Psychopharm

Journal of Psychopharmacology
20(2) (2006) 147–163

ISSN 0269-8811
SAGE Publications Ltd, London, Thousand Oaks, CA and New Delhi
10.1177/0269881106063268

MDMA in humans: factors which affect the neuropsychobiological profiles of recreational ecstasy users, the integrative role of bioenergetic stress

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Abstract

Many recreational ecstasy/MDMA users display neuropsychobiological deficits, whereas others remain problem free. This review will investigate some of the drug and non-drug factors which influence the occurrence of these deficits. Acute and chronic MDMA usage are both important. Intensive use within a session is often associated with more problems. In term of lifetime usage, novice users generally remain unimpaired, whereas most heavy users report memory or other psychobiological problems which they attribute to ecstasy. These complaints are confirmed by objective deficits in working memory, attention, frontal-executive, and episodic memory tasks. Psychobiological deficits include disturbed sleep, sexual dysfunction, reduced immuno-competence, and increased oxidative stress. Further MDMA-related factors which may contribute to these changes, include acute and chronic tolerance, and drug dependence. Around 90–95% of ecstasy/MDMA users also take cannabis, and this can independently contribute to the adverse neuropsychobiological profiles; although in some situations the acute co-use of these two drugs may be interactive rather than additive, since cannabis has relaxant and hypothermic properties. Alcohol, nicotine, amphetamine, and other drugs, can also affect the psychobiological profiles of ecstasy polydrug users in complex ways. Pure MDMA users are rare but they have been shown to display significant neurocognitive deficits. Psychiatric aspects are debated in the context of the diathesis-stress model. Here the stressor of ecstasy polydrug drug use, interacts with various predisposition factors (genetic, neurochemical, personality), to determine the psychiatric outcome. Recreational MDMA is typically taken in hot and crowded dances/raves. Prolonged dancing, feeling hot, and raised body temperature, can also be associated with more psychobiological problems. This is consistent with the animal literature, where high ambient temperature and other metabolic stimulants boost the acute effects of MDMA, and cause greater serotonergic neurotoxicity. In conclusion, the neuropsychobiological effects of MDMA are modulated by a wide range of drug and non-drug factors. These multiple influences are integrated within a bioenergetic stress model, where factors which heighten acute metabolic distress lead to more neuropsychobiological problems.

Keywords

MDMA, ecstasy, cannabis, memory, cognition, mood, bioenergy, stress, temperature

Introduction

Recreational ecstasy/MDMA users can experience a range of neuropsychobiological problems. In particular, they have been found to display functional deficits in neurocognitive test performance, altered cognitive-emotional information processing, raised psychiatric symptom profiles, disordered sleep, sexual dysfunctions, altered EEG patterns, modified event-related potentials, reduced immuno-competence, increased oxidative stress, and other psychobiological changes (Peroutka *et al.*, 1988; Creighton *et al.*, 1991; McCann and Ricaurte, 1991; Solowij *et al.*, 1992; Cohen 1995; Curran and Travill, 1997; Davison and Parrott, 1997; Williamson *et al.*, 1997; Bolla *et al.*, 1998; Parrott *et al.*, 1998; Schifano *et al.*, 1998; Dafters *et al.*, 1999; Jansen 1999; McCann *et al.*, 1999; Morgan, 1999; Topp *et al.*, 1999; Gouzoulis-Mayfrank *et al.*, 2000; McGuire 2000; Milani *et al.*, 2000; Rodgers, 2000; Tuchtenhagen *et al.*, 2000; Wareing *et al.*, 2000; Chang *et al.*, 2001; Croft *et al.*, 2001a, b; Fox *et al.*, 2001; Gamma *et al.*, 2001; Heffernan *et al.*, 2001; Kopelman *et al.*, 2001; MacInnes *et al.*, 2001; Parrott *et al.*, 2001; Ricaurte and McCann, 2001; Soar *et al.*, 2001; Verkes *et al.*, 2001; Zakzanis and Young, 2001; Fox *et al.*, 2002; Gouzoulis-Mayfrank *et al.*, 2002, Lieb *et al.*, 2002; Morgan *et al.*, 2002; Pacifici *et al.*, 2002; Parrott *et al.*, 2002; Back-Madruga *et al.*, 2003; Daumann *et al.*, 2003; Gerra *et al.*, 2003; Gouzoulis-Mayfrank *et al.*, 2003; Rodgers *et al.*, 2003; Simon and

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Mattick, 2003; Thomasius *et al.*, 2003; Verheyden *et al.*, 2003a,b; Connor, 2004; Curran and Verheyden, 2004; Curran *et al.* 2004; Dafters *et al.*, 2004; Daumann *et al.*, 2004; De Win *et al.*, 2004; Halpern *et al.*, 2004; Hanson *et al.*, 2004; Jacobsen *et al.*, 2004; McCardle *et al.*, 2004; Parrott *et al.*, 2004; Roiser and Sahakian, 2004; Soar *et al.*, 2004; Sumnall *et al.*, 2004; Von Geusau *et al.*, 2004; Wareing *et al.*, 2004; Zhou *et al.*, 2004; Daumann *et al.*, 2005; Fisk *et al.*, 2005; Mejias *et al.*, 2005; Milani *et al.*, 2005; Parrott *et al.*, 2005a, b; Quednow *et al.*, 2004; Rizzo *et al.*, 2005; Soar *et al.*, 2005; Thomasius *et al.*, 2005; Yip, *et al.*, 2005; many others). However amongst this extensive body of empirical data, most studies have also found that some groups/types of ecstasy user were not impaired, or displayed deficits on just a few measures. Hence this same literature provides extensive evidence for *unimpaired* neuropsychobiological functioning.

The topic for this review is to examine some of the factors which may be contributing to this variance in findings. The focus here will be on four areas. First, aspects of ecstasy/MDMA usage, in particular tablet purity, intensity of usage over a single session, and chronic or lifetime usage. Second, the role of other psychoactive drugs, especially cannabis, but also alcohol, amphetamine, nicotine, and others. Third, the interaction between external stressors, and internal predisposition factors. Fourth, concomitant stimulation from activities such as prolonged dancing in hot and crowded conditions. Many other factors have contributory roles, and they will also be briefly mentioned (e.g. age, sex, genetic polymorphism). This review is mainly concerned with functional aspects. Structural aspects will only be briefly mentioned, since they are being covered elsewhere in this issue (Reneman *et al.*, 2006; Thomasius *et al.*, 2006). The final section will integrate these multiple influences within a bioenergetic stress model (see Table 1).

Ecstasy/MDMA: purity, intensity, and lifetime usage

At the earlier Novartis Foundation meeting (see preface), Schifano (2000) noted that the constituents of ecstasy tablets were open to doubt, while the other speakers also commented that it was difficult to know whether a tablet contained MDMA or its dosage (Curran, 2000; McCann *et al.*, 2000; Parrott, 2000). The problem of unknown chemical constituents was debated in many reports from this period (DAWN, 2000; Rodgers, 2000; Fox *et al.*, 2001; Verkes *et al.*, 2001), although prior to then purity had not been described as an issue (Peroutka *et al.*, 1988; Solowij *et al.*, 1992). In order to investigate the origins and extent of this problem, a historical review was undertaken (Parrott, 2004a). The earliest documented cases of recreational ecstasy/MDMA were from the mid-1970s. Renfroe (1986) biochemically analysed American illegal street drug supplies from the previous 10 years, and found that 97% of tablets submitted as MDMA, MDA, ecstasy or Adam, contained MDMA or its close derivative MDA. It as noted that this purity level was far higher than with other street drugs (Renfroe, 1986; also Solowij *et al.*, 1992). This situation changed in the early 1990s, and throughout the mid-1990s many tablets sold as ecstasy contained other chemicals. In the largest survey which involved thousands of biochemical analyses, Spruit (2001) reported that MDMA alone was found in 44–60% of samples, although 80% contained MDMA, MDA, MDEA, or amphetamine, either alone or as mixtures. Non-amphetamine drugs, such as caffeine, ephedrine, paracetamol, or ketamine, comprised between 4 and 18% of street samples each year. During the late 1990s these purity problems were largely resolved, and since then the overwhelming majority of ecstasy tablets have comprised MDMA (Cole *et al.*, 2002; Parrott, 2004a). Unknown chemical constituents was therefore certainly an important issue between 1993 and 1998, and may help to explain some of the idiosyncratic reactions during that period (Baggott *et al.*, 2000; Curran, 2000; Schifano, 2000). Impurity is far less of an issue now, although unknown chemical constituents could become more relevant again in the future.

The two core aspects of ecstasy/MDMA usage are acute or within session aspects, and chronic or lifetime effects. With reference to acute dosing, MacInnes *et al.* (2001) noted that Beck Depression Inventory scores in drug-free regular ecstasy users, were significantly associated with the intensity of single occasion usage (number of tablets within 12 hours). Topp *et al.* (1999), interviewed over 300 ecstasy polydrug users, mainly regular dance clubbers/ravers, who had been using ecstasy/MDMA intensively. The overall sample reported an average of eight physical and four psychological problems which they attributed to ecstasy use. Around 35% reported bingeing on ecstasy, which was defined as using the drug on a continuous basis for +48 hours, and this was significantly associated with more problems. These findings contrast with another chronic Australian study (Hansen *et al.*, 2001), where ecstasy had been used less intensively, in which the participants showed other signs of health awareness, and fewer psychobiological problems were apparent. In a chronic dose study, Verheyden *et al.* (2003b) found positive correlations between amount of MDMA taken in a normal session, with STAI anxiety, HADS anxiety, and HADS depression scores. Zhou *et al.* (2004) assessed markers for oxidative stress (lipoperoxide levels, superoxide dismutase activity in erythrocytes, and other indices). They were all significantly higher amongst the MDMA users than healthy controls, while oxidative stress values also correlated both with daily MDMA dosage, and duration of usage (see later). However, it was unclear whether this was a chronic or sub-acute effect, since the duration of abstinence from the last MDMA session was not reported. Soar *et al.* (2005) found an association between average ecstasy dose and self-rated sexual dysfunctioning, in a subgroup of abstinent ecstasy users. In another chronic study, Thomasius *et al.* (2003) compared four groups where drug use was confirmed by urine and hair analyses. Regression analyses indicated that the psychopathology indices and serotonergic alterations 'were best predicted by the number of ecstasy tablets taken on a typical event' (see Thomasius *et al.*, 2006).

Turning to the topic of cumulative or lifetime usage, many studies have shown that heavy users are more impaired than light users. This has been shown in relation to various aspects of neurocognitive test performance, psychiatric symptoms, and other psychobiological functions (Schifano *et al.*, 1998; Fox *et al.*,

2001; Back-Madruga *et al.*, 2003; Curran and Verheyden, 2003; Parrott *et al.*, 2003; Verheyden *et al.*, 2003a, b; Butler and Montgomery, 2004; De Win *et al.*, 2004; Halpern *et al.*, 2004; Jacobsen *et al.*, 2004; Zhou *et al.*, 2004; Fisk *et al.*, 2005; Yip, *et al.*, 2005; note Bolla *et al.*, 1998, showed that intensity of monthly usage rather than lifetime usage was the crucial aspect of cumulative usage). Although again in many of these studies, there were no significant differences between light and heavy users on some assessment measures. There is also considerable variation regarding how much ecstasy needs to be taken before any problems become apparent. Parrott *et al.* (1998) found that novice ecstasy users (less than ten occasions), as well as the more experienced users (more than ten occasions), both demonstrated significant memory impairments (unfortunately the recency of the last MDMA was not recorded). In a sub-acute prospective study, Parrott and Lasky (1998) noted that memory recall was significantly impaired in both novice and more experienced ecstasy users (same group criteria), although to a comparatively greater extent in the heavier users. The memory deficits endured for 7 days post-ecstasy, in contrast to the mood problems which peaked mid-week and then returned to normal. In a chronic study, Jacobsen *et al.* (2004) found significant deficits in a small group of young very light MDMA users (mean age 17 years; mean of ten MDMA episodes), with longer reaction times during selective and divided attention tasks, and different fMRI hippocampal profiles during the verbal working memory task.

Many other studies have found that light ecstasy/MDMA users are not impaired. Halpern *et al.* (2004) investigated ecstasy users without a history of other drug use; they found unimpaired cognitive task performance those who had taken it less than 50 occasions, whereas significant impairments in mental processing speed were apparent on several tasks in the more experienced users. Back-Madruga *et al.* (2003) revealed visual memory deficits in those who had taken ecstasy on more than 50 occasions, whereas task performance was not impaired in those who had taken it fewer times. Mejias *et al.* (2005) found that high MDMA users (mean 232 pills) had significantly slower response latencies on an event-related potential (ERP) visual oddball task, than the low MDMA user group (mean 56 pills). Fox *et al.* (2001) found that low users (1–99 tablets/lifetime) were not impaired on any cognitive task, moderate users (100–499 tablets/lifetime) showed some evidence for impairment, while high users (+500 tablets/lifetime) showed more neurocognitive deficits; although on many tasks there were no deficits in any group. Wareing *et al.* (2000) demonstrated a range of working memory deficits in very heavy users (using twice a week over 4 years); basic information processing speed was unimpaired whereas task accuracy was compromised. Wareing *et al.* (2004) noted significant deficits on other measures of working memory, again in heavy users. Fisk *et al.* (2005) found logical reasoning impairments which correlated with several polydrug indices including total lifetime ecstasy/MDMA use; the heavier ecstasy users also showed qualitative changes in their problem solving behaviour.

In an earlier review, Morgan (2000) noted the crucial role of lifetime usage: 'There is growing evidence that chronic, heavy recreational use of ecstasy is associated with sleep disorders, depressed mood, persistent elevation of anxiety, impulsivity and hostility, and selective impairment of episodic memory, working memory and attention.' Subsequent neurocognitive/psychobiological findings have been broadly consistent with this conclusion (see above studies). The importance of cumulative dosage is also apparent in studies employing subjective measures. Parrott *et al.* (2003) found that the proportion of recreational users who complained of ecstasy-attributed problems, increased significantly in parallel with lifetime dosage. Future studies might usefully employ objective and subjective measures in parallel. This would address the topic of their relative sensitivity/validity as measures. For instance, do users complain of memory/cognitive problems before they become apparent on objective tasks, or can the objective tasks reveal problems before they become subjectively recognized? A related question is the relative sensitivity of structural and functional measures. For instance, Daumann *et al.* (2005) found reduced MRI hippocampal activity in ecstasy polydrug users whose memory performance was not significantly impaired. Whereas Thomasius *et al.* (2003) noted that former ecstasy users displayed significant memory deficits in the absence of structural deficits (see Reneman *et al.*, 2006).

Although acute and chronic aspects of ecstasy/MDMA dosage are therefore important, there can be methodological problems in estimating MDMA intake. Many regular users state that it is difficult to remember how many ecstasy tablets they have taken over months and years, and this problem can be exacerbated by variations in MDMA strength and purity (Curran 2000; Schifano, 2000; Cole and Sumnall, 2003; Parrott, 2004); although Barrett *et al.* (2005) found that rave attendees were reliable in their recall about details of the drugs they had taken. Another important factor is chronic pharmacodynamic tolerance. Many regular users state that the subjective efficacy of MDMA reduces over time (Peroutka *et al.*, 1988), and this is often accompanied by increased self-dosing. Novice users generally take a single tablet (or a half), regular users often take two to four tablets, while the most experienced can take more than ten tablets in a single session (Fox *et al.*, 2001). Despite taking more tablets, regular users tend to report less intensive subjective effects, using phases like 'losing the magic'. Chronic tolerance to ecstasy/MDMA is covered more fully elsewhere, where the underlying mechanisms are also debated (Parrott, 2005). For current purposes, it should be noted that chronic tolerance is closely linked with longer-term psychobiological profiles. So that differences in the rate of development of chronic tolerance, may help to explain the variance in psychobiological findings. Intermittent or occasional use seems to be associated with less chronic tolerance and fewer psychobiological problems, than more intensive usage (Parrott, 2005). In this regard MDMA is similar to many other psychoactive drugs (Parrott *et al.*, 1994a). Other topics of potential relevance include acute tolerance or tachyphylaxis, sub-acute rebound/withdrawal phenomena, and drug dependence (Curran and Travill, 1997; Parrott and Lasky, 1998; Janssen, 1999; Cottler *et al.*, 2001; Verheyden *et al.*, 2003a, b; Hanson *et al.*, 2004; Milani and Parrott, 2004). These topics have only been rarely studied, but they are likely to influence the rate of development of psychobiological problems.

Table 1 Bioenergetic stress model for recreational ecstasy/MDMA users: contributory factors and theoretical predictions

Drug factors

Acute MDMA heightens neurotransmitter release for several hours, leading to acute metabolic distress in the serotonergic pre-synapse, greater oxidative stress, and impaired cellular recovery/repair. Bioenergetic stress is greater after higher single doses and/or repeated doses over a session stressful (Huether *et al.*, 1997; Zhou *et al.*, 2004) Hence intensive single occasion usage leads to more psychobiological problems (MacInnes *et al.*, 2001; Parrott, 2002; Thomasius *et al.*, 2003).

Chronic MDMA repeated sessions of acute metabolic stress lead to more chronic distress (Darvesh and Gudelsky, 2005) Hence chronic users develop more neuropsychobiological problems over time (Back-Madruga *et al.*, 2003; Halpern *et al.*, 2004; Fisk *et al.*, 2005; Mejias *et al.*, 2005).
MDMA tolerance will lead to increased self-dosing, yet these increasing doses *may* have weaker acute metabolic effects. Users may compensate by dancing for longer, or using drug cocktails. Hence the metabolic aspects of chronic tolerance are likely to be complex. Neurochemical adaptation and serotonergic neurotoxicity probably both involved (Parrott, 2005).

MDMA dependence may be less of a problem with ecstasy/MDMA than with other CNS stimulants, because of its longer time-course profile (contrast with cocaine) However psychological dependence could facilitate continued drug use (and hence more chronic distress) even when users recognize their own Ecstasy-related problems (Topp *et al.* 1999; Cottler, 2001; Milani *et al.*, 2004).

Co-use of other CNS stimulants amphetamine, cocaine, and/or nicotine co-use may heighten acute metabolic stress, and so contribute to the adverse psychobiological profiles (Thomasius *et al.*, 2003).

Co-use of CNS depressants. Some depressant drugs *may* help to reduce acute metabolic distress, and hence also lessen any long-term problems related to chronic distress. However drugs such as cannabis and alcohol cause many psychobiological problems in their own right. Overall effects are generally cumulatively detrimental (Rodgers *et al.*, 2003; Rizzo *et al.*, 2004; Gouzoulis-Mayfrank, this issue), although with subtle interactive aspects (Parrott *et al.*, 2004a).

Non-drug factors

Temperature. High temperature increases serotonergic neurotoxicity in rats (Malberg and Seiden, 1998; Green *et al.*, 2003), while MDMA increases body temperature in humans (Freedman *et al.*, 2005) The increase in metabolic activity is greater under hot conditions (Tancer *et al.*, 2003), and recreational users report feeling hot and sweaty (Topp *et al.*, 1999) Subjective temperature ratings associated with self-reported psychobiological problems (Fig. 1).

Exercise/dancing may increase metabolic and physical distress in ecstasy/MDMA users (needs empirical investigation) Subjective reports of high levels of dancing/activity associated with more memory problems (Parrott *et al.*, 2005b) Fluid intake, sweating, and dehydration, also potentially important.

Other factors

Many further factors can influence to the psychobiological profiles of recreational ecstasy/MDMA users. Sometimes this will be via additional metabolic distress. Often these influences will comprise other forms of stressor.

Sleep and circadian aspects. Circadian aspects are affected by MDMA in rats and humans (McCann *et al.*, 2000) Inadequate rest/recuperation in regular dancers/ravers may contribute to psychobiological distress, either directly or indirectly.

Nutrition. MDMA can reduce appetite and lead to weight loss (Turner *et al.*, 1999) This may exacerbate bioenergetic stressors such as MDMA and/or other stimulant drugs, as well as being an independent stressor.

Immuno-competence. MDMA can reduce immuno-competence in humans (Pacifici *et al.*, 2002; Connor, 2004) This may reduce the ability to process any psychoactive drug, as well as contributing to general psychobiological distress and health in general.

Premorbid characteristics. Proneness towards anxiety, stress, depression, or other indications of heightened sensitivity, may increase the likelihood of acute/chronic abreactions to psychoactive drugs, including MDMA (Schifano 2000; MacInnes *et al.* 2001; Verheyden *et al.* 2003a; Butler and Montgomery, 2004; Roiser *et al.* 2005) Robust personality types may be more able to handle the stressor of repeated psychoactive drug use. This could reflect individual differences in cellular metabolism, or in numerous other mechanisms. Another complex topic.

Gender. Females often differentially sensitive to MDMA (Liechi *et al.*, 2001; Curran *et al.*, 2004). Metabolic and non-metabolic aspects probably both involved.

Genetics. Numerous drug and non-drug factors are related to acute and chronic MDMA effects (see text). Genetic aspects therefore likely to be complex and multi-factorial (Simantov, 2004).

Polydrug aspects: the role of cannabis

Most recreational MDMA/ecstasy users also take other psychoactive drugs. Cannabis is the most frequently encountered co-drug. In a survey of young Germans, Schuster *et al.* (1998) noted that 97% of ecstasy/MDMA users also took cannabis. While in American college students, Strote *et al.* (2002) found that 92% of those who had taken ecstasy/MDMA, also used cannabis. High rates of ecstasy–cannabis co-use have been noted in many studies (Topp *et al.*, 1999; Rodgers, 2000; Winstock *et al.*, 2001; Dafters *et al.*, 2004; Scholey *et al.*, 2004; Wareing *et al.*, 2004). Since cannabis alone can cause cognitive deficits (Hall and Solowij, 1998; Pope *et al.*, 2001), this raises the question of whether the adverse cognitive profiles of ecstasy polydrug users, are due to their use of cannabis rather than MDMA. This topic has been extensively investigated in the past few years, but a range of conclusions has been reached. A brief empirical review will be followed by a debate about some possible reasons for this variance in findings.

Croft *et al.* (2001a) found that ecstasy–cannabis users, and cannabis users, were both significantly impaired on some cognitive tasks, in comparison with the non-user controls. However there were no significant differences between the two active drug groups, which led to the conclusion that the cognitive deficits in the MDMA–cannabis group were probably due to cannabis rather than MDMA. Simon and Mattick (2002) compared a group of heavy cannabis users, with a group of heavy cannabis and moderate ecstasy users. There were no significant group differences on any cognitive task. But when the ecstasy–cannabis group was compared to the cannabis-alone group, there were borderline trends for worse auditory immediate memory, and worse auditory delayed memory in the co-drug users: Whereas in the regression analyses, current frequency of cannabis use predicted visual immediate memory, and showed a borderline predictive trend with the immediate memory model. In terms of drug attribution, it was concluded that cannabis rather than ecstasy was responsible for the cognitive deficits. Gouzoulis-Mayfrank *et al.* (2002) investigated the endocrine abnormalities of abstinent ecstasy users, and showed that the prolactin response to d-fenfluramine was related to the use of cannabis rather than MDMA. Daumann *et al.* (2004) showed that the psychopathological problems of recreational ecstasy polydrug users, were related to their use of cannabis rather than MDMA. Furthermore, abstinence from cannabis, rather than from ecstasy, predicted the remission of psychological complaints in former users. This agreed with some earlier findings from Morgan *et al.* (2002; see below). Dafters *et al.* (2004), compared four subject groups: cannabis users, light ecstasy–cannabis users, heavy ecstasy/cannabis users, and non-user controls. The three drug groups all showed significant memory impairments, whereas there were no significant differences between the cannabis and cannabis–ecstasy groups on any cognitive tasks. Hence a number of studies have found that cannabis, rather than MDMA, is responsible for the neuropsychobiological deficits of ecstasy–cannabis polydrug users.

Other studies have however shown that it is ecstasy rather than cannabis, which is related to the neuropsychobiological deficits. Croft *et al.* (2001b) compared three subject groups, and found that serotonergic dysfunction was significantly related to lifetime MDMA use, and was independent of cannabis use. Heffernan *et al.* (2001) found that regular ecstasy polydrug users reported higher prospective memory deficits than non-user controls, and this remained significant when cannabis use was partialed-out by co-variance. Fox *et al.* (2002) found significant impairments on neurocognitive tasks with known sensitivity to temporal lobe dysfunction, in a group of ecstasy–cannabis polydrug users, compared to cannabis polydrug users as the control group. Morgan *et al.* (2002) showed that memory/cognitive deficits were predicted by ecstasy use, and not by cannabis use; furthermore the memory problems did not recover after 2 years of abstinence from ecstasy. Parrott *et al.* (2000) found higher self-rated psychiatric symptoms in light and heavy ecstasy/MDMA polydrug users, compared to the control group which contained a similar proportion of cannabis users. Furthermore, the heavier ecstasy users were more impaired than the light ecstasy group. McCardle *et al.* (2004), revealed significant deficits in learning and memory in ecstasy users compared to non-user controls, and these were not related to the use of cannabis. Tuchtenhagen *et al.* (2000) found different auditory evoked potential patterns in abstinent ecstasy users, compared to both cannabis users and non-drug user controls, while the two latter groups did not differ from each other. Quednow *et al.* (2003) reported increased pre-pulse inhibition of a startle response in male MDMA users, compared to male cannabis users and non-user controls. Again the cannabis-alone group did not differ from the non-drug user control group. Wareing *et al.* (2004) found verbal working memory deficits in current and former ecstasy users compared to non-user controls, and these remained significant after controlling for cannabis use. Gouzoulis-Mayfrank *et al.* (2003) compared light ecstasy users, heavy ecstasy users, and the non-user controls (which included some cannabis users). Memory was significantly impaired in the heavy ecstasy user group, and the frequency of ecstasy use was significantly related to several memory measures. In contrast, the use of cannabis was not related to any of the cognitive/memory tasks.

Finally, many other studies have shown that *both* ecstasy/MDMA and cannabis are associated with neuropsychobiological problems. Rodgers (2000) found that cannabis users displayed significant deficits on verbal memory tasks, while in addition to these verbal memory problems, the ecstasy–cannabis users also showed significant deficits in the delayed memory measures. In a cross-cultural study involving two control and four illicit drug groups, Parrott *et al.* (2001) found raised psychiatric symptom profiles in the cannabis-alone group, the illicit polydrug group, also the light and heavy ecstasy polydrug user groups. Milani *et al.* (2000) undertook a breakdown of these polydrug influences and showed that several of the psychiatric symptom deficits were associated with lifetime ecstasy/MDMA use. Rodgers *et al.* (2003) found that cannabis use was associated with everyday memory problems, whereas ecstasy was associated with prospective memory difficulties. They also documented the level of problem being described by ‘typical’ ecstasy users and cannabis users, also noting that co-users of both drugs tended to report both types of memory problem. Thomasius *et al.* (2003) found that

certain aspects of auditory verbal learning performance were best predicted by ecstasy, whereas other aspects of task performance were best predicted by cannabis. In an investigation of car driving related skills, Rizzo *et al.* (2004) found a significant impairment in recently abstinent cannabis users, while the performance of the recently abstinent cannabis/ecstasy group was impaired to a significantly greater extent (more details below). Gouzoulis-Mayfrank *et al.* (2000) closely matched the level of cannabis use in their ecstasy–cannabis and cannabis-alone groups. There were no differences between the cannabis users and the non-user control group on any task. Whereas the ecstasy–cannabis users performed significantly worse than non-drug controls on most cognitive tasks, and they were significantly worse than the cannabis-alone group on tasks involving learning, memory, problem solving, and strategic planning. This led to the conclusion that ecstasy rather than cannabis was mainly responsible for the neurocognitive deficits. However amongst the MDMA group, heavy ecstasy use and heavy cannabis use were both associated with worse cognitive performance, on some tasks. Milani *et al.* (2005) found that heavy cannabis use exacerbated the psychobiological problems of recreational ecstasy users, whereas light cannabis use was associated with a *reduced* frequency of problems, in comparison with the MDMA group who did not use cannabis (see below).

Several factors may contribute to the diversity of findings. One crucial influence is the relative use of cannabis and ecstasy. For instance in Croft *et al.* (2001a), the mean lifetime use of cannabis was +10 000 occasions, whereas their use of ecstasy was 40 occasions. The comparatively higher use of cannabis, may have contributed to their finding that the cognitive deficits were related to cannabis rather than ecstasy. In another study by the same group (Croft *et al.*, 2001b), the mean use of cannabis was a more modest 2.3 joints/week, whereas the lifetime use of MDMA was higher at 225 tablets; here the structural problems were found to be associated with MDMA rather than cannabis (note: other factors also will have contributed to the differences in findings). The participants in Simon and Mattick (2002) were heavy cannabis users but generally lighter ecstasy users; this may have contributed to their conclusions about cannabis being more important. Several studies have matched the use of cannabis between groups, and this matching may have facilitated the specific contribution of MDMA to emerge (Gouzoulis-Mayfrank *et al.*, 2000; Fox *et al.*, 2002). Another relevant factor is the type of psychobiological function being assessed. Some cognitive tasks may be particularly sensitive to cannabis, whereas others are more sensitive to MDMA (Rodgers, 2000; Heffernan, 2001; Rodgers *et al.*, 2003; Parrott *et al.*, 2004b). This area should prove fruitful for future research, especially as their cognitive influences may overlap and interact (see below). In wider terms, the whole spectrum of psychopathological, neuroendocrine, cognitive, and other psychobiological functions, may be affected by the two drugs in different and/or overlapping ways. For instance, Morgan *et al.* (2002) found that psychopathological problems were most strongly related to cannabis, whereas the cognitive/memory deficits were predicted by ecstasy/MDMA use. This conclusion has also emerged in studies by the Köln group (Gouzoulis-Mayfrank, 2000, 2003; Daumann *et al.*, 2003, 2004). To summarize, cannabis and MDMA both contribute to the adverse neuropsychobiological profiles of ecstasy–cannabis polydrug users. Their relative contributions will depend on how much of each drug has been used, along with many other influences. This simple additive factors model in humans has been briefly outlined elsewhere (Parrott, 2003a), while Young *et al.* (2005) demonstrated a similar synergistic model for working memory impairments in rats.

The joint effects of cannabis and MDMA may be more interactive, especially when taken together (Parrott *et al.*, 2004a). This notion is based on their acute profiles, which are opposite in certain crucial aspects. MDMA is a powerful CNS stimulant whereas cannabis has sedative/relaxant properties; MDMA is hyperthermic whereas cannabis is hypothermic; MDMA increases oxidative stress while cannabinoids are powerful antioxidants (Hampson *et al.*, 2000; Grundy *et al.*, 2001; Croxford, 2003). This has generated the tentative hypothesis that when taken together, cannabis may help to ameliorate the stimulatory effects of MDMA. Furthermore if cannabis does reduce the acute neuronal overstimulation induced by MDMA, it may then also attenuate any drug-induced neurotoxicity (Parrott *et al.*, 2004a). There are some animal data which supports this model. Morley *et al.* (2004), co-administered the cannabinoid Delta 9-THC with MDMA to male Wistar rats. The addition of THC prevented the normal MDMA-induced hyperthermia, and it also tended to decrease the hyperactivity caused by acute MDMA administration. Delta 9-THC also partially prevented the depletion of 5-HT and 5-HIAA, which had been induced by MDMA when it was given alone. This partial neuroprotection was evident across several brain regions, and may reflect the hypothermic effects of THC, since other hypothermic agents are also neuroprotective (Colado *et al.*, 2002).

Turning to the human data, Daumann *et al.* (2003) compared cerebral activation patterns during working memory performance in pure MDMA users, polydrug ecstasy users, and matched controls. The pure ecstasy users demonstrated somewhat different activation patterns from the other two groups, whereas the polydrug ecstasy users did not differ from the non-user controls. Milani *et al.* (2005) investigated the effects of different cannabis usage patterns amongst recreational ecstasy users. Heavy cannabis use was associated with more long-term psychobiological problems, whereas light/moderate cannabis use ameliorated various aspects of psychobiological distress, when compared to the ecstasy-alone group. Parrott and Young (2005) measured the body temperatures of dance clubbers, and found higher mean temperatures amongst the ecstasy users than non-user controls (see below). The correlation between MDMA use and temperature was strongly positive ($p < 0.001$), whereas the correlation with cannabis was negative but statistically borderline ($p < 0.10$, two-tailed). Daumann *et al.* (2003) commented that their fMRI findings provided empirical support for the notion that cannabis might provide a degree of protection against MDMA-induced neurotoxicity, at the molecular and the neuro-functional level. This hypothesis may provide another interesting area for future research (Parrott *et al.*, 2004a). If confirmed, it could help explain some of the variance in functional and structural findings amongst recreational ecstasy–cannabis users. In overall terms however, it should be emphasized that co-users of these two drugs will generally

experience neuropsychobiological consequences which are broadly additive and cumulatively detrimental (see: Gouzoulis-Mayfrank and Daumann, 2006).

Polydrug aspects: the contribution of other psychoactive drugs

The majority of ecstasy users take a wide range of psychoactive drugs. Chang (2001) noted that ecstasy users often took a variety of other drugs, including stimulants and hallucinogens. Fox *et al.* (2001) found that significantly more ecstasy users had taken amphetamine, cocaine or LSD, than the cannabis-user controls. Scholey *et al.* (2004) revealed the following incidence rates: amphetamine 69%, LSD 60%, psilocybin mushrooms 56%, cocaine 56%, barbiturate-benzodiazepines 38%, opiates 23%, solvents 21% (all significantly higher than non-user controls). Furthermore the use of cocaine, amphetamine, LSD, and magic mushrooms, were significantly higher amongst heavy compared to light MDMA users. Parrott *et al.* (2001) documented that ecstasy users were not only more likely to use other illicit drugs, but were also heavy alcohol drinkers and tobacco smokers. Similar observations about greater polydrug use have been made in many other reports (Schifano *et al.*, 1998; Morgan, 1999; Pedersen and Skrondal, 1999; Topp *et al.*, 1999; Curran, 2000; McCann *et al.*, 2000; Milani *et al.*, 2000; Morgan, 2000; Parrott *et al.*, 2000; Schifano, 2000; Boys *et al.*, 2001; Heffernan *et al.*, 2001; Parrott, 2001; Morgan *et al.*, 2002; Parrott *et al.*, 2003; Thomasius *et al.*, 2003; Butler and Montgomery, 2004; Roiser and Sahakian, 2004; Sumnall *et al.*, 2004; Wareing *et al.*, 2004; Fisk *et al.*, 2005; Milani *et al.*, 2005; Sumnall and Cole, 2005).

The potentially confounding influence of these other drugs, has often been assessed using co-variance. Morgan (1999) confirmed that the memory deficits of ecstasy polydrug users remained significant after controlling for LSD use. Fox *et al.* (2001), confirmed that their selective neurocognitive deficits remained significant after controlling for amphetamine, cocaine, and LSD use, again by co-variance. Wareing *et al.* (2004) found significant impairments in visuospatial working memory span, in both current and former MDMA users; these deficits remained significant after controlling for alcohol, amphetamine, and cocaine use. Rizzo *et al.* (2005) found that the perception of self-motion or 'heading' (a crucial skill for car drivers), was most impaired in the ecstasy–cannabis user group. The concomitant use of alcohol and cocaine was again a potential confound, yet the deficits remained after they had been partialed out by co-variance. Fisk *et al.* (2005) revealed significant deficits in syllogistic reasoning ability in ecstasy polydrug users. The reasoning task deficits were related to several drug variables, including MDMA, cannabis, cocaine, and alcohol. However the strongest relationship was with ecstasy/MDMA, so that when full Bonferonni corrections were applied, only three variables remained significant: lifetime ecstasy usage, weekly ecstasy dose, and the ecstasy user/non-user group distinction. Many other studies have confirmed that the ecstasy group deficits remain after controlling for the potential influence of other psychoactive drugs (e.g. MacInnes *et al.*, 2001; Verkes *et al.*, 2001).

This shows that the significant ecstasy/MDMA group differences in the above studies, were not an artifact of other psychoactive drug use. However it does not indicate that these other drugs will not be having any neuropsychobiological effects. In order to investigate their actual contribution, studies need to be designed specifically for that purpose. In particular, adequate statistical power needs to be obtained through larger representative samples. For instance, there are strong theoretical grounds for predicting that the co-use of methamphetamine or other CNS stimulants, would exacerbate the acute effects of MDMA, and hence increase any longer term functional or structural problems (Huether *et al.*, 1997; Parrott, 2001, 2002; Green *et al.*, 2003; see final section). In order to test this hypothesis, the psychobiological performance of regular methamphetamine users, should be compared with an equivalent group of MDMA–methamphetamine *co-drug* users. I am not aware of any such study, although Brecht and von Mayrhauser (2002) undertook a non-psychobiological investigation of MDMA–methamphetamine polydrug users.

The co-effects of tobacco/nicotine and alcohol, have however been investigated using powerful factorial designs. Parrott *et al.* (2005a) compared two groups of regular cigarette smokers, ecstasy users and non-users as controls. Everyone was assessed over a day of normal smoking, and a day of tobacco abstinence, using a methodology taken from nicotine research (Parrott, 1999; Parrott and Kaye, 1999). Self-rated feelings of stress and arousal were similar for both groups, but self-rated feelings of pleasure were significantly lower amongst the ecstasy users, under both smoking and abstinence. More of the ecstasy using smokers reported 'smoking for pleasure', despite their mean daily pleasure ratings being consistently lower than those of the control group, supporting the notion that this motive reflects an attempt to 'reverse the pain of abstinence' (Parrott, 2003b). Self-rated uplifts, hassles, stresses, and cognitive failures at the end of the day, did not differ between groups when smoking, but were worse for both groups under abstinence, with the nicotine-deprived ecstasy users being significantly more impaired. Cortisol levels were similar for both groups on the smoking day, but were significantly higher after a day of abstinence, and again this increase was significantly greater amongst ecstasy/MDMA users. Self-rated memory deficits showed an additive influence for nicotine and ecstasy. Heffernan *et al.* (2005) also found significantly more self-rated memory problems in tobacco smokers. These findings illustrate a complex array of additive and interactive effects between nicotine and ecstasy/MDMA (Parrott *et al.*, 2005a).

The other major legal psychoactive drug taken with MDMA is alcohol (Schifano *et al.*, 1998; Barrett *et al.*, 2005; Milani *et al.*, 2005). Hernandez-Lopez *et al.* (2002) assessed the effects of acute MDMA and alcohol, both alone and in combination, using a 2×2 factorial design. Plasma concentrations of MDMA were increased under alcohol, whereas alcohol levels were slightly reduced by MDMA. Feelings of euphoria were more prolonged after the drug combination, while MDMA reversed the feelings of sedation induced by alcohol. Ling *et al.* (2003) revealed self-rated memory deficits and cognitive failures, which were significantly related to

alcohol use. Benzodiazepines, barbiturates, and opiates also cause neurocognitive/psychobiological deficits (Parrott *et al.*, 2004b), and they may comprise further drug factors. Roiser and Sahakian (2004) found that Beck Depression Inventory scores correlated not only with MDMA usage, but also with amyl nitrate exposure. Sumnall *et al.* (2004) noted that Beck Anxiety Inventory scores correlated significantly with alcohol and amphetamine use, as well as with ecstasy. Thomasius *et al.* (2003) found that cocaine use over the previous year, was additional to MDMA and cannabis as predictive drug factors for impaired task learning. Hence the neuropsychobiological profiles of ecstasy polydrug users are likely to reflect an amalgam of multiple drug influences.

The complexity of these polydrug influences raises the question of whether there are any 'pure' ecstasy/MDMA users. Three recent studies have assessed recreational users with minimal experience of other psychoactive substances. Halpern *et al.* (2004), investigated the neurocognitive performance of young ecstasy users from Salt Lake City. They mostly avoided all other psychoactive substances, including alcohol, nicotine, and cannabis. The ecstasy users with less than 50 experiences/lifetime displayed similar levels of cognitive performance to the non-user controls on all tasks, whereas the more experienced ecstasy users displayed significant deficits on several working memory tasks. Yip *et al.* (2005) investigated the cognitive functioning of young ecstasy/MDMA users in Hong Kong, who also reported very light usage of all other psychoactive substances. These relatively pure MDMA users produced significant deficits in verbal memory, non-verbal memory, complex attention, and verbal fluency tasks. Both studies involved young ecstasy users who were dancers/ravers (Halpern *et al.*, 2004; Yip *et al.*, 2005); the possible relevance of this factor is debated later. Zhou *et al.* (2004) compared 120 novice but intensive MDMA users, with 120 healthy controls in China. Recent MDMA use was confirmed by urine analysis and 'self-confession'. Drug abuse, sedative-hypnotics, cigarette smoking, and alcohol abuse, were amongst the strict exclusion criteria. Every biochemical marker for oxidative stress (see earlier) was significantly raised in the ecstasy group, and the increases were strongly correlated with both lifetime and daily MDMA usage.

Diathesis-stress models: psychiatric and other aspects

Although some early psychobiological investigations into the acute effects of MDMA considered that it was probably safe, they also noted that not enough was known about its long-term effects (Downing, 1986). Within a few years of its wider recreational usage, reports of psychiatric breakdown started to emerge (Creighton *et al.*, 1991; McCann and Ricaurte, 1991; Schifano and Magni, 1994; review by Soar *et al.*, 2001). Following these early case studies, larger cohort investigations confirmed that symptoms of depression, psychoticism, phobic anxiety, generalized anxiety, obsessive compulsive disorder, and bulimia, were often higher amongst ecstasy polydrug groups than non-user controls (Schifano *et al.*, 1998; Parrott *et al.*, 2000; Schifano, 2000; Parrott *et al.*, 2001; Morgan *et al.*, 2002; Parrott *et al.*, 2003; Verheyden *et al.*, 2003a, b; Roiser and Sahakian, 2004; Sumnall and Cole, 2005). This should not be seen as surprising, given that other recreational drugs such as dexamphetamine, cocaine, and amyl nitrate, are associated with enhanced levels of clinical distress (Parrott *et al.*, 2004a; Roiser and Sahakian, 2004; Sumnall *et al.*, 2004). Furthermore, community samples of illicit polydrug users who have never used MDMA, also tend to show raised psychiatric symptom profiles and other psychobiological problems (Williamson *et al.*, 1997; Parrott *et al.*, 2001). Sumnall and Cole (2005) undertook a meta-analysis of 16 published investigations into self-rated depression. They found a small but significant overall effect size due to ecstasy. Crucially their preferred comparison group was polydrug users rather than drug naive controls. Another important issue is to differentiate between psychopathological disorders which are apparent before recreational drug use, and premorbid dispositional characteristics since, in many cases of clinical distress, there is an overt history of psychiatric disorder prior to drug taking. In a prospective study of over 2000 adolescents and young adults, Lieb *et al.* (2002) reported that: 'First use of ecstasy was secondary to the onset of DSM-IV mental disorders in the majority of cases.' Many illicit drug users also display personality characteristics such as impulsivity and sensation-seeking, which may precede drug onset and/or be heightened by repeated stimulant usage (Butler and Montgomery, 2004; further discussion below). These factors all need to be considered when debating causation (Lieb *et al.*, 2002; Cole and Sumnall, 2003; Verheyden *et al.*, 2003b).

McGuire (2000) noted: 'Regular MDMA use can be associated with chronic psychiatric symptoms which persist after the cessation of drug use. However, it is difficult to determine whether MDMA use is directly responsible, triggers symptoms in subjects predisposed to mental illness, or is incidental.' In two of the earliest case studies, McCann and Ricaurte (1991) emphasized that both of them had a psychiatric history prior to taking ecstasy, and suggested that the breakdowns triggered by MDMA may have reflected this prior vulnerability. But is this found in all instances of MDMA-attributed psychiatric disorder? In order to address this question, Soar *et al.* (2001) undertook a review of the psychiatric case studies published in the previous 10 years. This revealed that 24% of cases had a previous psychiatric history, while 34% had a psychiatric illness amongst their first degree relatives. Hence a high proportion of cases had developed a clinical disorder without any known predisposition factors. Soar *et al.* (2001) also noted a temporal relationship between ecstasy use and psychiatric symptoms. Hence in some case histories drug cessation led to a reduction in symptoms, while in others the resumption of ecstasy use led to a recurrence of symptoms. Lifetime dosage was also noted as another factor. The conclusion that predisposition factors and drug factors could both be influential, was also reached by MacInnes *et al.* (2001). They noted that former chronic ecstasy/MDMA polydrug users were significantly more likely to report depressive symptoms than matched non-user controls. This increase in depression was not related to the use of alcohol, cannabis, or amphetamine, but it was associated with intensity of ecstasy use (tablets over 12 hours), with self-rated life stressors,

and with the personality dimension 'external locus of control'. MacInnes *et al.* (2001) had also excluded any volunteer with a psychiatric history, confirming that 'normal' non-clinical ecstasy users were at risk of developing psychiatric problems (see also Kopelman *et al.*, 2001).

Diathesis-stress models can provide a theoretical framework for understanding how internal factors and external events interact, and generate the particular psychiatric/psychobiological outcome. In the present context, the core question is how the numerous external factors surrounding ecstasy/MDMA polydrug usage, interact with a wide range of predisposition characteristics. MacInnes *et al.* (2001) debated their clinical findings in the context of a 'vulnerability model' of depression, which comprises a particular example of a diathesis-stress model. The essence of all these interactive models is that a wide range of psychobiological outcomes are possible, depending on the individual profile of predisposition factors, and the numerous external (drug and non-drug) stressors. One of the central tenets is that those individuals with high loadings on internal predisposition factors (genetic, bio-neurochemical, personality, psychiatric), will be at greatest risk of developing adverse drug reactions. Hence a vulnerable individual may show a severe abreaction to a single ecstasy/MDMA experience; indeed, several such case studies can be seen in Soar *et al.* (2001). In contrast, robust individuals without low loadings on predisposition factors, should be more able to cope with the stresses of repeated MDMA (Curran and Travill, 1997; Parrott, 2001, 2002; Verheyden *et al.*, 2003a, b). Hence many regular MDMA users may remain largely problem free for a period of time. Although even in these comparatively robust individuals, the diathesis-stress model predicts that problems will gradually develop as more drug is taken. Hence most heavy ecstasy users report multiple psychobiological problems (Topp *et al.*, 1999; Parrott *et al.*, 2003). In very heavy MDMA users, these problems can be pronounced and enduring, despite describing their initial experiences with ecstasy in positive terms (Jansen, 1999; Parrott, 2000; Soar *et al.*, 2004).

Diathesis-stress models may provide a useful framework for future MDMA research, since they have shown utility in other applied clinical areas (Monroe and Simons, 1991; Laviola *et al.*, 1999; Parrott, 2003b). One important question is the nature of the internal predisposition factors. These may include a range of biochemical, cellular-metabolic, neurochemical, genetic, age, gender, personality, and psychiatric aspects (Laviola *et al.*, 1999; Liechti *et al.*, 2001; Lieb *et al.*, 2002; Lynch *et al.*, 2002; Verheyden *et al.*, 2003b; Butler and Montgomery, 2004; Simantov, 2004; Simantov and Peng, 2004; Von Geusau *et al.*, 2004; Darvesh and Gudelsky, 2005; Milani *et al.*, 2005; Roiser *et al.*, 2005). With reference to gender, Lynch *et al.* (2002) suggested that females were more vulnerable to the reinforcing effects of psychostimulants during many phases of the drug-using cycle. Liechi *et al.* (2001) empirically demonstrated that the acute effects of MDMA could be more intense in females, and that they also experienced drug sequelae more frequently. Milani *et al.* (2005) also found differential gender effects in various recreational drug user subgroups, including light ecstasy users. Verheyden *et al.* (2002) found that female ecstasy users tended to report mid-week feelings of depression, whereas males were more prone to aggression during the post-MDMA period. M ter Bogt and Engels (2005) demonstrated different patterns of psychobiological and psychosocial sequelae, again related to gender. Rodgers *et al.* (2003) found no gender effect on memory questionnaire scores, despite large sample sizes and hence good statistical power. With reference to genetic aspects, these have mainly been investigated using laboratory species such as the mouse (Simantov, 2004; Simantov and Peng, 2004), and care needs to be taken in relating the animal findings to humans (e.g. De la Torre and Farre, 2004; Green *et al.*, 2003). However Roiser *et al.* (2005) empirically demonstrated functional polymorphism of the serotonin transporter gene in humans; aberrant emotional processing was evident only in particular genotypes of recreational ecstasy users.

Another key prediction of diathesis-stress models, is that premorbid characteristics will help to determine the nature of the clinical outcome. For instance, those initially predisposed to depression, would be most at risk from developing more severe depression (McInnes *et al.*, 2001); whereas those with a pre-drug tendency towards obsessive behaviour, would be more likely to develop Obsessive Compulsive Disorder. This model could be relevant not only for psychiatric aspects, but also to wider psychobiological functioning in general. For instance, one prediction is that those with poor sleep architecture pre-drug, will be most at risk of suffering greater sleep problems afterwards. In cognitive terms, it may be that those with less cognitive skills (low IQ?), might be more susceptible to the development of neurocognitive problems. It should also be emphasized that these models are best conceptualized as dynamic and multi-factorial. Hence the numerous internal and external factors, will interact in a complex way to generate a wide range of changing outcomes. This can be illustrated with reference to the notion of impulsivity, which can be assessed by either behavioural measures or questionnaire scores (Morgan, 1998; Butler and Montgomery, 2004; Butler and Harrison, 2005). Butler and Montgomery (2004) found a gradual increase in impulsivity as drug use intensified. On their behavioural measure of impulsivity, the high ecstasy user group scored significantly higher than the light ecstasy polydrug group. The authors debated their findings in terms of impulsivity being a personality characteristic in those who decide to use illicit drugs, with ecstasy then intensifying this inherent predisposition, possibly via serotonergic neurotoxicity. As in many other reports, it was emphasized that prospective studies were needed to empirically test these ideas (Butler and Montgomery, 2004). The crucial point is that the personality factor of trait impulsivity, is dynamically inter-related with its behavioural expression in terms of impulsive activities. Hence impulsivity has numerous inter-related aspects. It is a psychobiological dimension which pre-dates drug use. It can also influence the decision to use/not use drugs, and the ways in which they are then taken – carefully or recklessly. Impulsive behaviours can also be heightened by disinhibitory drugs such as alcohol, MDMA, or other drug cocktails. The key notion is that premorbid characteristics will influence the nature of the expressed behaviours. Furthermore many different types of behaviour may be affected, including those not traditionally described in pejorative terms as 'impulsive'; for instance, dancing for long periods despite feeling hot and tired (see later).

Diathesis-stress models also warn against the use of MDMA for psychotherapeutic purposes in clinically vulnerable individuals (as advocated by Doblin, 2002). Many empirical ecstasy/MDMA investigations have specifically excluded participants with a psychiatric history (e.g. Vollenweider *et al.*, 1998; MacInnes *et al.*, 2001; Hernandez-Lopez *et al.*, 2002; Daumann *et al.*, 2004). The latter study not only screened out subjects with a psychiatric disorder (personal or family), but also excluded those with low 'openness' and/or high 'neuroticism' personality questionnaire scores (Vollenweider *et al.*, 1998). The reason for this *additional* exclusion was that these personality types had been found to be 'particularly liable to prolonged and severe responses to stimulant and hallucinogenic drugs' (Dittrich, 1994). The primary concern is that those individuals with psychiatric vulnerability may be particularly prone to drug-induced abreactions. For instance, while acute MDMA increases positive moods, in the days afterwards poor moods such as irritability and depression predominate. The prediction is that these post-drug recovery problems will be most pronounced amongst those with psychiatric vulnerability (e.g. previous experiences of depression). Furthermore these problems may become even more apparent after repeated drug usage. This is related to the observation that those regular ecstasy users who display psychiatric symptoms, often demonstrated overt symptoms or pre-dispositional characteristics prior to drug use (see earlier). This whole topic is being debated more fully elsewhere (Parrott, in preparation).

Turning to the external stressors, Connor (2004) noted that: 'Many of the physiological changes elicited by MDMA closely resemble those induced by acute stress ... exposure to MDMA could be regarded as a chemical stressor'. Darvesh and Gudelsky (2005) similarly found that the acute administration of MDMA caused bioenergetic stress, leading to the 'dysregulation' of energy metabolism. The rationale for why a single dose of MDMA is metabolically stressful, and why intensive or repeated MDMA can be even more stressful, is described more fully in the final section. Other CNS stimulants may also act as metabolic-biochemical stressors, whereas some CNS depressants and/or antioxidants may help to protect against metabolic stress (Huether *et al.*, 1997; Green *et al.*, 2003; see earlier). Further external stressors include lifestyle factors, such as poor sleep, inadequate rest and recuperation, reduced food intake, weight loss, susceptibility to infections, and various occupational/interpersonal aspects (Connor, 2004; McCann *et al.*, 2000; Pacifici *et al.*, 2002; Parrott *et al.*, 2003; Topp *et al.*, 1999; Turner *et al.*, 1999). It should be emphasized that these external stressors all have their own characteristics, and will thus display very different patterns of interaction with the numerous internal factors. Finally, one crucial group of external factors are found at the venues where MDMA is mostly taken: dances and raves. The next section will therefore examine whether heat, exertion, and the other stimulating/energetic factors encountered at these venues, might also contribute to the neuropsychobiological effects of MDMA.

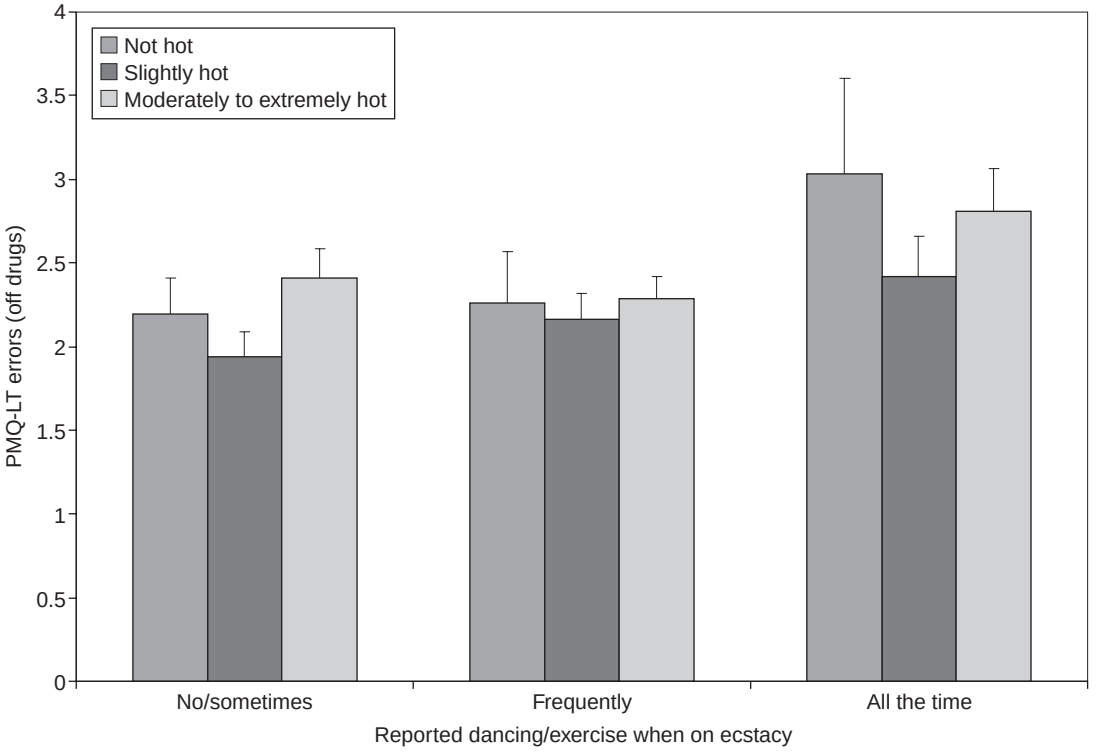

Figure 1 Prospective Memory Questionnaire long-term errors in nine subgroups of recreational ecstasy /MDMA users, stratified according to the self-reported extent of dancing when on ecstasy, and subjective feelings of being hot when on ecstasy (after Parrott *et al.*, 2005b).

Environmental aspects: heat, exertion, and other 'dance club' factors

In general population surveys, the proportion of young people who admit to having taken ecstasy is 5–15%, but when dance clubbers and ravers are sampled, far higher usage rates of 80–95% emerge. Winstock *et al.* (2001) found that 96% of UK dancers and ravers reported having taken ecstasy. In a very large Dutch rave, Wijngaart *et al.* (1997) found that 81% had tried ecstasy at least once, while 64% had taken it the previous night. Tossman *et al.* (2001) noted that dance party enthusiasts were far more prone to using ecstasy than similar aged cohorts. This association has led to ecstasy/MDMA being described as a 'dance' or 'club' drug (DAWN, 2000; Riley *et al.*, 2001; Bellis *et al.*, 2002; Yacoubian *et al.*, 2003; Barrett *et al.*, 2005;). The conditions at dance clubs and raves are typified by crowded conditions, prolonged dancing, loud music, bright light shows, and high temperature (Suy *et al.*, 1999). The aim of this section is to debate the psychobiological implications of this parallel environmental stimulation (Parrott, 2004b).

Laboratory animal research has shown that the acute and chronic effects of MDMA are modulated by a range of environmental factors. Temperature is crucial, since MDMA impairs hypothalamic thermal control mechanisms, leading to overheating under normal and high ambient temperature conditions (Gordon *et al.*, 1991; Dafters and Lynch, 1998; Malberg and Seiden, 1998). Brown and Kiyatkin (2004) assessed brain and body temperatures in male rats given an acute dose of MDMA. Under normal environmental temperature conditions (23 °C at rest), MDMA induced a prolonged hyperthermia, with temperatures in the nucleus accumbens and hippocampus increasing more than in body muscle. Under high temperature conditions, body temperatures increased to dangerous and often fatal levels (Brown and Kiyatkin, 2004). The increase in ambient temperature can however make MDMA more positively reinforcing. Cornish *et al.* (2003) noted that MDMA self-administration was significantly enhanced under a cage temperature of 30 °C compared to 21 °C. In a parallel fashion, social interaction in pairs of rats was significantly enhanced under the higher temperature condition (Cornish *et al.*, 2003). This may reflect a form of aggregate toxicity, since the stimulatory effects of amphetamines are enhanced in socially grouped animals (Gunn and Gurd, 1940; Green *et al.*, 2003). Brown and Kiyatkin (2004) also found that social interaction with a female rat, potentiated the hyperthermic response of male rats to MDMA at 23 °C. Green *et al.* (2004) found that prior treatment with MDMA, reduced the ability of rats to handle *subsequent* doses of MDMA in the heat. Loud noise/music has been found to exacerbate the stimulatory effects of amphetamine and dexamphetamine, and it may also heighten the acute effects of MDMA; this needs to be empirically investigated (Morton *et al.*, 2001). Another factor is hydration, since water deprivation acutely increases the hyperthermic response of MDMA-treated rats under high ambient temperature conditions (Dafters, 1995).

The influence of these factors in animals, has led to the prediction that humans may also be affected by the environmental conditions. The different temperature regulation mechanisms of rats and humans should however be acknowledged, since laboratory rats are more prone to thermal distress (Green *et al.*, 2003). One key hypothesis is that the subjective effects of MDMA might be intensified by the hot and crowded conditions; the limited evidence on this notion is outlined elsewhere (Parrott, 2004b). With reference to body temperature, Vollenweider *et al.* (1998) assessed the effects of acute MDMA on humans in a restful laboratory setting. They reported that it produced 'a discrete increase of body temperature of about 0.2 to 0.5 °C, which however did not reach statistical significance'. Mas *et al.* (1999) also found that MDMA did not affect human body temperature significantly, although the trend was again for higher mean values. In another placebo-controlled laboratory study, Tancer *et al.* (2003) showed that acute MDMA produced a significant increase in body temperature and metabolic rate in humans. Rectal temperature increased to a similar extent under the two ambient temperature conditions, but the increase in metabolic rate was greater in the high ambient temperature condition. In a follow-up study employing a more sophisticated measure of core body temperature (an ingested radiotelemetry device), Freedman *et al.* (2005) confirmed that MDMA significantly increased core body temperature, under both warm and cold conditions. De la Torre *et al.* (2005) studied the pharmacokinetics of MDMA in ten human volunteers, one of whom happened to be a poor MDMA metabolizer. They noted a slight temperature increase in the good metabolizers, but a stronger temperature rise in the poor metabolizer; they hypothesized that this might reflect their higher plasma MDMA.

In a field study, Parrott and Young (2005) found that dance clubbers who were on ecstasy had significantly higher body temperatures, than other dancers at the same venues. Subjective feelings of being hot were also significantly higher amongst these ecstasy users, while the objective temperature measure (ear thermometer) and the subjective thermal ratings were significantly correlated. Cole *et al.* (2005) reported that ecstasy users did not differ in body temperature from non-users out clubbing. They also found that the ambient temperature at the club was not particularly hot, and questioned whether dance clubs should be conceptualized as hot thermal environments. Questionnaire surveys have however shown that feeling hot, sweaty, and dehydrated, are typical experiences for ecstasy/MDMA users (Davison and Parrott, 1997; Topp *et al.*, 1999). Rest and fluid replacement are often the best treatment for physical exhaustion at raves (Suy *et al.*, 1999); although the marked increase in psychophysiological arousal and metabolic activity, means that taking MDMA at dance/rave environments can sometimes be medically dangerous (Fantegrossi *et al.*, 2003). Indeed these hyperthermic reactions occasionally prove fatal (Cohen, 1998; Henry *et al.*, 1992; Parrott, 2002; Green *et al.*, 2003; Schifano *et al.*, 2006).

With reference to the longer-term consequences, many animal studies have shown that the neurotoxic actions of MDMA are exacerbated by environmental stimulation. Ambient temperature is the most extensively studied of these factors. High ambient temperature leads to greater 5-HT terminal axon loss in animals, whereas cool temperatures are neuroprotective (Dafters and Lynch, 1998; Malberg and Seiden, 1998). For a detailed coverage of the literature on animal neurotoxicity, see Green *et al.* (2003).

In relation to the functional consequences in animals, McGregor *et al.* (2003) administered MDMA under ambient temperature conditions of 16 °C and 28 °C, then assessed the rats on a performance test battery several weeks later. MDMA pre-treatment led to significantly poorer object recognition performance, but only when it had been administered at the higher temperature. In contrast the other behavioural indices (e.g. for anxiety and depression), were adversely affected by the MDMA pre-treatment at *both* temperature conditions. Hence it is not only humans, that show differential effects with MDMA, according to the behavioural measure being employed.

In order to assess the influence of these non-drug factors in humans, 205 volunteers were asked to describe their extent of dancing when on ecstasy, and the degree to which they felt hot or overheated (Parrott *et al.*, 2005b). Those who reported dancing 'all-the-time' when on ecstasy, reported significantly more prospective memory problems, than those who danced intermittently. Furthermore those who felt very hot when on ecstasy also reported more memory problems. But against our predictions, those who did not feel hot when on ecstasy also reported more memory problems, in comparison with those who only felt slightly hot (Fig. 1). Further studies are needed to investigate these phenomena, and assess the integrity of homeostatic thermal control mechanisms. In a related study, Parrott and Young (2005) found significant mood gains amongst ecstasy users when clubbing, which were followed by marked mood decrements 2 days later. Body temperature was significantly increased amongst ecstasy users (see earlier), but whereas body temperature did not correlate with mood states while clubbing, it did correlate with some of the mood decrements afterwards. Those with the highest body temperatures while clubbing, reported the most tiredness and low-elation 2 days later. Self-rated memory problems while clubbing, were found to correlate with lifetime ecstasy use, with 'hot and cold flushes in the past 6 months', but *not* with body temperature at the club. However poor memory 2 days later did correlate with high body temperature while clubbing. These preliminary findings into the effects of temperature and dancing (Parrott and Young, 2005; Parrott *et al.*, 2005), suggest that it may prove an interesting area for future research.

Bioenergetic stress: an integrative model for ecstasy/MDMA

Huether *et al.* (1997) outlined an animal model which explained how various drug and non-drug factors could modulate the acute and chronic effects of MDMA. In neurochemical terms a single dose of MDMA indirectly stimulates the release of large amounts of serotonin from the pre-synapse. During this period of axon terminal overstimulation, the normal cellular processes of metabolic recovery and repair become stressed. This explains why MDMA is inherently neurotoxic, also why the neural damage is restricted to the distal axon terminals (Table 1). Any factors which contribute to acute neurotransmitter release, will further increase the extent of neuronal damage. Hence higher and repeated doses will each be more damaging, as will its combined use with other CNS stimulants, or taking it under hot thermal conditions (Huether *et al.*, 1997). The core underlying notion of energetic distress, was also noted by Darvesh and Gudelsky (2005): 'MDMA produces a dysregulation of energy metabolism which contributes to the mechanism of MDMA-induced 5-HT neurotoxicity'. Zhou *et al.* (2004) have confirmed that recreational MDMA users display enhanced levels of oxidative stress, as predicted by the model. Another important aspect of the model is that it can explain neuroprotective factors. Hence low temperatures, drugs which inhibit neurotransmitter release, and other hypothermic influences, can all protect against MDMA-induced neurotoxicity in laboratory animals (Green *et al.*, 2003; McGregor *et al.*, 2003; Morley *et al.*, 2004).

One strength of Huether's model is its width of applicability, since it can encompass a range of drug and non-drug influences. It is therefore well suited for explaining real world phenomena such as recreational ecstasy/MDMA, where a multitude of factors are involved. This review has revealed how numerous drug and non-drug factors can influence their neuropsychobiological profiles, while this explanatory model provides a clear rationale for how they may be integrated together (Parrott, 2001). The intensity of single occasion usage, lifetime usage, and other indices of cumulative drug usage (Bolla *et al.*, 1998), all contribute to metabolic-neuronal distress, and therefore readily fit the model (Huether, 1987; Parrott, 2002, 2004b). Polydrug aspects are also important, although their effects are far more complicated to integrate. In general, the parallel use of other CNS stimulants will increase acute neuronal distress, and so heighten any long-term neuropsychobiological problems, whereas sedative drugs which reduce neuronal activity should reduce the acute stimulation, and so lessen any longer term problems (Table 1). The diathesis-stress concept can also be integrated into the model. It states that the influence of the many external stressors (drug and non-drug, bioenergetic and more general non-bioenergetic), will depend on how they interact with the various premorbid predisposition characteristics. One core prediction is that drug-related abreactions will develop most readily in those with the worst premorbid profiles. The various susceptibility factors may include age, gender, personality, psychiatric status, cognitive ability, and a host of neurochemical, metabolic, and genetic aspects. Their influence needs to be further studied.

With reference to environmental factors, stimulatory/hyperthermic conditions will exacerbate acute and chronic drug reactions, whereas relaxant/hypothermic conditions should be neuroprotective (Huether *et al.*, 1997; Green *et al.*, 2003; Parrott, 2004; Parrott *et al.*, 2005a, 2005b). Hence another practical strength of the model is that it explicitly encompasses positive and negative influences. The following predictions may be therefore offered (Parrott, 2004). When used at low intermittent doses, while resting quietly, in low temperature conditions, with sedative or hypothermic co-drugs, MDMA will lead to low rates of neuropsychobiological problems. Whereas when used intensively and repeatedly, with other CNS stimulants as co-drugs, in hot thermal environments, with prolonged physical exercise, MDMA will lead to high rates of psychobiological problem. Dances, raves, and other socially stimulating arenas, may help to boost the acute

effects of ecstasy/MDMA, but this may also make them more problematic in the longer term. Finally it should be noted that many of the psychobiological problems of MDMA users may reflect the operation of non-bioenergetic stressors. Numerous neuroadaptive processes can accompany repeated drug use, and these will often be independent of acute metabolic distress and chronic serotonergic neurotoxicity. Several of these more general psychopharmacological influences are briefly noted in Table 1, but they will be debated more thoroughly in a later paper (Parrott, in preparation).

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