerra et al. 2000).

Aggression and hostility

In addition to reporting that heavy ecstasy users showed persistent reductions in impulsiveness and CSF 5-HIAA, McCann et al. (1994) reported that these ecstasy users had *lower* scores than control participants on the Buss Durkee Hostility Inventory (BDHI; Buss and Durkee 1957) indirect hostility scale. Again this finding is surprising in view of the consensus that low levels of CSF 5-HIAA are normally associated with elevated levels of aggression and hostility (see, for example, Brown et al. 1979; Coccaro 1989). In a subsequent study of light ecstasy users, however, Morgan (1998a,b) reported that there were no significant differences between the scores of light ecstasy users, polydrug users who had never taken ecstasy and non-drug controls on the State/Trait Anger Expression Inventory (Spielberger 1988). Furthermore, there were no significant differences in scores on the hostility factor of the SCL-90 between light users and non-using controls (Parrott et al. 2000).

There is some evidence that heavier exposure to ecstasy is associated with elevated hostility that appears to ameliorate with protracted periods of abstinence (see Table 2). Parrott et al. (2000) reported that heavy ecstasy users (who had used the drug on 30–1,000 occasions) had significantly higher scores than control participants on the hostility factor of the SCL-90. Similarly, Gerra et al. (1998) reported that compared to control participants, exclusive, heavy ecstasy users showed significantly elevated scores on the BDHI direct aggressiveness subscale after 3 weeks of abstinence. After 12 months of abstinence, however, these participants showed a significant reduction of their BDHI direct aggressiveness subscale score compared to their score after 3 weeks of abstinence (Gerra et al. 2000).

In summary, there is growing evidence that heavy use of ecstasy is associated with persistent depression of mood and elevated impulsiveness, novelty seeking and sensation seeking. Heavy use also appears to be associated with prolonged elevation of anxiety, hostility and aggressiveness but there is some evidence of remission of these affective states after protracted periods of abstinence.

Persistent neuropsychological sequelae of ecstasy use

Memory performance

There is some preclinical evidence that repeated treatment of rats with high doses of MDMA produces persistent impairments of learning and memory. An MDMA-induced 73% depletion of neocortical 5-HT resulted in a mild impairment of the ability to develop an efficient search strategy in a place navigation task (Robinson et al. 1993). Furthermore, a selective, delay-dependent deficit in delayed non-match to place performance developed 12 days after rats were exposed to high doses of MDMA for 3 days (Marston et al. 1999). There is also growing evidence from human studies that chronic exposure to ecstasy may be associated with persistent impairment of memory. McCann and Ricaurte (1991) presented a case study of persistent neuropsychiatric abreaction to ecstasy, which included severe memory problems, and more recently another case study of a pure amnesiac syndrome after ingestion of ecstasy was reported (Spatt et al. 1997). The authors of a growing number of open trial studies have also reported that recreational ecstasy

Table 3 Persistent cognitive sequelae of recreational ecstasy use in relation to measures of consumption. Recent, open trial studies provide evidence that recreational use of ecstasy is associated with impaired episodic and working memory performance and deficits in other cognitive processes including attention. There are also reports of relationships between measures of ecstasy consumption, brain 5-HT depletion and the degree of impairment of memory performance. (– Indicates that the variable was not reported)

Authors	Date	Number in ecstasy group	Mean lifetime number of tablets used	Mean s duration of use in year	Mean t weeks drug free pretes	Controlled for other drug use?[b]	Impaired memory and/or learning?	Other cognitive deficits?	Other cognitive deficits observed in tests of:
Parrott et al.	1998	10	>10	–	–	N	Y	N	
Parrot and Lasky	1998	15	>18	–	–	N	Y	N	
Schifano et al.	1998	150	26	0.6	–	N	Y	Y	Planning (Tower of London)
Morgan	1999	25	50	4.1	9	Y	Y[c]	Y	Matching familiar figures (accuracy)
Bolla et al.	1998	30	60	4.7	4[f]	N	Y[c,d]	–	
Gouzoulis-Mayfrank et al.	2000	28	93	2.3	6[f]	Y	Y[c]	Y	Selective and divided attention
Krystal et al.	1992	9	100[f]	5.1	9	N	Y	N	
Reneman et al.	2000	5	100[f]	–	19	N	Y[d]	–	
Verkes et al.[a]	2000	21	169	4.4	2	Y	Y	N	
Klugman et al.	1999	36	235	4.3	11	Y	Y	N	
McCann et al.	1999a	22	585[f]	4.5	14	N	Y	Y[c]	Logical reasoning, code substitution
Verkes et al.[a]	2000	21	741	4.5	1	Y	Y	Y	Simple and choice reaction time[e]
Wareing et al.[a]	2000	10	1200[f]	4.1	1	N	Y	Y	Matching 9-letter strings (accuracy)
Wareing et al.[a]	2000	10	1200[f]	3.9	46	N	Y	Y	Matching 9-letter strings (accuracy)

[a] Different groups from same study
[b] Used statistical techniques to control for the previous use of other illicit drugs
[c] Reported significant dose response relationships between measures of consumption of ecstasy and the degree of impairment of memory performance
[d] Reported significant relationships between the extent of depletion of brain 5-HT and impairment of memory performance
[e] Indicates that these effects diminished after ANCOVA, mainly due to education level and depression scores
[f] Estimated from lifetime dose in tablets or from frequency and duration of use

users exhibit persistent deficits in memory performance compared to ecstasy-na control participants. The details of 12 of these studies are presented in Table 3.

There are reports that novice ecstasy users (who had taken it 1–9 times) and moderate users (who had taken it 10 times or more) exhibit impaired memory performance compared to ecstasy-na controls (Parrott and Lasky 1998; Parrott et al. 1998). However, there are interpretative difficulties with these studies. The investigators did not report the period elapsed since the last use of ecstasy or histories of use of other illicit drugs, and did not control for the possible influence of other illicit drugs. Schifano et al. (1998) employed the Rivermead Behavioural Memory Test (RMBT; Wilson et al. 1985) to compare the episodic memory performance of 150 light to moderate ecstasy users, who had used the drug from 1 to 125 times, with that of 20 drug-na control participants. The ecstasy users showed significant impairment of memory performance compared to the control participants. Unfortunately, however, the ecstasy users in this study cannot be considered to be representative because they were all self-referred and many suffered from psychiatric disorders. There is no other empirical evidence that a pattern of relatively light ecstasy use is associated with persistent impairments of learning and memory.

There is a more substantial body of evidence relating to the memory performance of heavy recreational ecstasy users. Krystal et al. (1992) reported that heavy ecstasy users, who had consumed an average of about 130 tablets and had not used it for 3–26 weeks, showed a pattern of mild-to-moderate impairment in the initial and delayed paragraph test of the Wechsler Memory Scale (Wechsler 1945). There were a number of methodological problems with this study, however. Some of the participants had psychiatric histories, all had been administered tryptophan prior to testing and the performance of recreational ecstasy users was compared with age-matched norms rather than with that of non-users. Finally, although all participants were requested to abstain from psychoactive drugs for 3 weeks prior to testing, several reported previous use of amphetamine, cocaine, marijuana and LSD.

McCann et al. (1999a) compared heavy ecstasy users, who had taken ecstasy an average of 215 times and had been drug free for an average of about 14 weeks, with ecstasy-na control participants. On the first day of testing, the results of a serial add and subtract task indicated that the baseline working memory performance of ecstasy users was not different from that of control participants. However, the ecstasy users produced significantly lower scores on the second and third days of testing. Furthermore, the results of a delayed recall task revealed that the ecstasy users produced significantly lower baseline memory scores than control participants. Subsequently, Reneman et al. (2000) presented further evidence of persistent memory deficits in heavy ecstasy users. These investigators compared five ecstasy users, who had taken, on average, 218 tablets in their lifetime and had remained drug free for 2–11 months, with drug-na control participants. Ecstasy users showed significant deficits in delayed verbal recall compared to controls. There are also interpretative difficulties with these studies, however, because of the small sample size in the latter study, and because the investigators did not employ statistical techniques to control for the possible influence of the previous use of other illicit drugs by ecstasy users.

Nevertheless, other recent investigations have provided more compelling evidence that persistent impairments in learning and memory performance are primarily associated with a history of heavy recreational use of ecstasy. Morgan (1999) reported that immediate and delayed recall performance in the RMBT was markedly impaired in users, who had consumed an average of 50 tablets and had been drug free for an average of about 9 weeks, compared to ecstasy-na polydrug users and drug-na control participants. These group differences remained statistically significant after controlling for LSD use with analysis of covariance (ANCOVA). Klugman et al. (1999) compared a group of heavy ecstasy users, who had used a lifetime average of 235 tablets and had been drug free for an average of 11 weeks, with drug-na control participants. Ecstasy users showed significant impairments in immediate word recall, recognition memory for faces and in learning a repeatedly administered word list and sequence of digits. Associative tasks revealed impairment in the learning of spatial information. The use of other drugs did not correlate significantly with the deficits found in ecstasy users.

Gouzoulis-Mayfrank et al. (2000) compared heavy ecstasy users, who had taken, on average, about 94 tablets and had been drug free for 41 days, and who were also regular of users of cannabis, to two matched control groups, a non-user and a cannabis-user group. The ecstasy users had impaired immediate word recall compared to non-users and impaired immediate figure recall compared to participants in both control groups. They also displayed impaired performance in a verbal working memory task (digit span backward) compared to non-users. Furthermore, Wareing et al. (2000) presented evidence that working memory impairments in heavy ecstasy users persisted for at least 6 months after abstinence. These investigators compared a group of current heavy users with a group of previous heavy users who had abstained for at least 6 months, and a group of ecstasy-na controls. Both user groups, who reported that they had used an average of about 300 ecstasy tablets a year for 4 years, were significantly impaired in a random letter generation task compared to control participants. These group differences remained statistically significant after controlling for LSD, marijuana and amphetamine use with ANCOVA. Finally, Verkes et al. (2000) compared three groups of regular visitors to "rave" parties. One group comprised heavy ecstasy users who had taken ecstasy an average of 230 times and had been drug free for an average of 9 days. Another comprised moderate users who had taken ecstasy an average of 73 times and had been drug free for an average of about 16 days, and the third comprised ecstasy-na control participants. Both

groups of ecstasy users exhibited significantly shorter memory spans than non-users and the heavy users also displayed significantly poorer word and figure recognition compared to participants in the other two groups. Multiple regression analysis showed no influence of cumulative or recent use of any illicit drug other than ecstasy.

Despite the growing evidence that heavy ecstasy users display impaired memory performance, however, there are reports to the contrary. For example, Morgan (1998b) reported that there were no group differences in spatial span performance between moderate ecstasy users, who had taken an average of 35 tablets, polydrug control participants and non-drug control participants. Bolla et al. (1998) reported that there were no significant differences in overall memory performance between ecstasy users, who had taken 25–300 tablets, and ecstasy-naive control participants. Wareing et al. (2000) reported that there were no group differences between ten non-users, ten current heavy users and ten previously heavy users who had abstained from taking ecstasy for at least 6 months on measures of word span, pattern memory or spatial memory. Klugman et al. (1999) reported that performance in verbal and non-verbal working memory tests was unimpaired in heavy ecstasy users. Finally, Dafters et al. (1999) administered the RMBT and a memory span task to recreational ecstasy users, who had used between 1 and 60 tablets in the previous year, and found that memory performance did not correlate with ecstasy use in the previous 12-month period. However, the lack of evidence of impaired memory performance in the latter studies may be attributable to the use of relatively small sample sizes (see, for example, Wareing et al. 2000) or relatively moderate ecstasy users (see, for example, Bolla et al. 1998; Morgan 1998b; Dafters et al. 1999).

Further evidence that persistent impairments in learning and memory performance are primarily associated with a history of heavy recreational use of ecstasy is provided by reports of significant dose-response relations between the extent of memory impairment and the degree of previous exposure to ecstasy. Bolla et al. (1998) reported that when the average monthly dose of ecstasy was included in the regression models, dose was found to be associated with impairment in immediate verbal memory and delayed visual memory. Morgan (1999) reported trends towards statistically significant correlations between immediate recall performance and both the average dose of ecstasy used and the duration of use in years. Semple et al. (1999) reported that greater lifetime consumption of ecstasy was associated with reduced verbal memory performance. Finally, Gouzoulis-Mayfrank et al. (2000) reported that poor performance in immediate word recall and working memory tasks was associated with heavier ecstasy use.

Although McCann et al. (1999a) did not find any significant correlations between CSF 5-HIAA and cognitive performance, other investigators have reported that the degree of reduction in brain 5-HT is related to the extent of memory impairment in ecstasy users. Bolla et al. (1998) reported that the extent of memory impairment was correlated with the degree of reduction in brain 5-HT, as indexed by CSF 5-HIAA. Gerra et al. (2000) reported that, after a year of abstinence from ecstasy, prolactin AUCs were inversely correlated with previous exposure to ecstasy. Verkes et al. (2000) also reported that memory span performance correlated significantly with the placebo-corrected AUC of cortisol. Finally, Reneman et al. (2000) reported that cortical 5-HT$_{2A}$ binding (an indirect measure of 5-HT depletion) was associated with worse performance on delayed memory tests.

In summary, the growing number of independent reports of impaired recall and working memory performance in moderate to heavy recreational ecstasy users suggests that this is a reliable phenomenon. It is always possible that this may result from poor motivation rather than a selective cognitive deficit. However, the evidence that many other cognitive functions in ecstasy users are unimpaired suggests that this is unlikely.

Other cognitive deficits

A number of investigators have reported that ecstasy users exhibit selective deficits in memory performance without impairment of any other aspects of cognitive processing. Parrott et al. (1998) reported that light to moderate ecstasy users exhibited impaired memory performance without deficits in simple reaction time, choice reaction time, vigilance performance and Sternberg task reaction time. Parrot and Lasky (1998) reported that visual search performance of regular ecstasy users was not significantly different from those who had not taken ecstasy. Krystal et al. (1992) reported that, other than a pattern of mild-to-moderate memory impairment, heavy ecstasy users displayed a high level of cognitive function as reflected in a mean full scale IQ of 115 and the absence of a difference between verbal and performance IQ. Klugman et al. (1999) reported that performance in verbal fluency tests was unimpaired in heavy ecstasy users. Wareing et al. (2000) also reported that performance in verbal fluency tests was unimpaired in current and previous heavy ecstasy users. Finally, Morgan (1998b) reported that there were no differences between moderate ecstasy users, polydrug controls and non-drug controls in planning ability measured by a variant of "Tower of London" test (TOL; Shallice 1982).

However, other investigators have reported that, in addition to impairments of memory, heavy ecstasy users display impairments of planning, attention and accuracy in cognitively demanding tests. Schifano et al. (1998) reported that a group of 150 moderate ecstasy users showed significant impairment in TOL performance compared to 20 drug-na controls. The difference between the findings of Morgan (1998b) and Schifano et al. (1998) may be attributable to the larger sample size in the latter study. Furthermore, there is tentative support for the findings of Schifano et al. (1998) from Dafters et al. (1999). These investigators reported that sorting accu-

racy, following a rule change in the Behavioural Assessment of the Dysexecutive Syndrome test (Nelson 1976), was negatively correlated with extent of ecstasy use in the previous year.

Morgan (1998b) also reported that both moderate and heavy ecstasy users commit more errors on a Matching Familiar Figures test (Cairns and Cammock 1978). This test involves a trade-off between speed and accuracy and has been proposed to reflect cognitive impulsivity although it may also reflect visual discrimination, attention and/or central executive function. The task requires participants to match stimulus figures to an identical target among an array of six alternatives as quickly and accurately as possible. A group of moderate ecstasy users, who had taken an average of 35 tablets, committed significantly more matching errors than polydrug control participants and non-drug control participants. In a follow-up study, a group of heavier ecstasy users, who had taken an average of 50 tablets, were also found to commit significantly more matching errors than non-drug control participants (Morgan 1998b). The latter cognitive deficit is reminiscent of the findings of Wareing et al. (2000). These investigators reported that ecstasy na controls were consistently more accurate than current heavy users, and ex-heavy users in an information processing speed task that required them to classify nine letter strings as the same or different as quickly as possible. Verkes et al. (2000) also reported that simple and choice reaction times were longest in heavy ecstasy users, but these differences diminished after controlling for education level and mood.

Finally, Gouzoulis-Mayfrank et al. (2000) reported that ecstasy users displayed impaired selective and divided attention compared to cannabis users. However, the performance of the ecstasy users did not differ from that of control participants on the Stroop test or tests of visual scanning, visual-spatial memory span, word fluency, forward digit span and simple tests of attention. Further evidence that heavy ecstasy use is associated with selective deficits in attention and/or working memory is provided by McCann et al. (1999a). The latter investigators reported that, compared to ecstasy-na controls, heavy ecstasy users displayed impaired performance in a code substitution task and a logical reasoning task, but were unimpaired in tests of visuospatial rotation, time estimation and matching to sample.

Methodological problems and interpretative difficulties

Open trial studies of ecstasy users are subject to a number of methodological problems that create interpretative difficulties. Methodological problems include inadequate sampling and verification of drug histories, varying degrees of control for the possible influence of other illicit drugs and lack of baseline data concerning premorbid levels of functioning. The interpretative difficulties that arise include problems with the representativeness of samples, reliability of drug histories, and determination of causality of any psychological problems observed.

All of the studies reviewed above investigated self-referred ecstasy users who had responded to advertisements for volunteers, or employed a "snowball" technique to recruit participants (see, for example, Solowij et al. 1992). This constitutes an unknown bias, and, therefore all of these studies can be criticised on the grounds of inadequate sampling and possible lack of representativeness of their samples of ecstasy users. Furthermore, in open trial studies there is no control over which drugs have been consumed, their purity or potency, and investigators have tended to rely upon drug histories provided by participants. Clearly these are unlikely to be completely accurate for a number of reasons including fears about divulging information about engagement in an illegal activity, dishonesty, poor recall and inability to distinguish illicit drugs, particularly when taken in tablet form. Nevertheless, Schifano et al. (1998) reported that urine analyses were consistent with self-reported drug histories. Sherlock et al. (1999) reported that 29 of 31 respondents who reported taking ecstasy tablets on the night of the study had MDMA in their urine. Kikura et al. (1997) detected MDMA in all of the hair samples from seven individuals who reported that they had used ecstasy. Finally, Semple et al. (1999) reported that hair analysis generally confirmed the drug history given by ten heavy ecstasy users.

Previous investigations of the persistent psychological effects of ecstasy have also been hampered by uncertainties about drug purity. Tablets sold as "ecstasy" generally contain MDMA, or the related compounds MDEA and MDA, that produce similar neurotoxic effects (see, for example, Hegadoren et al. 1999). But they may also contain mixtures of a range of other psychoactive drugs including amphetamine, caffeine, ephedrine, selegiline or ketamine (Saunders 1995, 1997; Wolff et al. 1995). Nevertheless, annual assays of large samples of ecstasy tablets (2,400–4,500) in the Netherlands indicated that MDMA, MDEA or MDA was present in 77–90% of cases (Konjin et al. 1997). Similarly, assays of ecstasy tablets in Italy suggest that about 85–90% of more than 20,000 ecstasy tablets seized contained MDMA as the active ingredient, at a dosage of 100–150 mg per tablet (Schifano et al. 1998). Furthermore, Saunders has published extensive assay data for many brands of ecstasy available in Europe in his two books (Saunders 1995, 1997). Of samples of 69 branded pills with a logo and 46 unbranded tablets without a logo, only 5 (4%) of the tablets did not contain any MDMA or MDEA (Saunders 1997). Thus, although some tablets sold as "ecstasy" do not contain any MDMA or MDEA, most of them do.

In addition to using ecstasy, however, the vast majority of users also regularly use other illicit drugs including cannabis/marijuana, amphetamine, cocaine, LSD, psilocybin mushrooms and, to a lesser extent, benzodiazepines, barbiturates and ketamine (see, for example, Morgan 1999). Unfortunately, it is difficult to adequately

control for the use of other illicit drugs by relying on statistical techniques alone because the extent and duration of use of ecstasy tends to be highly correlated with that of other illicit drugs (see, for example, Morgan 1999). However, some investigators have catered for this problem by employing a design that incorporates a critical control group of individuals who have never used ecstasy but, otherwise, have similar histories of use of other illicit drugs (see, for example, Morgan 1998a,b, 1999; Gouzoulis-Mayfrank et al. 2000).

Finally, a fundamental difficulty of how to interpret the causality of associations between outcome measures and recreational use of ecstasy remains. Any differences between ecstasy users and non-users could indicate either a persistent effect of exposure to the drug or pre-existing differences between the two groups. For example, impulsiveness, and related personality traits such as venturesomeness, sensation seeking and novelty seeking, would be expected to be higher in young people who go on to use illicit drugs than in those who do not. Thus, individuals with low serotonergic function may both be more impulsive and more predisposed to using ecstasy (Gerra et al. 1998; Morgan 1998b), possibly in an attempt to self-medicate their serotonergic deficiency (Gerra et al. 1998). Nevertheless, it is also possible that extensive ecstasy use might induce further serotonergic depletion that could exacerbate premorbid differences in trait impulsiveness. This would be consistent with a report that recreational users who had consumed the most ecstasy in their lives had the most elevated trait impulsiveness scores (Morgan 1998b).

It is also possible that differences in affective state between ecstasy users and non-users may reflect premorbid differences that antedate the use of ecstasy and that individuals with low serotonergic function may both be depressed and predisposed to using ecstasy. However, reports that transient reductions in 5-HT activity produce a rapid lowering of mood (Young et al. 1985; Smith et al. 1987), and relapse in depressed patients (Delgado et al. 1990), suggest that it is also possible that depressed mood might be a persistent effect of ecstasy-induced neurotoxicity. Elevations of anxiety and hostility in heavy ecstasy users are more likely to be an effect of ecstasy-induced neurotoxicity because there is tentative evidence of remission of these affective states after 12 months of abstinence (Gerra et al. 2000).

Bolla and colleagues (1998) acknowledged that it is possible that differences in memory function and CSF 5-HIAA between ecstasy users and non-users might both be premorbid conditions, and that people with low 5-HT may both have memory problems and be predisposed to ecstasy use. However, they argue that the dose-related decreases in both memory and CSF 5-HIAA (similar to the decreases observed in primates who have been exposed to MDMA) make this unlikely. The conclusions of Bolla et al. (1998) are supported by other reports of dose-related decreases in memory performance (Morgan 1999; Semple et al. 1999; Gouzoulis-Mayfrank et al. 2000) and correlations between the extent of memory

impairment and reductions in brain 5-HT (Gerra et al. 2000; Reneman et al. 2000; Verkes et al. 2000). There is also preclinical evidence that MDMA causes persistent impairment of memory performance in rats (see, for example, Robinson et al. 1993; Marston et al. 1999). Thus, although some of the personality differences between ecstasy users and non-users may reflect premorbid individual differences, on balance, it would appear that the evidence suggests that extensive exposure to ecstasy *causes* the selective affective disturbances and cognitive impairments, including deficits in memory performance, exhibited by heavy ecstasy users.

Brain regions implicated

If some of the psychological problems observed in heavy ecstasy users are indeed attributable to neurotoxic lesions of central serotonergic systems, questions arise about which systems are most affected, how much serotonergic depletion is necessary for the manifestation of persistent psychological deficits and the prognosis for recovery. Some recent neuroimaging studies provide some evidence relating to the first question. Chang et al. (2000) used SPECT to study cerebral blood flow (CBF) and reported that abstinent heavy ecstasy users showed no significantly different global or regional CBF (rCBF) compared to control subjects. However, within 3 weeks of administration of a total dose of 3.5 mg/kg MDMA (comprised of two oral doses), rCBF remained decreased in the visual cortex, the caudate, superior parietal and dorsolateral frontal regions. On the other hand, two ecstasy users who were scanned 2–3 months after MDMA administration showed increased rather than decreased rCBF.

There is other neuroimaging evidence that suggests that the occipito-parietal region of the cortex may be especially affected by extensive exposure to ecstasy. In a recent SPECT study, Reneman et al. (2000) reported that 5-HT$_{2A}$ receptor binding was significantly elevated in the occipital cortex of heavy ecstasy users compared to drug-na controls. Dafters et al. (1999) reported that ecstasy use was positively correlated with absolute power in the alpha and beta frequency bands, and was negatively correlated with EEG coherence at sites that overly the main visual association pathways. Gamma et al. (2000) reported global increases of eyes open theta, alpha1 and beta2/3 power in heavy ecstasy users compared to ecstasy-na subjects, and spectral analysis revealed a right posterior increase of alpha2 power. Reduced coherence levels are associated with dysfunctional connectivity in the brain and increases in alpha and beta power suggest disturbed alertness mechanisms. Thus, these results may be consistent with evidence that heavy ecstasy users show deficits in attention (see, for example, McCann et al. 1999a) and tasks that demand visual discrimination (see, for example, Morgan 1998b; Wareing et al. 2000).

There is also neuroimaging evidence that the hippocampus, amygdala and frontal region of the cortex may

be particularly affected by extensive exposure to ecstasy. Obrocki et al. (1999) employed 2-[^{18}F]-flouro-2-deoxy-D-glucose PET to investigate regional brain glucose metabolism in seven heavy ecstasy users, who had used between 12 and 840 single doses and had remained drug free for 2–16 months. The ecstasy users exhibited reduced glucose metabolic uptake in the hippocampus, amygdala and cingulate cortex bilaterally. This is consistent with preclinical reports that the neocortex, hippocampus, caudate/putamen and thalamic nuclei are particularly vulnerable to MDMA neurotoxicity.

The serotonergic innervation of the amygdala and hippocampus by the dorsal raphe are believed to mediate anxiogenic effects (see, for example, Graeff 1993), and depletion of 5-HT in the amygdala facilitates aggressive behaviour (see, for example, Sarter and Markowitsch 1985). The hippocampus is important for memory functioning (see, for example, Hatzidimitriou et al. 1999), and combined lesions of the hippocampus and amygdala have been reported to produce severe amnesia in primates (see, for example, Mishkin 1978). Furthermore, lesions of three corticothalamic circuits, the dorsolateral prefrontal circuit, the lateral orbitofrontal circuit and the anterior cingulate circuit, are all associated with clinical syndromes that include poor recall of recently learned information, "executive function" deficits, depression and disinhibition (see, for example, Cummings 1993). Thus, the preliminary PET, SPECT and EEG findings, and the preclinical evidence, are consistent with the psychological evidence reviewed above that extensive exposure to ecstasy is associated with elevated anxiety, impulsiveness, aggression, hostility, depressed mood and persistent impairments of learning, episodic memory, working memory and attention.

The extent of damage to serotonergic systems that is necessary for the manifestation of overt cognitive deficits will vary from region to region and between individuals. In general, however, it is believed that neural compensatory mechanisms prevent reductions in the activity of specific monoamines in young people from having overt consequences. For example, behavioural deficits are not observed in Parkinson's disease until dopamine depletion has exceeded 80% (Hornykiewicz 1966). Hunter (1988) has argued that the same may be true of serotonergic denervation of the neocortex. Young people may be able to sustain a considerable degree of serotonergic depletion without, necessarily, exhibiting obvious manifestations in day to day behaviour because it is believed that they have what amounts to "surplus capacity". Cognitive impairments would not be expected to accompany ecstasy-induced neurotoxic lesions until the extent of damage exceeds certain thresholds. Nevertheless, Scheffel et al. (1998) reported an 89% loss of 5-HT transporters in the neocortex of a baboon that had been administered 5 mg/kg MDMA twice daily, for 4 consecutive days, between 13 and 40 days earlier. This suggests that MDMA can produce marked cortical depletion of 5-HT, and the evidence, presented earlier, that heavy ecstasy users exhibit persistent psychological problems

suggests that they may have exceeded a critical threshold of serotonergic depletion at which such deficits become apparent.

As indicated above, however, behavioural impairments do not necessarily accompany neurotoxic damage: they may only become evident if the neurotoxic damage is sufficiently extensive. Therefore, although ecstasy-induced neurotoxicity may be extremely persistent, it is possible that recovery from psychological impairments may occur if affected regions recover to above threshold levels. If, however, 5-HT function declines with age (see, for example, McEntee and Crook 1991), and an ecstasy-induced loss of serotonergic function fails to recover fully, then a subsequent age-related decline in serotonergic function may result in the re-emergence of psychological problems.

Clinical significance

The recent report that heavy ecstasy users scored significantly higher than controls on paranoid ideation, psychoticism, somatisation, obsessionality, anxiety, hostility, phobic anxiety, altered appetite and restless sleep factors of the SCL-90 (Parrott et al. 2000) suggests that heavy ecstasy use may result in clinically significant psychopathology. This view is consistent with case study reports of a range of psychiatric problems in ecstasy users including psychotic breakdown, paranoia, depression, panic disorder and various eating disorders (see, for example, McCann and Ricaurte 1991; McGuire et al. 1994; Schifano and Magni 1994; Series et al. 1994; Parrott and Lasky 1998).

Morgan (1999) reported that ecstasy users recalled about 75% of the number of ideas recalled by control participants in both the immediate and delayed story recall conditions of the RMBT (Wilson et al. 1985). Story recall in this test has been reported to be the best laboratory predictor of everyday memory performance (Sunderland et al. 1986). The differences reported by Morgan (1999) are in line with the findings of others (see, for example, McCann et al. 1999a; Gouzoulis-Mayfrank et al. 2000; Verkes et al. 2000). Although clinically small, these differences are comparable to memory deficits in refractory epilepsy patients produced by anticonvulsant agents (Verkes et al. 2000).

It is more difficult to evaluate the clinical significance of other cognitive impairments in ecstasy users. Impairments of working memory and attention have only been reported in particularly heavy ecstasy users (see, for example, McCann et al. 1999a,b; Gouzoulis-Mayfrank et al. 2000; Verkes et al. 2000; Wareing et al. 2000). Furthermore, even though subclinical cognitive decline in these functions may be present in heavy users, they might not notice these higher-order cognitive deficits over a long period of time. Therefore, they are likely to continue to use ecstasy and put themselves at substantial risk of further cognitive deterioration. Because widespread ecstasy use is a relatively new phenomenon and

users are typically young, it remains to be determined whether an age-related decline in 5-HT function increases their risk of developing dementia later in life.

Directions for future research

All of the methodological shortcomings with the previous research, outlined earlier, should be addressed in future studies. In future, it might be possible to randomly select a large sample of individuals with different patterns of drug use and then investigate the persistent psychological sequelae of a variety of different illicit drugs simultaneously (see, for example, Hammersley et al. 1999). Researchers should also attempt to corroborate self-reported current drug use and prior drug use with urine analysis and hair assays, respectively. If it is not possible to recruit exclusive ecstasy users, investigators should consider employing a design that facilitates the statistical control of previous use of other illicit drugs (see, for example, Morgan 1999).

A prospective, randomised, study of the chronic effects of pharmaceutical MDMA would be necessary to definitively determine its persistent effects on human behaviour, but ethical and legal constraints prevent such a study. It may be possible in future, however, to conduct a prospective, longitudinal study of the psychological sequelae of recreational ecstasy use. For example, it might be possible to assess a large sample of adolescents before they have taken ecstasy, and then again at subsequent time points, on the assumption that at least 10% will go on to experiment with the drug. Clearly, however, even this type of study would be fraught with ethical issues.

Future research should also explicitly investigate which aspect of recreational ecstasy use plays the most significant role in determining subsequent persistent psychological problems. The results of some of the studies reviewed earlier suggest that a gross estimate of lifelong exposure to ecstasy can predict the risk of future persistent psychological problems. But is likely that the pattern of use also plays a significant role. For example, Topp et al. (1999) have recently reported that young, female polydrug users, and those who binged on ecstasy for 48 h or more, appeared at most risk of experiencing harm that they attributed to their ecstasy use. Thus, it will be useful to further investigate the relationship between ecstasy exposure variables (for example, total past ecstasy dose, average monthly dose, frequency of use, bingeing, etc.) and cognitive dysfunction and determine if risk factors for the development of ecstasy-related cognitive deficits can be identified (for example, gender, IQ, psychiatric history).

There is also a pressing need for more information concerning the longevity of the psychological impairments exhibited by heavy ecstasy users. Clearly, further research with older participants with extensive histories of ecstasy use, as well as young participants who have abstained from using the drug for many months, or even years, is needed to clarify the long-term clinical implications of the psychological impairments seen in current users. In addition, very little is currently known about the decline of serotonergic function in humans over the life span. One possible direction for future research would be to compare markers of 5-HT transporter binding in healthy young people with those of healthy elderly individuals with SPECT or PET. It will also be important to determine whether similar cognitive deficits are seen in populations of individuals exposed to other selective 5-HT neurotoxins, such as fenfluramine (McCann et al. 1997). Finally, other new neuroimaging procedures, such as O^{15} PET, MEG and fMRI with EEG, are required to investigate the effects of experimentally manipulated 5-HT transmission on brain activity and cognitive function in ecstasy users.

Summary and conclusions

Since the late 1980s recreational use of ecstasy (MDMA) has become increasingly widespread, particularly in association with the "rave" dance scene and considerable evidence has accumulated that MDMA is a potent, selective neurotoxin that produces persistent depletion of the neurotransmitter 5-HT in both animals and humans. It is now clear, that chronic, heavy, recreational use of ecstasy is associated with sleep disorders, depressed mood, persistent elevation of anxiety, impulsiveness and hostility, and selective impairment of episodic memory, working memory and attention. There is tentative evidence that some of these cognitive impairments persist for at least 6 months after abstinence, whereas elevations of anxiety and hostility remit after a year of abstinence. The possibility that some of these psychological problems are caused by ecstasy-induced neurotoxicity is supported by preclinical evidence of MDMA-induced memory deficits, evidence of depleted serotonin in heavy ecstasy users and by dose-response relationships between the extent of exposure to ecstasy and the severity of cognitive impairments. Therefore, hundreds of thousands of young, heavy ecstasy users in the UK, and perhaps millions world wide, are at significant risk of persistent cognitive impairments and disturbances of affect and personality. Some of these problems may remit after protracted periods of abstinence. If the underlying neurotoxic lesions of 5-HT systems do not fully recover, however, and if the "surplus capacity" of brain 5-HT systems declines with age, then many heavy ecstasy users may also be at risk of recurrent psychopathology and premature cognitive decline in later life.

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