

Human psychopharmacology of Ecstasy (MDMA): a review of 15 years of empirical research

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MDMA (3,4-methylenedioxymethamphetamine) or 'Ecstasy' was scheduled as an illegal drug in 1986, but since then its recreational use has increased dramatically. This review covers 15 years of research into patterns of use, its acute psychological and physiological effects, and the long-term consequences of repeated use. MDMA is an indirect monoaminergic agonist, stimulating the release and inhibiting the reuptake of serotonin (5-HT) and, to a lesser extent, other neurotransmitters. Single doses of MDMA have been administered to human volunteers in double-blind placebo-controlled trials, although most findings are based upon recreational MDMA users. The 'massive' boost in neurotransmitter activity can generate intense feelings of elation and pleasure, also hyperactivity and hyperthermia. This psychophysiological arousal may be exacerbated by high ambient temperatures, overcrowding, prolonged dancing and other stimulant drugs. Occasionally the 'serotonin syndrome' reactions may prove fatal. In the days after Ecstasy use, around 80% of users report rebound depression and lethargy, due probably to monoaminergic depletion. Dosage escalation and chronic pharmacodynamic tolerance typically occur in regular users. Repeated doses of MDMA cause serotonergic neurotoxicity in laboratory animals, and there is extensive evidence for long-term neuropsychopharmacological damage in humans. Abstinent regular Ecstasy users often display reduced levels of 5-HT, 5-HIAA, tryptophan hydroxylase and serotonin transporter density; functional deficits in learning/memory, higher cognitive processing, sleep, appetite and psychiatric well-being, and, most paradoxically, 'loss of sexual interest/pleasure'. These psychobiological deficits are greatest in heavy Ecstasy users and may reflect serotonergic axonal loss in the higher brain regions, especially the frontal lobes, temporal lobes and hippocampus. These problems seem to remain long after the recreational use of Ecstasy has ceased, suggesting that the neuropharmacological damage may be permanent. Copyright © 2001 John Wiley & Sons, Ltd.

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HISTORICAL INTRODUCTION AND RECREATIONAL USE

MDMA (3,4-methylenedioxymethamphetamine) was patented by the German pharmaceutical company Merck in 1914. Apart from some US Army trials in the 1950s, it remained largely forgotten until the mid-1970s, when it was re-synthesised by the Californian experiential psychopharmacologist Alexander Shulgin. This led to the first descriptions of its recreational effects in humans, when it evoked: 'An easily controlled altered state of conscientiousness with emotional and sensual overtones' (Shulgin

and Nichols, 1978; Shulgin, 1986, p. 299). For several years, MDMA was one of many legal recreational agents taken by 'new age' seekers for spiritual enlightenment (Dye, 1982; Millman and Beeder, 1994; Shulgin, 1986). It was also sometimes used as a psychotherapeutic aid (Greer and Tolbert, 1986). The increasing popularity of MDMA, coupled with empirical evidence for its neurotoxicity in laboratory animals, led to its being temporarily scheduled by the American Food and Drug Administration (FDA) in June 1985. Heated debate followed this preliminary classification, but in November 1986 the FDA permanently scheduled it as a Class 1 illicit drug without any known medical uses (Cohen, 1998; McDowell and Kleber, 1994). The public controversy led to a number of newspaper and magazine articles, fuelling wider interest. Similar changes occurred in Europe. In the

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mid-1980s it was used by a few drug cognoscenti who spent their summers on the Mediterranean islands of Ibiza and Majorca. One of their favourite venues was a small beach club soon renamed Amnesia. Newspaper articles warned against this latest designer drug, but again this only raised its profile, so that many youngsters wanted to try it. The earlier street name of 'empathy' also fell out of favour, with Ecstasy sounding far more exciting (Parrott and Yeomans, 1995).

The popularity of MDMA increased during the late 1980s and early 1990s. During this period the archetypal pattern of use was single tablets taken intermittently. In a 1987 survey, Meilman *et al.* (1990) reported that few of their American college users had taken Ecstasy more frequently than once a month. Peroutka *et al.* (1988) surveyed a hundred American recreational Ecstasy users and found a lifetime usage ranging between 1 and 38 occasions. In a similar survey of 100 Australian users, 32% had taken it 3 times or fewer, 48% had used it on 4–15 occasions, while 20% had taken it more than 15 times (Solowij *et al.*, 1992). McDowell and Kleber (1994, p. 129) noted that, compared with most other illicit psychoactive drugs, patterns of Ecstasy use were unusual, with most users taking it occasionally and 'escalating usage uncommon'. In a British survey from 1993–94, the majority of the sample had taken it 10 times or fewer (Davison and Parrott, 1997). However during the early to mid-1990s, consumption patterns became more intense, so that by the late 1990s surveys revealed far higher usage rates. Reneman *et al.* (2000) reported an average lifetime consumption of 218 tablets in Holland (range 50–500). McCann *et al.* (1998) reported a mean usage of 228 tablets in the USA (range 70–400). The heavy Irish users in Parrott *et al.* (2000) had taken the drug on 371 occasions (range 30–1000). In the north of England, Heffernan *et al.* (2001, p. 339) defined regular users as those who took it '10 or more times per month'.

In terms of overall prevalence, the findings are strongly dependent on the population being sampled. In a Europe-wide study, 1–2% of the overall population reported having 'ever used' it (Griffiths and Vingoe, 1997), whereas surveys of younger age groups generate higher rates. Spruit (1999) sampled Dutch high-school children in the age range 12–18 years. The percentage who reported having 'ever taken' Ecstasy ranged from 5% of students attending regular schools to 9% of students at special schools and 29% of school truants. European school surveys in 1995–96 revealed rates that varied from around 8–9% in the Netherlands, the UK and Ireland, to 1–2% in Denmark, Finland and Sweden (Spruit, 1999). In a German

survey of 3021 14–24 year olds, Ecstasy use increased with age, was higher in males than females and had doubled between 1990 and 1995, while over that period the age of first use had decreased (Schuster *et al.*, 1998). In a British survey of 3699 second-year university students, 13% reported having ever taken Ecstasy, while 3% were regular users (Webb *et al.*, 1996). Most recreational users are regular dance clubbers, so that the highest rates of use emerge in surveys of clubbers and 'ravers'. Schifano (2000) reported a 59% prevalence of lifetime use among Italian disco clubbers. Wijngaart *et al.* (1997) found that 81% of attendees at 10 large Dutch raves or house parties had ever used Ecstasy, while 64% had taken it the previous night.

The illicit manufacture of MDMA is not a difficult chemical procedure, and most Ecstasy tablets do contain MDMA, although other drugs or drug mixtures are also found. Often they comprise ring-substituted amphetamine derivatives such as MDA (3,4-methylenedioxyamphetamine) or MDE (3,4-methylenedioxyethylamphetamine). Neurochemically these are very similar to MDMA; indeed, one of the metabolic breakdown products of MDMA is MDA (De la Torre *et al.*, 2000). The acute behavioural and physiological effects of MDMA, MDA and MDE seem to be very similar (Gouzoulis-Mayfrank *et al.*, 1998; Hermle *et al.*, 1993; Spruit, 2001), and they are all strongly neurotoxic in laboratory animals (Huether *et al.*, 1997; Ricaurte *et al.*, 2000). The World Health Organization (1996, p. 6) concluded that the term 'Ecstasy' was 'virtually generic' for substituted amphetamines such as MDA, MDE and MDMA. Several surveys have investigated the percentage of tablets which contain MDMA or other constituents. An Italian survey found that around 90% comprised pure MDMA, while most of the others contained MDA or MDE (Schifano *et al.*, 1998). In London, most Ecstasy tablets contained MDMA, although MDE and MDMA/MDE mixtures were occasionally found, while 10% of samples contained ketamine mixed with amphetamine or ephedrine (King, 2001). Amphetamine, codeine, caffeine, salicylates or pharmacologically inert placebos may also be sold as 'Ecstasy', while Baggott *et al.* (2000) found many dextromethorphan pills in their survey in the West Coast of the USA. In the Netherlands, the national Drug Information Monitoring System found that around 75% of samples contained MDMA, although MDE was very common in some years. Their most recent survey concluded that 'The percentage of MDMA pills increased more than ever before, indicating among other things that consumers prefer the conventional product' (Spruit, 2001, p. 23).

NEUROPHARMACOLOGY OF MDMA

MDMA and other ring-substituted amphetamine derivatives such as MDA and MDE are potent indirect monoaminergic agonists and reuptake inhibitors. They readily diffuse across the cell membrane, and in the presynapse cause an efflux of serotonin (5-hydroxytryptamine or 5-HT) from vesicular stores. This cytoplasmic 5-HT is then released into the synaptic cleft by the actions of the serotonin transporter (Berger *et al.*, 1992). An acute dose of MDMA can release around 80% of central serotonin stores (Green *et al.*, 1995; Huether *et al.*, 1997). Ring-substituted amphetamine derivatives such as MDMA have been termed 'neurochemically messy', because although their main effects are on serotonin, they also boost dopamine, noradrenaline, acetylcholine and histamine (Liechti and Vollenweider, 2001; McDowell and Kleber, 1994). Many of these neurochemical effects are interlinked. For instance, the MDMA-induced activation of 5-HT_{2A} receptors facilitates the release of dopamine (Huether *et al.*, 1997). Drugs which increase cytosolic serotonin, either by increasing synthesis or decreasing degradation, tend to enhance the MDMA-induced release of serotonin, whereas drugs that deplete serotonin presynaptic vesicle stores, or block its synthesis, tend to attenuate the MDMA response (Huether *et al.*, 1997). This area is a minefield of potential drug interactions, which may help explain why so many regular Ecstasy users tend to be polydrug users (Fox *et al.*, 2001a; Parrott *et al.*, 2000, 2001; see final section).

The pharmacokinetics of MDMA have been described as non-linear: a small increase in dosage leads to a 'disproportionate rise' in drug plasma concentration, thus possibly explaining why some individuals develop acute toxic reactions after apparently normal doses (De al Torre *et al.*, 2000, p. 104). This may also contribute to the higher rates of physical and psychological side effects occasionally noted in females (Topp *et al.*, 1999), due to their lower mean body weight. Another potentially important factor is the level of the hepatic enzyme CYP2D6, which regulates the desmethylation and metabolic breakdown of MDMA and MDA. Around 10% of the white population are deficient in this enzyme, and it has been hypothesised that the resulting high or prolonged serum concentrations may make them particularly susceptible to adverse drug reactions (Tucker *et al.*, 1994). The after effects of MDMA, and the neurochemical effects of repeated doses, are covered in later sections.

ACUTE MDMA USE

Controlled laboratory studies in humans

Studies of single acute doses of MDMA, employing standard double-blind placebo-controlled procedures, have been undertaken in the laboratory. Gamma *et al.* (2000) administered 1.7 mg/kg body weight MDMA and matching placebo to 16 drug-naïve volunteers. Positron emission tomography (PET) scans showed increased blood flow in the ventromedial frontal cortex, occipital cortex, inferior temporal lobe and cerebellum, together with decreased blood flow in the motor cortex, somatosensory cortex, temporal lobe and other regions. Psychometric self-ratings indicated slight feelings of derealisation, heightened mood, greater extraversion, mild perceptual alterations and difficulties in concentration. These findings were similar to those reported in an earlier study of 13 healthy volunteers by the same Swiss group (Vollenweider *et al.*, 1998). These findings were then combined with a third study of 45 medically screened volunteers in an overview that focused on gender differences (Liechti *et al.*, 2001). The combined data revealed that MDMA significantly altered nearly every dependent variable. Physiological measures of heart rate, blood pressure, body temperature and other sympathetic indices were all significantly increased. On the psychological scales nearly every mood state was significantly boosted, which generated a somewhat surprising overall pattern of mood changes. Thus self-rated extraversion was significantly increased, but so was self-rated introversion. Similarly, there was a highly significant increase in every positive mood state, yet this was accompanied by statistically significant increases in depressiveness and anxiety. In overall terms, MDMA seemed to have a general releasing function, in some ways not dissimilar from that of LSD (see Table 1 in Liechti *et al.*, 2001). In another laboratory study, Gouzoulis-Mayfrank *et al.* (1998) found a similar range of responses to an acute dose of 2 mg/kg MDE: 'Intense euphoria was present in two subjects; however, sad feelings were also reported. Most subjects displayed increased energy, drive and talkativeness. However two subjects were rather quiet and withdrawn.' Returning to MDMA, several gender differences were apparent, despite the doses being weight corrected (Liechti *et al.*, 2001). Thus females showed significantly greater perceptual change, thought disturbance, fear of loss of body control and total side effects, whereas males showed greater activation and increase in blood pressure. The same group of researchers has undertaken a series of selective receptor antagonist studies, involving

Table 1. Drug use characteristics of low, medium and high ecstasy users and non-user controls (Fox *et al.*, 2001a)

Drug group	Control	Low use	Medium use	High use	<i>p</i> -value (ANOVA)
<i>Ecstasy use (tablets)</i>					
Lifetime (defining criterion)	0	1–99	100–499	500+	
Usual tablets per occasion	—	1.8	2.2	3.7	< 0.01
Max. no. tablets ever taken	—	3.6	5.1	10.9	< 0.01
<i>Other Drugs (% users)</i>					
Cannabis	100	100	100	100	
Amphetamine	55	93	100	100	< 0.001
Cocaine	25	71	93	100	< 0.001
LSD	20	86	93	100	< 0.001
Opiates	10	14	64	64	
Psilocybin mushrooms	20	50	86	91	< 0.001
Barbiturates	15	0	57	36	
Nicotine	60	71	64	82	
Alcohol	95	79	79	73	

For details of the paired group comparisons see Fox *et al.* (2001a).

citalopram, ketanserin and haloperidol, in MDMA-treated volunteers. They concluded that carrier-mediated serotonin release was mainly responsible for its positive mood and entactogenic properties, while dopamine functions underlay the stimulant/elatory properties (Liechti and Vollenweider, 2001, this issue).

The publication of Vollenweider *et al.*'s (1998) laboratory study stimulated a debate about the ethics of MDMA administration in humans. Gijsman *et al.* (1999, p. 597) argued: 'Although the described effects of MDMA are very interesting, we believe that this study should not have been performed because of the risk of long-term effects . . . It cannot be excluded and even seems likely that administration of a single dose of MDMA to humans causes damage of serotonergic neurones.' Many of the commentaries and replies focused on the question of whether a single dose of MDMA could cause statistically significant levels of neural damage in animals and by implication, humans (Lieberman and Aghajanian, 1999; McCann and Ricaurte, 2001a; Vollenweider *et al.*, 1999, 2001). That there is empirical evidence for significant neural damage after single high doses in animals (McCann and Ricaurte, 2001a), together with evidence of severe abreaactions in humans after just half a tablet (Spatt *et al.*, 1997), is of great concern. It also leaves open the question of whether single doses produce slight changes which are not measurable using standard statistical estimation procedures, yet which accumulate to produce quantifiable damage after several doses. The USA's National Institute of Mental Health (NIMH) convened a workshop to debate the ethical issues in this and related issues; they concluded that volunteers must be fully informed of

all risks, and that any risks must be fully justified in terms of potential gains (Lieberman and Aghajanian, 1999). Future studies should ensure that all participants are fully conversant with the extensive literature on the neurotoxicity of MDMA (e.g. by informed doctors or psychopharmacologists) and should be designed to generate novel information of considerable importance.

Although the laboratory-controlled studies of ring-substituted amphetamine derivatives are designed to minimise any immediate risks, some adverse reactions have been reported. Hermle *et al.* (1993) administered 140 mg MDE and/or placebo to eight male academics. Reactions were favourable in seven of the volunteers, who experienced feelings of stimulation, greater communication, insight, empathy and peace. However the eighth suffered a severe anxiety reaction, in which unpleasant thoughts and somatic feelings predominated. In a follow-up study of three male and three female academics (Hermle *et al.*, 1993), five had positive on-drug experiences, but one developed severe psychotic symptoms, with delusions of reference, auditory and visual hallucinations, and loss of control of thought. The researchers provided reassurance during this untoward experience, which lasted for 2.5 h. One of the five participants who had experienced positive moods while on the drug reported a brief depressive episode several days later (see section on rebound effects). Adverse drug responses, together with unpleasant sequelae on the day after drug administration, have also been reported in laboratory studies of MDMA (Liechti *et al.*, 2001). Thus acute abreaactions can occur even under closely controlled laboratory conditions, with healthy volunteers resting at normal temperatures.

The natural environment

The euphoric feelings of recreational Ecstasy users are illustrated in the following descriptions of American clubbers: 'On Ecstasy, happiness and beauty consume every thought, feeling, sensation, and desire' . . . 'Very intense. I felt as if nothing could be wrong or make me feel unhappy' . . . 'A very peaceful high. I felt much in love with everyone around.' Sometimes these euphoric feelings were described in sexual terms: 'Like having the most fantastic four hour orgasm' . . . 'Waves of kisses, accompanied by a sonic hug, like your body is covered with sexually responsive skin' . . . 'Floating, flying, highly sexual' (Cohen, 1998, p. 80–81). These feelings seem to be more intense and pleasurable than those described in the laboratory (like cannabis), reflecting the importance of expectancy and environment. However, it may also be that the acute mood effects are enhanced by temperature, overcrowding and exercise, since animal research shows that the MDMA-induced monoaminergic release is increased by these stimulatory factors (Huether *et al.*, 1997). This is discussed more fully in the final section.

Ecstasy has been termed the 'love drug' (Saunders, 1995), and a questionnaire survey of Californian users revealed that 70% had experienced sexual intercourse under its influence. Around 88% of females and 74% of males reported that the sensuality of the experience was enhanced. Males often reported that orgasm was delayed, so prolonging and enhancing pleasure, although the maintenance of an erection was sometimes difficult. Some females reported it was easier to reach orgasm, whereas others stated it was unchanged or less easy. One frequent comment was that MDMA was a 'sensual not a sexual drug' (Buffum and Moser, 1986, p. 358). MDMA has also been used in psychotherapy (like LSD), where the emotional insights and non-judgmental feelings are said to be beneficial for re-establishing positive interpersonal relationships (Greer and Tolbert, 1986, 1998). But, as noted in the laboratory, not every reaction to Ecstasy is positive. One American clubber noted: 'I felt like I was surrounded by water and drowning. It must have been panic' (Cohen, 1998, p. 82). Twenty-five percent of a British sample reported having at least one drug abreaction, in which unpleasant bodily sensations predominated (Davison and Parrott, 1997). Dizziness, numbness, blurred vision, inability to urinate, tremors/shakes and vomiting were listed as adverse on-drug experiences by Australian users (Topp *et al.*, 1999).

Ecstasy is usually taken as oral tablets or 'pills', but there are three alternative administration routes: injection, intranasal and smoking. In Topp *et al.*'s (1999) Australian survey, 16% had injected it, while 30% had snorted MDMA powders. The Ecstasy injectors comprised polydrug users who had previously injected heroin or amphetamine. Their reasons for injecting it included curiosity, the rush or high, that friends had tried injections and that it was more economical. However, most had returned to the oral or nasal route because of adverse health effects, dependency, the hit was too intense to enjoy or the come-down was too rapid. Smoking cannabis/Ecstasy joints has occasionally been reported, but I am not aware of any empirical studies investigating this particular drug combination. There is also little empirical information on the effects of Ecstasy powders, although one experienced user recently informed me that the 'hit' from Ecstasy powders was far more intense than that from tablets, but shorter lasting. He also noted that his skin became hot to the touch. The club venue where many clubbers were using these Ecstasy powders had arranged for staff to circulate amongst the dancers and spray them with cold water from plastic bottles.

Physiological effects and the serotonin syndrome

The acute physiological effects of MDMA can be very powerful. The boost in central and peripheral monoamine activity stimulates core bodily functions such as respiration, blood pressure and heart rate. This sympathomimetic stimulation is probably exacerbated by the environmental conditions. MDMA induces hyperkinesis in laboratory rats (Dafters, 1994), and similar increases in physical activity and movement are apparent in humans. The repetitive rhythmical music at the club venues also encourages prolonged periods of dancing. Overcrowding probably also heightens these effects, since the behavioural effects of amphetamines in laboratory rats are exacerbated by overcrowding or 'aggregate toxicity' (Green *et al.*, 1995). One of the most important physiological effects of MDMA is impaired thermoregulation. When MDMA-treated rats are placed in a cold environment they cool down excessively, whereas in hot environments they overheat in a dose-dependent manner (Dafters, 1994; Gordon *et al.*, 1991). This increase in core body temperature also heightens the resulting serotonergic neurotoxicity. Marlberg and Seiden (1998) found that MDMA-treated rats not only increased their core body temperature as the ambient temperature increased (saline-treated rats maintained normal body temperature), but that the degree of

serotonin nerve damage was a direct function of the prevailing environmental temperature. Most clubs are hot and crowded, with inadequate temperature and humidity control, so that a major problem for Ecstasy users is overheating and the development of hyperthermia (Wijngaart *et al.*, 1997). One clubber noted: 'Feels like your blood is 115 degrees Fahrenheit' (Cohen, 1998, p. 82), while Henry *et al.* (1992) recorded a body temperature of 43°C in one of their medical emergencies. Subjective reports of increased body temperature, sweating and dehydration were noted by 80–90% of Ecstasy-using clubbers and dancers (Davison and Parrott, 1997). Over the years a number of Ecstasy users have died of hyperthermia, through associated medical complications such as acute renal failure, cardiac arrest, disseminated intravascular coagulation (with death by bleeding from multiple sites), liver failure, convulsions or cerebral haemorrhage (Cohen, 1998; Green *et al.*, 1995; Henry *et al.*, 1992).

The majority of Ecstasy users are aware of the dangers of overheating and wear scanty clothing while dancing (Suy *et al.*, 1999). Spontaneous nude sessions have even been reported at some club venues (Mixmag, 2001), although the more boring and conventional clubbers visit 'chill-out' rooms to recuperate, where the relaxed ambience and more meditative music help prevent the hyperthermia from reaching lethal levels (Wijngaart *et al.*, 1997). The animal literature confirms that when MDMA-treated rats are placed in a cooler environment, they soon become less hyperthermic (Dafters, 1994). However, after cooling down many clubbers return to the dance floor, where they overheat again. These periods of increased body/brain temperature are probably important for causing neurotoxicity (see final sections). Although most reports are of overheating, periods of shivering are also described; these are due to the MDMA-induced impairments in homeostatic temperature control. Topp *et al.* (1999) noted that 'hot and cold flushes' and 'profuse sweating' were two of the most commonly reported physical side effects of Ecstasy.

Fluid control is another crucial factor. Following a number of hyperthermia-induced deaths in the mid-1990s, the importance of fluid replacement to reverse that lost through sweating became more widely recognised. Unfortunately excessive fluid intake can cause hyponatraemia: the dilution of electrolytes such as sodium and potassium in the systemic circulation. This condition can also prove fatal (Green *et al.*, 1995; Henry *et al.*, 1992). This was illustrated in the case of the British teenager Leah Betts, who was so

concerned about fluid loss that she drank several litres of water after having taken an Ecstasy tablet, but developed lethal hyponatraemia; her autopsy revealed MDMA uncontaminated by other substances (Parrott, *in press*).

The serotonin syndrome is caused by drugs or drug combinations that produce a rapid boost in intrasynaptic 5-hydroxytryptamine (Gillman, 1998). Its symptoms include behavioural hyperactivity, mental confusion, agitation, hyperreflexia, hyperpyrexia (fever), tachycardia, shivering, clonus, myoclonus, ocular oscillations and tremor (Gillman, 1999; Huether *et al.*, 1997). The serotonin syndrome has sometimes been conceptualised as rare or idiosyncratic, but Gillman (1998) noted that it comprised a continuum of responses from mild to severe. The mild serotonin syndrome was defined as three symptoms from the above list, whereas severe serotonergic syndrome responses comprised most of them. Inspection of the above symptoms reveals that most Ecstasy users develop a mild serotonin syndrome each time they take the drug. Tachycardia, hyperthermia and overarousal are routinely noted in field trials of recreational users (Davison and Parrott, 1997; Topp *et al.*, 1999), and sympathomimetic stimulation also develops when MDMA is administered in the laboratory (Liechti *et al.*, 2001). Mental confusion and impaired thought control are typical on-drug experiences (Davison and Parrott, 1997; Liechti *et al.*, 2001), while mental task performance is objectively impaired (Curran and Travill, 1997; Parrott and Lasky, 1998). There are many further signs of serotonin overactivity (Green *et al.*, 1995), which include trismus (jaw clenching) and bruxism (tooth grinding), explaining why many clubbers chew gum and develop dental problems. Many other drugs, medicines and herbal remedies affect serotonin, dopamine and noradrenaline. These may all interact with external stimulatory factors (temperature, overcrowding, noise) to increase the strength and unpredictability of any acute monoaminergic response to MDMA (Parrott, *in press*). The initial triage of casualties within the club/rave environment is described by Suy *et al.* (1999), while the medical treatment of toxic drug reactions is covered by Cohen (1998), Gillman (1997, 1998) and Green *et al.* (1995).

TOLERANCE AND DEPENDENCE

There are various indications that the positive effects of MDMA subside with repeated use. Alexander Shulgin, the Californian pharmacologist and drug synthesiser who initiated the recreational use of

MDMA in the late 1970s, commented that its positive effects declined after the first seven experiences. American college students in the late 1980s also stated that the positive effects weakened with repeated use, whereas unwanted side effects increased (Peroutka *et al.*, 1988). Merrill (1996) similarly noted that regular Ecstasy users often increased their self-dosage in order to overcome short-term tolerance. Parrott and Lasky (1998) noted that the novice users reported taking slightly fewer tablets than more experienced users. Fox *et al.* (2001a) contrasted three Ecstasy user subgroups: low users (1–99 tablets in lifetime), medium users (100–499 tablets) and high users (500+ tablets). As lifetime experience increased, there was a parallel increase in the number of tablets normally consumed per occasion, together with a greater maximum number of tablets taken on any one occasion (Table 1). In the most recent studies, some of the most experienced users have taken very large numbers of tablets on single occasions. Reports of 5–10 tablets per occasion were very rare a few years ago, but now reports of 10–20 tablets are not infrequent. The most we have encountered is 50 tablets in one night, in an individual with severe psychobiological problems (Soar *et al.*, in preparation; see below). Many regular users also complain that the tablets are getting 'weaker' (Turner *et al.*, 1999). Chronic pharmacodynamic tolerance and dosage escalation are the norm with cocaine and amphetamine. The evidence for Ecstasy is also strongly indicative of marked tolerance, although this is another area where more systematic empirical data are needed.

Unlike the classic drugs of addiction, Ecstasy shows few indications of physical dependence or drug craving. In the late 1980s and early 1990s dependence was certainly not seen as a problem. Solowij *et al.* (1992) noted that only 2 of 100 users felt they were dependent on Ecstasy. Yet a more recent survey by the same Australian team (Topp *et al.*, 1999) found that 17% of recreational users who had injected MDMA reported dependency. Thus the prevalence of dependency seems to have increased as usage has intensified. Janssen (1999) described three case studies of Ecstasy dependence, where each individual had increased their self-dosing, suffered problems directly related to their heavy drug use, and experienced difficulties when attempting to quit. However, all three became abstinent from MDMA, although two remained dependent on alcohol or opiates, and all were still tobacco smokers. Thus even when physical dependence on Ecstasy does develop, in comparison with other psychoactive drugs it seems easier to resolve. There are, however, informal indications for

psychological dependence on Ecstasy, with some of our regular users stating that they need Ecstasy to enjoy themselves and feel bored without it. This is another under-researched area, although one of the first empirical studies is published in the current issue (Cottler *et al.*, 2001). Despite the young age of these users (mean 19.3 years), 43% of this US sample met the DSM-IV criteria for Ecstasy dependence, and 34% met the criteria for abuse.

Another important topic is how and why recreational users decide to stop using Ecstasy. In the absence of published human data, the findings from a study of intravenous self-administration in rhesus monkeys may be relevant. Fantegrossi *et al.* (2001, p. S34) noted: 'Intriguingly, monkeys gradually ceased responding for MDMA after an extended period (approximately 2 years) of self-administration; however, responding for cocaine and amphetamine was not diminished.' Informal interviews with former users have revealed that while some gradually reduced their usage before quitting, others stopped more abruptly after a bad experience (Parrott, 2000). However, continuing users often report an increased frequency and/or intensity of use. The reasons for these individual differences probably reflect a complex array of psychobiological and socioeconomic factors. The psychobiological and socioeconomic problems of many regular users are described below. The crucial factor may be a changing cost-benefit ratio, when the numerous problems associated with repeated drug use (Schifano *et al.*, 2000; Parrott *et al.*, 2000; Topp *et al.*, 1999) gradually outweigh the earlier apparent gains.

REBOUND EFFECTS: MID-WEEK DEPRESSION AND ANHEDONIA

One frequent complaint is of poor moods in the days after taking Ecstasy. In laboratory studies of acute MDMA administration, fatigue and negative feelings were reported in the 24 h afterwards (Liechti *et al.*, 2001); unfortunately moods were not assessed for longer than 24 h, so any deficits in subsequent days would have been missed. Rebound depression has however been documented in two laboratory studies of MDE (Gouzoulis-Meyfrank *et al.*, 1998; Hermle *et al.*, 1993). These findings demonstrate that rebound abreactions to the ring-substituted amphetamine derivatives can occur under closely controlled laboratory conditions. These poor moods probably reflect reduced monoamine levels, although this does not seem to have been empirically investigated in humans. Animal research shows a dose-dependent decrease in cerebrospinal 5-HT and 5-HIAA (5-Hydroxyindoleacetic acid)

for several days after MDMA administration (Battaglia *et al.*, 1988). There are numerous descriptions of adverse psychobiological sequelae in field studies. Curran (2000) surveyed over 400 recreational users, 83% of whom reported low moods and concentration or memory difficulties in the days following weekend Ecstasy use. Curran and Travill (1997) monitored the moods of young British clubbers soon after they had self-administered Ecstasy, then at 1 and 4 days later. The Ecstasy users reported comparatively better moods on-drug than the controls, who were mainly alcohol drinkers. The Ecstasy users then reported worse moods in the days afterwards, with several showing clinically borderline levels of mid-week depression. Parrott and Lasky (1998) found excellent moods in both Ecstasy users and non-user controls who were clubbing with their friends on a Saturday night. However, 2 days later the novice and regular Ecstasy users reported feeling significantly more sad, unsociable, depressed and unpleasant than the non-user controls. Since the on-drug moods of the Ecstasy users were not significantly better than those of the controls, over the whole week the average moods in the Ecstasy users were paradoxically slightly worse than in the non-users. One intriguing effect was the strong rebound effect in the novice users in both of the above studies (Curran and Travill, 1997; Parrott and Lasky, 1998). This might be a reflection of relatively unimpaired serotonin systems, which would make them initially sensitive to the positive mood effects of MDMA (Shulgin, 1986; see earlier section), while suffering strong depletion effects afterwards.

MDMA NEUROTOXICITY IN LABORATORY ANIMALS

The damaging effects of MDMA on serotonin neurones in animals were first demonstrated in the mid-1980s. The neurotoxic effects of stimulants such as methamphetamine were systematically investigated, but when the ring-substituted derivatives MDA and MDMA were tested, the serotonergic neural damage was found to be far more pronounced (Ricaurte *et al.*, 1985; Schmidt *et al.*, 1986). The main finding was the loss of distal axon terminals in the higher brain regions, such as the neocortex and hippocampus. The cell bodies in the raphe nuclei of the brain stem were not damaged, but during the months afterwards there was a proliferation of new axon growth nearer to the cell body, a pattern of neuroanatomic changes termed 'neuronal pruning' (Fischer *et al.*, 1995). This neural damage occurred after very high single doses or after successive moder-

ate doses. In contrast, other monoaminergic neural systems were spared. This serotonergic damage has been confirmed across a variety of animal species, including monkeys and other primates. Neuronal recovery is most apparent in phylogenetically lower species such as rats, whereas monkeys and other primates show only partial recovery even after a prolonged period (Ricaurte *et al.*, 2000). Since the doses involved are quite high, some commentators have questioned their relevance to humans (Saunders, 1995). However when standard inter-species scaling formulae are applied, the animal doses are firmly within the recreational dosage range for humans (McCann and Ricaurte, 2001a; Ricaurte *et al.*, 2000).

METHODOLOGICAL COMPLEXITIES OF HUMAN RESEARCH

The animal findings raise the question of whether serotonergic neural damage also occurs in humans. Double-blind placebo-controlled trials involving repeated doses would obviously be completely unethical (Parrott, 2000). Instead the same procedures need to be followed as with other illicit drugs such as cocaine or heroin, namely to compare Ecstasy users with non-users. The self-selected nature of these groups does however cause numerous methodological problems and interpretative difficulties—which make this research topic so intriguing. Many studies do not attempt to include a control group (Dafters, 1999; Davison and Parrott, 1997; Schifano, 1998; Topp *et al.*, 1999; Zakzanis and Young, 2001). Most do include a control condition, although one recurring problem is how the group should be defined. Age, gender and educational background are generally not too difficult to assess and match. The most difficult question is what drug history the control group should demonstrate. Some studies use legal drug users (Curran and Travill, 1997; Gerra *et al.*, 1998), others use regular cannabis users (Gouzoulis-Mayfrank *et al.*, 2000; Rodgers, 2000), while some use polydrug users with a wider illicit drug history (McCann *et al.*, 1999; Verkes *et al.*, 2001). Several studies have used two control groups. Morgan (1998, 1999) assessed both legal drug users and an illicit polydrug group who had never taken Ecstasy. Gouzoulis-Mayfrank *et al.* (2000) and Rodgers (2000) similarly used one control group of legal drug users and a second control group of cannabis smokers matched with the Ecstasy users on past cannabis use. Ecstasy users tend to use not just cannabis, but a wide range of illicit drugs such as amphetamine and cocaine (Pedersen and Skrandal, 1999). Parrott *et al.* (2001) therefore investigated six

groups: non-drug users, legal drug users, cannabis users, illicit polydrug users who had never taken Ecstasy, light Ecstasy polydrug users, and heavy Ecstasy users. It was found that as drug use widened, so it also intensified. The heavy Ecstasy polydrug users were not only heavy alcohol drinkers and tobacco smokers, but also the most extensive users of stimulants and hallucinogens (Milani *et al.*, 2000; Parrott *et al.*, 2001).

Recreational Ecstasy users also tend to display irregular circadian patterns, with weekend nights spent dancing and clubbing, followed by periods of 'crashing out' for physical and mental recovery. Verkes *et al.* (2001) controlled for this factor by using a control group of regular ravers and clubbers who followed similar patterns of irregular and disrupted sleep. Zakzanis and Young (2001) ensured that their regular Ecstasy users had 'at least seven nights of 7 to 9 hours of continuous sleep' before being administered the cognitive test battery. Another related factor is the drug-free period required before testing. Some studies require an Ecstasy-free period of 1–3 weeks (Gouzoulis-Mayfrank *et al.*, 2000; McCann *et al.*, 1999), and this procedure should be recommended for any future studies. Others have required an Ecstasy-free period of just 2 or 3 days (Croft *et al.*, 2001; Morgan, 1998, 1999), or failed to define a cut-off point (Heffernan *et al.*, 2001; Parrott *et al.*, 1998; Wareing *et al.*, 2000), which means that some of the participants may still have been experiencing rebound effects. There is also the problem of other psychoactive drug effects, whether legal (alcohol, nicotine) or illicit (cannabis, amphetamine, opiates). Should normal drug consumption be allowed to continue, in which case their residual effects may be evident, or should a period of drug withdrawal be required, in which case the deleterious effects of abstinence may be evident? For further debate on the many methodological complexities in this area, Curran's (2000) comprehensive review is recommended.

CHRONIC OR REPEATED ECSTASY USE

Neuropharmacological aspects

The integrity of the serotonin (5-HT) system in the living human brain can be estimated in several ways. (Note: I am not aware of any postmortem studies of former users.) Ricaurte *et al.* (1990) measured levels of the 5-HT metabolite 5-HIAA in cerebrospinal fluid and found significant reductions in the Ecstasy users; this was confirmed by McCann *et al.* (1994) and Bolla *et al.* (1998). Another standard procedure is to

challenge with a serotonergic agonist, such as l-tryptophan or d-fenfluramine. This generates an acute boost in prolactin and cortisol; so by measuring the peak response and 'area under the curve' the strength of serotonergic functioning can be indirectly estimated. In two early studies, Price *et al.* (1987) found a non-significant trend towards a reduced prolactin response, while Peroutka *et al.* (1988) found unchanged levels of these serotonergic metabolites. These early studies used college students with comparatively light experience of taking Ecstasy. More recent studies involving heavier users have found some significant deficits. Gerra *et al.* (1998) demonstrated that the prolactin and cortisol responses to a fenfluramine challenge were significantly reduced. It should be noted that Gerra employed a tough inclusion policy, aimed at excluding many polydrug users from the Ecstasy group. Verkes *et al.* (2001) also found a significantly reduced cortisol response to fenfluramine in both moderate and heavy Ecstasy users, compared with regular clubbers and ravers who had never used Ecstasy. The prolactin response to the fenfluramine challenge was non-significant, with high variance within each group. In a PET scan study, McCann *et al.* (1998) found a reduced density of serotonin transporter sites, which correlated with the extent of past Ecstasy use. In a single photon emission computed tomography (SPECT) study, Semple *et al.* (1999) uncovered a reduced density of 5-HT transporter sites in the cerebral cortex, while dopamine receptor binding was normal. Indeed, most of the above studies found that dopaminergic markers were normal. However, McCann *et al.* (1994) found that female regular users displayed a significant reduction in Horovanillic acid (HVA), whereas males showed a non-significant reduction in that dopaminergic index. This gender effect was also apparent in the serotonergic markers, with females showing comparatively stronger 5-HIAA reductions (–46%) than males (–20%). For a more comprehensive description of brain imaging techniques and MDMA findings see Reneman *et al.* (2001, this issue).

Serotonin is known to be involved in various psychobiological and psychiatric functions. In a non-pharmacological review of its functional aspects, Naughton *et al.* (2000, p. 402) concluded: 'Serotonin is involved in the regulation of mood, sleep, vigilance, memory and learning, feeding and sexual behaviour.' Psychiatric disorders with strong serotonergic aspects include depression, schizophrenia, anxiety, impulsivity, aggressiveness and obsessive-compulsive disorder (Naughton *et al.*, 2000). Thus any alteration in the integrity of the serotonin system would be predicted

to cause a range of functional impairments. The extensive empirical evidence on functional deficits in chronic users is reviewed in the three following subsections on memory and cognition, psychiatric well-being and psychobiological functions such as sleep, eating and sex.

Cognitive and memory aspects

Memory deficits were first described in an individual case study in which 18 months of regular Ecstasy use had led to self-reported problems in short-term and long-term memory, together with many other psychobiological complaints (McCann and Ricaurte, 1991). Significant memory impairments were then reported in a group of nine regular users who had taken Ecstasy for around 5 years but had been abstinent for 20–180 days (Krystal *et al.*, 1992). On a neurocognitive test battery the performance of these users on most tasks was generally similar to age-matched norms; however, on the Wechsler Adult Intelligence Scale (WAIS) memory subscales several participants produced scores far lower than age-matched norms. There were, however, methodological limitations with the study, since many participants had psychiatric and extensive illicit drug histories, and they had been administered a tryptophan challenge prior to testing. Parrott (1996) and Parrott *et al.* (1998) reported significant memory deficits in both novice and regular Ecstasy users, compared with a age-matched control group who had never taken Ecstasy. Performance of the two groups on most of the standard cognitive tests was similar, although on immediate and delayed word recall tasks the Ecstasy users recalled significantly fewer words than the non-user controls. Memory deficits were confirmed in a follow-up study, where again both the novice (<10 occasions of Ecstasy use) and regular (>10 occasions) Ecstasy users showed significant verbal memory deficits, compared with controls (Parrott and Lasky, 1998). Morgan (1999) found significantly poorer prose recall in abstinent Ecstasy users than in two control groups of non-drug users and illicit polydrug users (e.g. LSD, amphetamine, cannabis), whereas the memory scores for the two control groups were similar. Verkes *et al.* (2001) found significant deficits in word recognition, Corsi block span and figure recognition in recreational Ecstasy users, compared with non-user controls. Word recognition was also significantly worse in heavy than in moderate Ecstasy users. The three groups comprised regular visitors to 'rave parties' and were broadly similar on most demographic variables. Tough exclusion criteria had been applied to exclude regular users of alcohol,

cocaine, amphetamine and opiates, but despite this the Ecstasy users had more extensive illicit drug histories and differed in other potentially confounding variables. However, when analyses of covariance were applied, none of these other factors altered the significant memory deficits (Verkes *et al.*, 2001).

Cannabis is the illicit drug of most concern, since its regular use is known to be associated with deficits in concentration and working memory. Several groups have therefore focused on cannabis, investigating whether it might explain the memory deficits found in Ecstasy users. Gouzoulis-Mayfrank *et al.* (2000) administered an extensive battery of cognitive tests to three equally sized groups: non-drug users, regular Ecstasy users who also took cannabis, and a cannabis group closely matched with the Ecstasy group on past cannabis use. There were no performance differences between the cannabis users and the non-drug users on any task. In contrast, the Ecstasy + cannabis users performed significantly worse than the non-drug users on most tasks. Furthermore, the Ecstasy + cannabis users did significantly worse than the cannabis users and non-user controls on tests involving learning, memory, problem solving and strategic planning. The only tasks in which Ecstasy users showed no impairment were basic measures such as simple reaction time. Finally, although the cannabis group was not cognitively impaired, the use of cannabis by the Ecstasy users was associated with stronger cognitive deficits. Croft *et al.* (2001) compared heavy cannabis users with Ecstasy users who also used large amounts of cannabis and non-user controls. Their conclusions were rather different. The cannabis group and Ecstasy + cannabis group each performed significantly worse than non-user controls on tests of memory, learning, word fluency, speed of processing and manual dexterity. However, there were no significant performance differences between the cannabis and Ecstasy + cannabis groups, which led the authors to suggest that 'Previously reported cognitive impairment in MDMA users may have been caused by coincident cannabis use' (p. 373). This study, however, suffered from certain limitations. The inclusion criteria for past Ecstasy use were not specified, and the group appears to have contained some participants with just a few experiences of MDMA. This may be important, given the small size of the Ecstasy + cannabis group ($n = 11$), compared with the cannabis users ($n = 18$) and non-user controls ($n = 32$). The lifetime use of cannabis was also much higher (Ecstasy + cannabis group: 10 964 joints; cannabis group: 7762 joints) than the lifetime experience of Ecstasy (mean 41.9 tablets; SD 49.3) (Croft *et al.*, 2001).

Rodgers (2000) compared three equally sized groups: Ecstasy + cannabis users, cannabis users and non-drug users. The past use of cannabis was again heavy (mean of 4 days/week for 10 years) in comparison with the past use of Ecstasy (mean of 20 occasions over 5 years). Both the Ecstasy + cannabis users and the cannabis users displayed significant memory and learning impairments compared with the controls. However, the Ecstasy + cannabis group performed significantly worse than the cannabis group on two tasks: delayed recall of verbal paired associates and delayed recall of visual paired associates. Bolla *et al.* (1998) also found that MDMA users were significantly more impaired on visual and verbal memory tasks than a non-user control group, which included several cannabis users. The degree of deficit in delayed visual recall was also significantly correlated with monthly Ecstasy intake. Heffernan *et al.* (2001) assessed self-ratings on a prospective memory questionnaire, which covered 'remembering to do things in the near future'. Regular Ecstasy users reported higher memory deficits than non-user controls, and this remained significant when cannabis use was partialled out by covariance. Further cognitive studies by Heffernan *et al.* (2001) and Rodgers *et al.* (2001) are reported in this issue. The latter study comprised a web-based study of self-rated memory ability, involving an initial sample of 490 participants. Everyday memory and short-term prospective memory deficits were found to be related to cannabis use, whereas longer-term prospective memory deficits (e.g. remembering an appointment) and deficits in questionnaire completion were related to Ecstasy use (Rodgers *et al.*, 2001).

Zakzanis and Young (2001) tested a group of Ecstasy users on a battery of retrospective and prospective memory tasks, on two occasions 1 year apart. Significant decline was evident on some of the memory tasks, with the extent of decline positively correlated with intensity or frequency of Ecstasy use over that year. Reneman *et al.* (2000) investigated the relationship between SPECT indices of 5-HT_{2A} receptor density and performance on the Rey Auditory Verbal Learning Test (RAVLT). Regular Ecstasy users, with an average lifetime consumption of 218 tablets, demonstrated a general increase in 5-HT_{2A} receptor density, which was significant in the occipital cortex. This was interpreted as postsynaptic receptor up-regulation, following drug-induced serotonergic depletion. On the RAVLT task, the Ecstasy users recalled significantly fewer words (8.1) than the controls (12.3), while 'In the MDMA group, but not in the controls, mean cortical binding was highly correlated

with recall (Spearman's $r = +0.98$, $p < 0.005$)'. In a follow-up study, this association between receptor density and RAVLT was not, however, confirmed (Reneman *et al.*, 2001). Significant deficits in RAVLT performance have been replicated by Fox *et al.* (2001a). Fox *et al.* (2001b) compared regular Ecstasy users who complained of 'psychobiological problems', which they attributed to their use of Ecstasy, with an equivalent group of regular Ecstasy users who stated that they had not developed any such problems. There were no significant differences in the cognitive performance of these two groups. Cognitive deficits were evident on some tasks (e.g. Tower of London planning time, spatial memory), compared with non-user controls, but these deficits were a monotonic function of past Ecstasy use in both user groups. Thus heavy Ecstasy users were the most cognitively impaired and light users the least impaired, irrespective of whether they complained of problems or not (Fox *et al.*, 2001b).

Many of the above studies assessed a wide range of cognitive functions and generally found that simple basic cognitive performance was not impaired. However, several reported significant decrements on some of the more difficult or complex tasks. The unimpaired tasks included simple and choice reaction time (Parrott *et al.*, 1998; Rodgers, 2000), finger oscillation (Krystal *et al.*, 1992), attention and vigilance (Parrott *et al.*, 1998; Rodgers, 2000), verbal fluency (Wareing *et al.*, 2000), visual scanning and visual search (Gouzoulis-Mayfrank *et al.*, 2000; Parrott and Lasky, 1998), and the Tower of London task (Morgan, 1998). However, this last higher cognitive task was found to be significantly impaired in Schifano *et al.*'s (1998) heavier Ecstasy users, while significant deficit in the Matching Familiar Figures Test was reported by Morgan (1998). This was interpreted as a behavioural index of impulsivity, since the abstinent Ecstasy users tended to respond rapidly but incorrectly. These deficits on the more complex cognitive tasks suggest that higher executive information processing may also be impaired (Morgan, 2000; Parrott, 2000). So, just as the memory deficits may reflect serotonergic changes in the hippocampus, the higher cognitive or executive deficits may reflect frontal cortical damage (Morgan, 1998; Parrott, 2000; Verkes *et al.*, 2001). However, Fox *et al.* (2000) used the Cambridge Automated Neuropsychological Test Battery (CANTAB) and found: 'Verbal fluency deficits which multiple regression indicated were due to failure to implement semantic and phonemic strategies, rather than age or intelligence . . . and significant deficits in pattern recognition but not spatial recognition, also significant deficits in

Table 2. Memory and learning tasks among drug-free recreational ecstasy users who displayed significant performance deficits

Memory task	Example reference source
Auditory prose passage: immediate and delayed recall	Zakzanis and Young, 2001
Calev matched word recall and recognition task	Fox <i>et al.</i> , 2001
Cambridge Neuropsychological battery (CANTAB): spatial working memory	Fox <i>et al.</i> , 2000
Cognitive Drug Research battery (CDR): immediate and delayed word recall	Parrott <i>et al.</i> , 1998
Corsi Block memory span	Verkes <i>et al.</i> , 2001
Figure recognition: simultaneous and serial	Verkes <i>et al.</i> , 2001
Prospective Memory Questionnaire (PMQ): self-rated deficits	Heffernan <i>et al.</i> , 2001a
Rey Auditory Verbal Learning (RAVLT): English edition	Fox <i>et al.</i> , 2001b
Rey Auditory Verbal Learning (RAVLT): Dutch edition	Reneman <i>et al.</i> , 2000
Rey Auditory Verbal Learning (RAVLT): German edition	Gouzoulis-Mayfrank <i>et al.</i> , 2000
Rey-Osterreith Complex Figure: delayed visual recall	Bolla <i>et al.</i> , 1998
Rivermead paragraph memory: immediate and delayed recall	Morgan, 1999
Spatial recall (windows-in-houses task): brief delay	Fox <i>et al.</i> , 2001a
Supraspan auditory word list: brief delay, written recall	Parrott and Lasky, 1998
Verbal paired associates: delayed recall	Rodgers, 2000
Visuo-spatial Memory (VIG): complex shape learning	Gouzoulis-Mayfrank <i>et al.</i> , 2000
Visual paired associates: delayed recall	Rodgers, 2000
Weschler memory (WAIS): immediate and delayed paragraph recall	Krystal <i>et al.</i> , 1992
Word recognition: simultaneous and serial	Verkes <i>et al.</i> , 2001
Working memory: information processing accuracy	Wareing <i>et al.</i> , 2000
Working memory: serial subtraction	Curran and Travill, 1997
Working memory: serial add and subtract	McCann <i>et al.</i> , 1999

Note: a single reference is provided for each task. On many tasks significant deficits were also reported by other groups. Many of the studies also found deficits in additional memory measures.

spatial working memory, in a manner strikingly similar to temporal lobe patients' (Fox *et al.*, 2000, p. s325).

Memory deficits have therefore been demonstrated by many different research groups, using a wide variety of assessment measures (Table 2). Morgan (2000) also noted that there was a positive association between the lifetime use of Ecstasy and the extent of the memory or learning deficits (e.g. Bolla *et al.*, 1998; Gouzoulis-Mayfrank *et al.*, 2000; Morgan, 1999; Semple *et al.*, 1999). This association was confirmed by Fox *et al.* (2001b, current issue), where RAVLT task performance deficits were directly related to the heaviness of past Ecstasy use. However, not every study has found significant learning or memory deficits. The reticence of academic journals to publish non-significant findings is well known, but this can generate an unbalanced overall view. We have reported non-significant memory task findings as conference papers (Turner *et al.*, 1998a, 1999) but were unsuccessful in our subsequent attempts at full publication. I am aware of other groups who have found unimpaired memory or learning task performance, but whose reports have not been published. Furthermore, several studies reporting significant deficits on certain memory tasks have reported normal scores on the other memory measures (e.g. Fox *et al.*, 2000, 2001a; Zakzanis and Young, 2001; Rodgers

et al., 2001). The characteristics of those regular users who do not display memory problems are an important topic. Finally, we have reported two studies where abstinent Ecstasy users displayed particularly good visual-cognitive skills. In one study, involving a virtual reality target detection and memory task, there was significantly better peripheral/incidental attention towards two of the non-target stimuli than control group performance (Turner *et al.*, 1998a; Parrott, 2000). In the other study, abstinent Ecstasy + LSD users displayed significant verbal memory deficits, but also comparatively faster mental rotation ability than non-users ($p < 0.07$, two-tailed; Peppas *et al.*, 2001). These results obviously need replication, but they do parallel the findings from a study of tryptophan depletion in normal volunteers; memory consolidation was significantly impaired, while focused attention was significantly improved (Schmitt *et al.*, 2000). These findings have been interpreted as possibly indicating reduced cortical inhibition, consequent upon the reduced serotonin activity (Parrott, 2000; Peppas *et al.*, 2001; Schmitt *et al.*, 2000).

Psychiatric aspects

Clinical reports of psychiatric disorders following the recreational use of Ecstasy first emerged as published

case studies. Major depression, panic disorder, psychotic breakdown, aggressiveness and phobic anxiety were each described (Creighton *et al.*, 1991; McCann and Ricaurte, 1991; Schifano, 1991; Schifano and Magni, 1994). In some cases the individuals had no psychiatric history, whereas in other cases there was evidence that childhood or adolescent problems had been exacerbated by drug use. McCann and Ricaurte (1991) described an 18 year old female, who after a 'model childhood' had joined a rebellious and disruptive peer group, among whom drug experimentation was encouraged. She took Ecstasy twice and had favourable experiences. Some time later she took several tablets at once, and after another positive, powerful on-drug experience developed severe panic attacks and depression. These dominated her life for the next 6 weeks and were accompanied by sleep disruption, eating disorders and marked weight loss. After 6 weeks she experienced a brief 2 h period of 'feeling normal', and over time these periods of normality became more frequent. Several months later she remained very anxious, emotionally labile and tearful, with frequent panic attacks. Other clinical case studies can be seen in the various reviews (McCann and Ricaurte, 1991; McCann *et al.*, 1996; McGuire, 2000; Schifano *et al.*, 1998; Schifano, 2000; Schifano and Magni, 1994; Soar *et al.*, 2001).

The main limitation of using individual abreacons as evidence is that they may be seen as idiosyncratic or atypical. McCann *et al.* (1996, p. 108) noted: 'Individual case studies might be perceived as anecdotal and can therefore be ignored or trivialized'. In order to gauge how normal or abnormal various psychiatric abreacons to Ecstasy are, systematic survey data are required. Schifano *et al.* (1998) administered a battery of psychiatric and psychobiological assessment measures to 150 young attendees at a drug treatment centre and found a number of disorders. In descending order of frequency these were: depression, psychotic disorder, cognitive impairment, bulimia, impulse control disorder and panic attacks. Those Ecstasy users who reported problems had a higher lifetime use of Ecstasy (47 tablets) than those reporting no problems (3 tablets). One limitation of the study was that it was based at a clinical unit, and the clients may not have been typical drug users. In a non-clinical survey, Parrott *et al.* (2000a) assessed 50 youngsters in an Irish town where drug use was highly prevalent. On the SCL-90 self-report psychiatric symptom inventory, the heavy Ecstasy users (30–1000 occasions) reported significantly higher scores than non-users on the following factors:

general anxiety, phobic anxiety, hostility, obsessiveness, paranoid ideation, psychoticism, somatisation, altered appetite, restless sleep and impulsiveness. The scores of moderate Ecstasy users (1–20 occasions) were intermediate, with scores on two SCL factors significantly raised. One important confounding factor was the use of other psychoactive drugs, since most Ecstasy users had taken a wide variety of illicit drugs (Figure 1).

In a larger cross-cultural follow-up study, six drug-use subgroups from four European cities, Rome, Padua, Manchester and London, were compared (Parrott *et al.*, 2001). The researchers contacted 768 volunteers at coffee bars, campuses, clubs and other youth venues. They were divided into six drug-use subgroups: non-drug users, legal drug users (alcohol and/or nicotine), cannabis users, illicit polydrug but not Ecstasy users, light Ecstasy polydrug users and heavy Ecstasy polydrug users (subgroup mean ages: 18.8–23.6 years). The SCL-90 psychiatric symptom check list was supplemented with 30 questions covering positive life experiences: positive moods, positive psychobiological functions (good sex, good health, enjoyment of music and dancing), sociability and life contentment. The six groups did not differ significantly on any of the four positive life factors but did on all the psychiatric factors, symptom scores increasing with greater drug use (Figure 1). The polydrug user groups reported the highest SCL-90 factor scores, although there were only slight differences between those who had taken Ecstasy and those who had not (Parrott *et al.*, 2001). This also confirmed the link between illicit use of drugs such as cocaine, amphetamine and LSD and psychiatric distress. When the group of 234 Ecstasy polydrug users was analysed, the number of Ecstasy pills ever taken was found to be positively correlated with anxiety, phobic anxiety, psychoticism, MDMA side effects and total negative feelings (Milani *et al.*, 2000). Furthermore, when the contributory influences of the other psychoactive drugs were investigated, as expected cocaine and amphetamine contributed to some of the detrimental symptom scores, but the worst co-drug was nicotine, which significantly raised the distress scores on nearly every SCL-90 factor and was also associated with low scores on the 'positive' factors. Nicotine dependency leads to increased stress and depression during adolescence (Parrott, 1999, 2000b, 2000c), and the detrimental effects of MDMA and nicotine dependency may simply be additive. Alternatively, given the high prevalence of tobacco smoking amongst Ecstasy users, there may be a closer interaction between the two drugs.

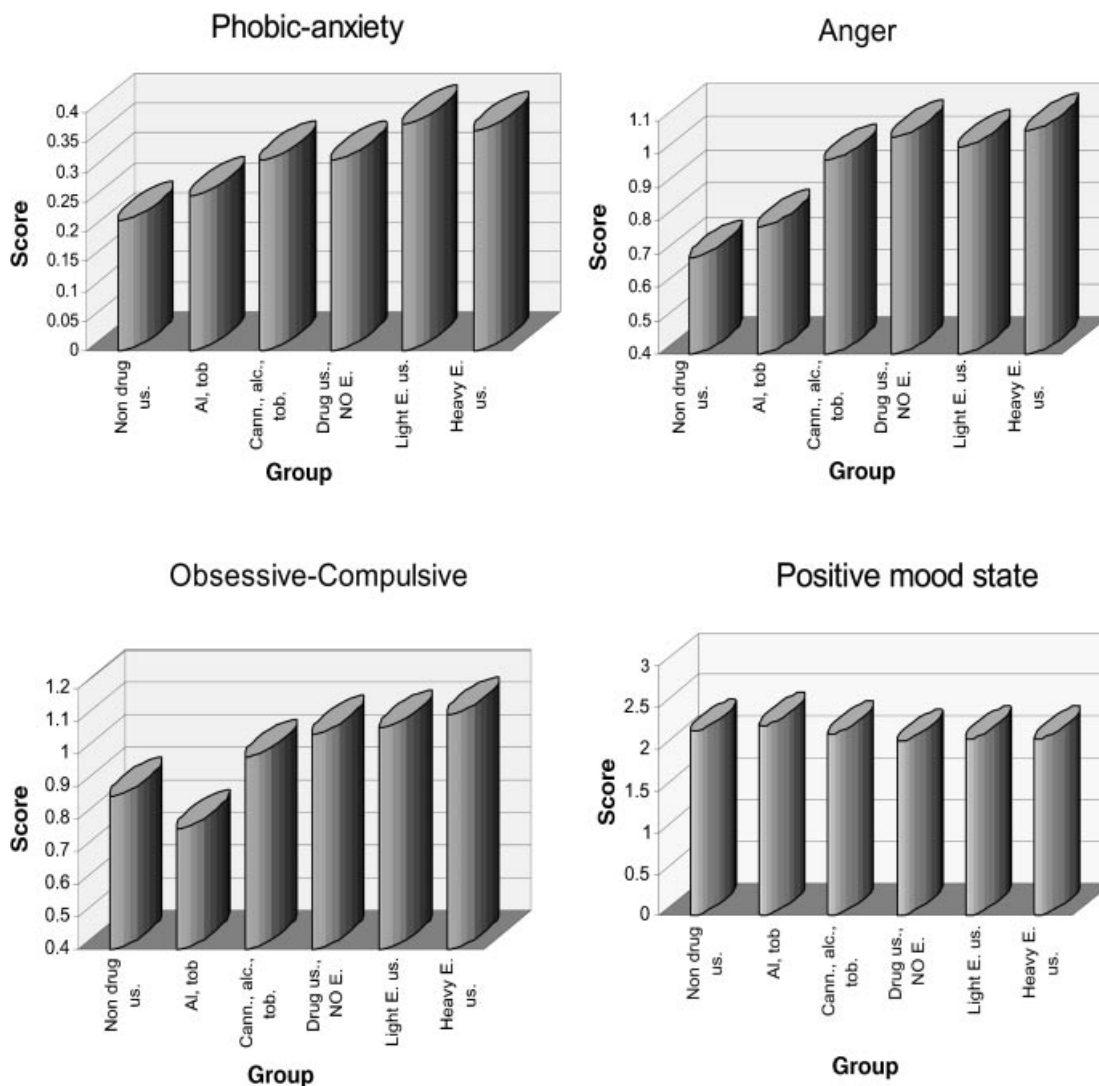


Figure 1. Self-rated positive mood states, phobic anxiety, anger and obsessive-compulsive behaviour in 768 young adults from Britain and Italy: 150 non-drug users, 185 alcohol/tobacco users, 97 cannabis users, 102 illicit polydrug but not ecstasy users, 115 light ecstasy polydrug users and 119 heavy ecstasy polydrug users (after: Milani *et al.*, 2000; Parrott *et al.*, 2001). (Note: the ANOVA group effect was significant for the three negative symptom scales but was non-significant for positive mood state)

Psychobiological aspects

Another finding from Parrott *et al.*'s study (2001) was that 14% of the heavy Ecstasy polydrug users reported 'loss of sex interest or pleasure', compared with 4% of the non-drug users ($p < 0.05$) (*New Scientist*, 13 January 2001). Loss of sex urge during the past 6 months was reported by 12% of Ecstasy users in Topp *et al.*'s (1999) Australian survey, although they had no

control group data. In a follow-up study, sexual difficulties have again been reported by a number of heavy users (Milani *et al.*, in preparation). We have also encountered sexual impotence in a male former heavy user, despite being abstinent for several years (Soar *et al.*, in preparation). Altered sleep architecture has been documented in two overnight EEG studies. Allen *et al.* (1993) found reduced total sleep time, due mainly to reduced stage 2 non-REM sleep, in

abstinent recreational users. In a later study, the same group documented longer overall sleep times, mainly due to an increase in stage 3 and 4 non-REM sleep (McCann *et al.*, 2000). It is not known why the findings from their two studies were so different, although the authors emphasised that non-pharmacological research shows that serotonergic changes can alter sleep in various ways (McCann *et al.*, 2000).

Chocolate and carbohydrate cravings in some regular and heavy users, together with other psychobiological complaints, were described by Schifano and Magni (1994). Furthermore, in a survey of 150 Ecstasy users attending a drug dependency clinic, 24% complained of bulimia (Schifano *et al.*, 1998). In a sub-chronic prospective study Turner *et al.* (1998b) noted a mean reduction in calorific intake of 500 kcal/day for the whole week after taking Ecstasy, coupled with significant reductions in appetite and meal enjoyment. Several participants reported that they often failed to eat the food they had cooked for themselves. Regular users may therefore experience reduced food intake for extended periods of time, leading to weight loss. The underground pamphlet 'The E-Plan Diet' recommends taking MDMA regularly to control weight (Lifeline, 1994).

These changes in eating and sleeping habits are just part of a wider range of psychobiological alterations in recreational drug users. Ecstasy is generally taken in the early evening, with users then staying up for most of the night, so that chronological rhythms are often disrupted, which may contribute to psychobiological distress. The desire to dance and party overnight is often increased by the use of further Ecstasy tablets, or other illicit sympathomimetic stimulants, which thus contribute to these problems (see below). Another factor is drug use during holidays, since many youngsters party every night instead of just at weekends. In an airport survey of 800 British youngsters returning from their holidays in Ibiza, 43% stated that they had taken Ecstasy on 5 or more days in 1 week, whereas only 3% stated that they took the drug this frequently when in the UK (Bellis *et al.*, 2000). Foetal development is another crucially important issue. McElhatton *et al.* (1999) found an increased incidence of congenital defects in babies who had been exposed to in utero to maternal recreational Ecstasy. The deleterious developmental effects of MDMA have been demonstrated in rats. Broening *et al.* (2001) found that MDMA administration in neonatal rats (equivalent to third trimester exposure in humans) led to reduced weight gain and dose-related impairments in spatial learning and memory.

MDMA AND SEROTONERGIC NEUROTOXICITY: AN EXPLANATORY MODEL

The conditions under which serotonergic neurotoxicity develops have been extensively studied in the laboratory in a variety of animal species. The most important factors are dose, repetition of dosing, ambient temperature and other drugs. High doses cause greater axon terminal damage than low doses, while repeated doses are more destructive than single doses. McCann and Ricaurte (2001) reported that closely spaced doses were particularly effective at inducing neurotoxic damage in squirrel monkeys. Ambient temperature is also crucial. Marlberg and Seiden (1998) found that increasing the ambient temperature led to impaired temperature regulation and a significant rise in core body temperature of MDMA-treated rats. This led to greater neurotoxic nerve damage, with the degree of damage increasing as a direct function of the increase in environmental temperature. Huether *et al.* (1997) outlined an explanatory model for how MDMA may cause the serotonergic neural damage in animals and functional deficits in humans; other models have been proposed by Schmidt (1987) and Sprague *et al.* (1988). The essence of Huether's explanation is that MDMA causes a massive release of serotonin, which severely stresses the basic energy metabolism processes within the presynapse. Thus any factors which contribute to the 'the profound wastage of energy' will heighten the resulting cellular damage (Huether *et al.*, 1997, p. 771). Exercise, hyperthermia and dopaminergic and serotonergic stimulant drugs will all exacerbate the cellular exhaustion and thus contribute to the resulting axonal terminal damage. This model is based largely on data from animal studies, in which MDMA was administered under closely controlled conditions of dosage, timing, temperature and humidity; however, it also consistent with the findings from human studies.

Recreational Ecstasy users seem to seek out those conditions that boost the acute serotonergic response. Prolonged exercise or dancing in hot and crowded conditions, together with the use of other stimulant drugs, heightens sympathetic and cortical arousal. These factors may therefore heighten the euphoric mood states induced by Ecstasy. However, the animal literature shows that these sympathomimetic factors also exacerbate long-term neurotoxic nerve damage (Huether *et al.*, 1997). According to this explanation, the long-term neuropsychobiological damage is a direct function of the frequency and intensity of the acute stimulatory episodes, as typified in the mild serotonin syndrome reactions (see above). Thus

long-term damage is greater with the more drug that is taken, the higher the doses used and the more it is consumed in stimulating and hyperthermic conditions. The practical implications of this explanatory model are discussed more fully in the final section.

There is also the crucial question of serotonergic repair. Are there any signs of serotonergic or functional recovery after recreational use of Ecstasy has ceased? Empirical evidence on this question is limited. In an early report based on just three volunteers, Morgan (1999) suggested that memory functions recovered after 6 months free from Ecstasy. However, in a more extensive study of 15 former users, significant memory deficits remained evident after an average Ecstasy-free period of 2 years (Morgan, personal communication). Wareing *et al.* (2000) also found that 10 former users displayed significant central executive cognitive deficits, despite having remained Ecstasy-free for at least 6 months. I am not aware of any study systematically assessing psychobiological functions or psychiatric symptoms in former users. However, many of the published individual case studies reported that the problems remained for a period after MDMA use had ceased (see above). The prolonged nature of these problems is illustrated by a case study from our own laboratory. This young male had taken large amounts of Ecstasy, in escalating dosages to a maximum of 50 tablets in one night. He developed severe problems during this time, which eventually led him to stop taking it. But the problems had not resolved, despite his not having taken any MDMA for 7 years. He remained sexually impotent and had severe sleep problems, recurrent panic attacks, poor neurocognitive task performance and severe depression, and had made suicide attempts (Soar *et al.*, in preparation). Other laboratories have described similar cases of severe and enduring problems (Schifano and Milani, personal communication). With the current widespread use of Ecstasy in increasing amounts, one prediction is that these neurocognitive and psychiatric problems will increase in the future. Even in 'moderate' MDMA users, current borderline serotonergic problems may hasten the development of neurodegenerative disorders in later life. Long-term prospective studies are needed to provide empirical data on this question.

CONCLUSIONS AND HISTORICAL OVERVIEW

In the mid-1980s, advocates for MDMA often described its effects in glowing terms: 'When people feel well, centered, unthreatened and aware of their

own strengths and loveliness, they are able to drop many of their usual barriers. Habitual users of tobacco have no need to smoke. Chain smokers of marijuana do not need their weed. Nail biters leave their fingers alone. Compulsive talkers become quiet' (from *The Chemical Pursuit of Ecstasy*, Dye, 1982; cited by Shulgin, 1986, p. 302). However, the first reports of neurotoxicity in laboratory animals were then emerging, which led to predictions that longer-term neural damage would also probably occur in humans: 'It can poison the nervous system, possibly irreversibly. It may very well be that a young healthy adult who is exposed to these drugs is not going to show frank symptoms which are likely to be picked up by a clinician. But what we do not know is whether 20 or 30 years from now, at the age of 45 they may begin to be showing central nervous system signs that ordinarily would not be seen until they get to be 70 or 80.' Shulgin (1986, p. 302) argued that both these views were extreme, and that 'as with everything that combines both promise and threat', the true picture lay somewhere in between.

Fifteen years of empirical human research have generated a scenario even more worrying than the adverse neuroscientific view outlined by Shulgin in 1986. The prediction that MDMA would provide a chemical route to happiness (Dye, 1982) has not been supported by the empirical evidence. There are no indications that recreational Ecstasy users lead happier, more contented or more enlightened lives (Parrott *et al.*, 2001). Instead, Ecstasy users report marked mood fluctuations, with brief periods of elation while on MDMA, followed by lethargy and depression for days afterwards (Curran, 2000; Curran and Travill, 1997; Parrott and Lasky, 1998). The long-term effects are even more damaging and become apparent soon after users take up Ecstasy. Neurocognitive deficits are thus apparent in abstinent Ecstasy user groups, whose average age is 20–23 years (Gouzoulis-Mayfrank *et al.*, 2000; Morgan, 1999; Parrott *et al.*, 1998, 2000; Parrott and Lasky, 1998; Reneman *et al.*, 2000; Verkes *et al.*, 2001). Memory deficits have been demonstrated in light users with an average lifetime Ecstasy consumption of 10–20 occasions (Parrott *et al.*, 1998; Rodgers, 2000), although the worst functioning is generally found in the heavier users (Bolla *et al.*, 1998; Fox *et al.*, 2001a,b; Verkes *et al.*, 2001; see Table 3 in Morgan, 2000). Selective memory and learning deficits have been demonstrated in many countries on a wide variety of tasks (Table 2). Other cognitive functions generally remain normal, although higher cognitive deficits have occasionally been reported. Numerous psychobiological disorders

have also been noted in non-clinical Ecstasy polydrug users: impaired sleep, reduced appetite, phobic anxiety, impulsivity, reduced sexual interest, depression and suicide, psychotic symptoms, obsessive-compulsive behaviour, and socioeconomic difficulties (MacInnes *et al.*, 2001; McCann *et al.*, 1996; Parrott *et al.*, 2000, 2001; Schifano *et al.*, 1998; Schifano, 2000; Topp *et al.*, 1999). Serotonergic loss has also been demonstrated using PET, MRI and SPECT and more indirect indices of neuronal functioning (Kish *et al.*, 2000; McCann *et al.*, 1994, 1998; Reneman *et al.*, 2000, 2001; Semple *et al.*, 1998; Verkes *et al.*, 2001).

Despite the wealth of empirical evidence for MDMA-related problems, there are still those who state that MDMA would be beneficial if used properly (Greer and Tolbert, 1998; Grob, 2000; Saunders, 1996). Grob (2000, p. 581) proposed 'To sanction studies which will finally and honestly elucidate the true risk/benefit ratio for this misunderstood drug'. He argued that current human Ecstasy research is methodologically flawed and provides little information about pure MDMA: 'What is the genuine relevance of such poorly controlled data collected from populations of young polydrug users who have frequented for extended periods of time the fast lane of the contemporary rave scene?' (Grob, 2000). As noted earlier, Ecstasy researchers are well aware of these methodological issues, and the neurocognitive deficits remain even after controlling for potentially confounding factors such as other drug use and altered sleep or circadian rhythms (Fox *et al.*, 2001; Gouzoulis-Mayfrank *et al.*, 2000; Heffernan *et al.*, 2001; Rodgers, 2000; Verkes *et al.*, 2001; Zakzanis and Young, 2001). It should also be emphasised that the problem with MDMA is not just its neurotoxicity. Psychoactive stimulants such as amphetamine and cocaine, with mood-enhancing properties linked to monoaminergic release, are invariably problematic when used recreationally. To propose that MDMA might somehow become problem-free if it were used differently is neurochemically naive.

However, this does raise two important questions about how MDMA is used. Firstly, why is Ecstasy so strongly associated with the dance/rave scene? Secondly, why do regular MDMA users often become heavy polydrug users? As noted earlier, there is a clear neurochemical rationale for using MDMA in hot and crowded conditions. Animal research shows that the serotonergic and other physiological effects of MDMA are markedly increased in high ambient temperatures (Dafters, 1994; Gordon *et al.*, 1991). The behavioural effects of amphetamines are also intensi-

fied by overcrowding and dehydration (Green *et al.*, 1995). Thus it is probably not a coincidence that humans seek out those conditions where the positive mood effects of MDMA might be intensified: heat, dancing, overcrowding and, possibly, dehydration (Dafters, 1994). Pedersen and Skrondal (1999, p. 1695) noted that Ecstasy 'is used by adolescents who use other legal and illicit substances in a polydrug-use pattern'. There is probably a strong neurochemical rationale for multiple drug use. Dye (1982) optimistically proposed that MDMA users would not feel the need to take any other drugs. Instead the opposite has occurred. I am not aware of any published studies of 'pure' Ecstasy users, despite the many research groups seeking them (e.g. Rodgers, 2000, p. 20); almost invariably Ecstasy users take other drugs. Furthermore, the use of these drugs seems to increase in parallel, so that while light Ecstasy users report comparatively light use of other illicit drugs, heavy Ecstasy users often display extensive and intensive drug histories (Table 1 from Fox *et al.*, 2001a; Pedersen and Skrondal, 1999; Parrott *et al.*, 2000, 2001). Serotonergic release is heightened by the parallel administration of dopaminergic stimulants such as amphetamine (Huether *et al.*, 1997), and interviews with heavy users reveal that they often use amphetamine or cocaine to intensify the Ecstasy experience, while cannabis and opiates are often used to relieve the post-MDMA come-down.

Shulgin (1986, p. 300) stated: 'MDMA does not lead itself to overuse, because its most desirable effects diminish with frequency of use.' Like many of the other predictions from that period, this has not been confirmed by subsequent events. Dosage escalation is the norm, with Ecstasy users adopting behavioural strategies that probably help to maintain the on-drug experience. Novice Ecstasy users generally take single pills and modulate their behaviour by moving between the dance floor and the chill-out room. In contrast, heavy regular users often take several pills at once or consume successive tablets over long and protracted sessions of partying and dancing. These behavioural and pharmacological strategies probably reflect these users' impaired serotonergic systems. Thus the combination of strong stimulatory factors (heat, continual dancing), other stimulant drugs and increasing doses of MDMA probably help to maintain the on-drug experience in the face of diminishing serotonergic efficacy. But unfortunately they also maximise the pharmacological and hyperthermic conditions that cause further serotonergic loss.

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