

Human Research on MDMA (3,4-Methylenedioxymethamphetamine) Neurotoxicity: Cognitive and Behavioural Indices of Change

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Key Words

MDMA (3,4-methylenedioxymethamphetamine) · Ecstasy · Serotonin · Cognition · Memory · Impulsivity · Neurotoxicity

Abstract

Laboratory animals can develop serotonergic neurotoxicity after repeated doses of 3,4-methylenedioxymethamphetamine (MDMA) or 'Ecstasy'. If similar neural damage occurs in humans, this may be evident in cognitive or behavioural impairments. In a review of the behavioural skills shown by drug-free recreational Ecstasy users, three aspects of cognitive performance are often affected: reduced memory for new information (Rivermead Behavioral Memory, supraspan word recall), impaired higher executive processing (Wisconsin Card Sort, Tower of London), and heightened impulsivity (Impulsiveness, Venturesomeness and Empathy Questionnaire, Matching Familiar Figures test). Performance on other more basic cognitive functions is generally unimpaired (simple reaction time, choice reaction time, number vigilance, Stroop, trail making). Some Ecstasy users also complain of poor memories and/or concentration difficulties, which they attribute to MDMA use. There are

many methodological problems and uncertainties with research in this field: non-random allocation of subjects to drug conditions, the deleterious effects of other psychoactive drugs, and the possibility that these adverse profiles reflect pre-existing personality characteristics in Ecstasy users. However, this particular pattern of cognitive decrements in humans, is consistent with the animal data on those brain areas showing serotonergic damage following MDMA: the frontal cortex (impulsivity and higher cognitive impairments), and hippocampus (memory deficits). Finally, this profile of cognitive deficits is also consistent with a *hypothetical* integrative construct: namely reduced cortical inhibition.

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Introduction

MDMA (3,4-methylenedioxymethamphetamine) or 'Ecstasy', is widely used as a recreational drug by young people [Saunders, 1995]. In a survey of illicit drug use amongst British university students, 13% stated that they had taken Ecstasy at least once, while 3% used it regularly [Webb et al., 1996]. In a sample of 3,021 German adolescents, 7.6% of the 22- to 24-year-olds stated that they had

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used Ecstasy or Ecstasy-like drugs, while 0.4% of the 14- to 15-year-olds admitted having taken it; moreover this survey also indicated: 'A substantial increase in the use of ecstasy ... the increase is strongest in the youngest age groups' [Schuster et al., 1998, p. 75]. The recreational use of Ecstasy seems to be increasing in every westernized country studied [Handy et al., 1998; NIDA, 1997; Schifano et al., 1998]. This widespread use is, however, of great concern, since laboratory animal research has shown that repeated doses of MDMA can cause prolonged serotonergic neurodegeneration [Green et al., 1995; Ricaurte et al., 1992; Ricaurte et al., 2000, in this issue; Steele et al. 1994]. This raises the crucial question of whether MDMA is also neurotoxic in humans. However, being a class A scheduled drug, it is difficult to assess its effects in humans, using traditional double-blind methodologies, with random allocation of volunteers to active/placebo drug conditions. Although some single-low-dose studies have been authorized [Curran, 2000, in this issue; Vollenweider et al., 1998], it would clearly be unethical to administer repeated larger doses in order to investigate the putative development of permanent neural damage! Instead, we can only assess recreational Ecstasy users, and compare them with similar-aged controls who have never taken Ecstasy. There are numerous limitations of this approach which are noted briefly below, and debated more fully by Curran [2000] and McCann et al. [2000] in this issue.

Cognitive Abilities of Drug-Free Recreational Ecstasy Users

The first published report of memory problems in a drug-free Ecstasy user was an individual case study of a 33-year-old who had used it heavily for over 2 years [McCann and Ricaurte, 1991]. He developed a range of psychiatric complaints (paranoia, hallucinations, depression) and cognitive problems (in both short-term and long-term memory) which persevered for a year and a half after discontinuing MDMA. Eventually, these problems were partially relieved by the continuous use of fluoxetine, a selective serotonin reuptake inhibitor. The first report of cognitive/memory problems in a *group* of drug-free Ecstasy users was by Krystal et al. [1992]. Nine regular Ecstasy users, who had taken this drug recreationally for around five years, their last tablet being around 66 days ago (range 20–180 days), were assessed on a neuropsychological test battery. On most tasks (Boston naming, Benton visual retention, tactual performance, trail mak-

ing, the Tokens test, Lafayette pegboard and grip strength) performance levels were similar to age-matched norms. In contrast, the memory task performance of several subjects was lower than expected: 'Five subjects showed mild-to-moderate impairment on the Wechsler Memory Scale delayed paragraphs test', together with similar impairments on other measures of the same scale: initial paragraphs recall, and immediate and delayed figural recall [Krystal et al., 1992, p. 338]. There were, however, methodological problems with this study: the lack of a control group, adverse premorbid psychiatric histories, the heavy past use of other illicit drugs, also the administration of a tryptophan challenge 3 h prior to testing.

Parrott et al. [1998] included a control group of young people who had never taken Ecstasy, and compared them with two groups of Ecstasy users: regular users who had taken it on at least ten occasions and novice users who had taken Ecstasy on less than ten occasions. The Cognitive Drug Research test battery was undertaken on a day when the subjects were drug free. On most tasks (simple reaction time, choice reaction time, Sternberg reaction time, number vigilance) there were no significant differences between groups. However, on immediate and delayed word recall, both groups of Ecstasy users recalled significantly less words than the non-user controls. However, again there were methodological weaknesses, with the use of other illicit drugs not recorded [Parrott, 1997]. Furthermore, although the subjects had been asked to turn up for testing when they had not taken any Ecstasy recently, this was not objectively defined, and if some had been taken during the previous few days, residual drug effects may still have been present. The duration of Ecstasy's psychodynamic profile was investigated in our next study. Parrott and Lasky [1998] compared three subgroups – defined as in the earlier study. Four assessment periods were involved: pre-drug baseline; at a Saturday night dance club while under the influence of self-administered recreational drugs (generally either Ecstasy or alcohol for the controls); then again 2 days later, and finally 7 days later. Two cognitive tests were given: visual scanning on an Apple Messagepad hand-held microcomputer and supra-span word recall [Parrott and Lasky, 1998]. Visual scanning was significantly impaired in the Ecstasy users while on the drug, but was not generally impaired at the other sessions. As expected, memory recall was also significantly impaired when on Ecstasy. However, the memory scores of the regular Ecstasy users were also significantly lower than the controls at every other session when off the drug (fig. 1). This confirmed our earlier findings that regular Ecstasy users displayed poor memories when off the

drug. One limitation of this study, however, was that a full history of the past use of other illicit drugs had not been taken; although the use of other psychoactive drugs at the club was recorded, and was broadly similar across the three groups [Parrott and Lasky, 1998].

Morgan [1998, 1999] included the crucial control group of recreational polydrug users who had *never* used Ecstasy; the other two groups comprised regular Ecstasy users (+20 occasions) and non-drug user controls who had never taken any illicit psychoactive drugs. Everyone was tested when drug free. On the Rivermead Behavioral Memory test, where salient points from a prose passage need to be remembered, the Ecstasy users recalled significantly fewer prose points than either of the other two groups, on both immediate and delayed recall. In contrast, the recreational polydrug users who had never used Ecstasy, remembered a similar amount of information to the non-drug users [Morgan, 1999]. On the Matching Familiar Figures task, the Ecstasy users produced significantly more errors, coupled with a non-significant trend towards faster responses. When these parameters were combined into a standard index of behavioural impulsiveness, the Ecstasy users were significantly higher than either of the two control groups. Furthermore, on the self-rated impulsiveness measure, the Impulsiveness, Venturesomeness and Empathy (IVE) Questionnaire, again the Ecstasy users reported significantly higher impulsiveness than the other two groups (note: both groups of drug users scored higher on venturesomeness than the non-users). No significant group differences were apparent on the spatial span task, nor on Tower of London (TOL): 'A test of planning which taxes central executive function ... it demands that participants plan out the solution to the problem, prior to the first move' [Morgan, 1998]. However, the regular Ecstasy users demonstrated a non-significant trend towards fast initial TOL responses, coupled with greater errors. Thus, the pattern of performance displayed by drug-free Ecstasy users on the TOL task was very similar to the profile they displayed on the Matching Familiar Figures test – fast but error-prone initial responses. The methodological strength of Morgan's study, was the attempt to control for the use of other illicit psychoactive drugs, through the inclusion of a polydrug control group [Morgan, 1998, 1999]. However, while they were broadly similar to the Ecstasy users, in terms of their past use of several psychoactive drugs, they had used more of some drug types. Nevertheless when these differences in past drug history were statistically controlled, the significant memory decrements and greater impulsiveness in the Ecstasy group still remained [Morgan, pers. commun.].

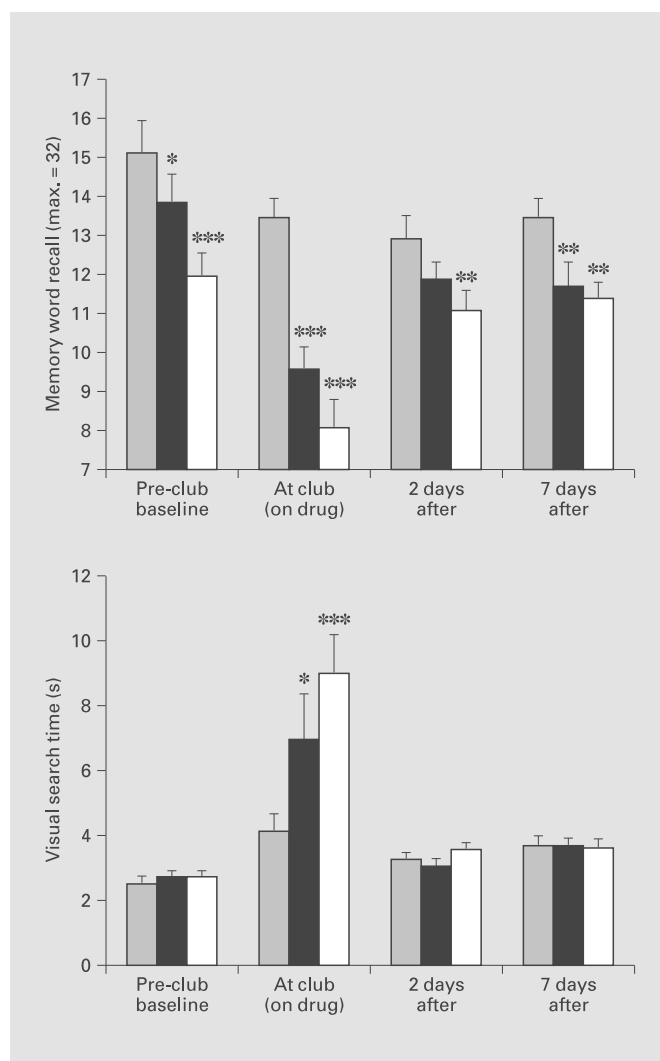


Fig. 1. Memory word recall (\pm SE) and visual search times (\pm SE), in Ecstasy users and alcohol-drinking controls over the week. $n = 15$ per group; Duncan's paired comparison test with controls (two-tailed): * $p < 0.10$, ** $p < 0.05$, *** $p < 0.01$. Further details in Parrott and Lasky, [1998]. \square = Non-user control; \blacksquare = novice MDMA user; \square = regular MDMA user.

Milani [1997; summarized in Schifano et al., 1998], compared 10 recreational Ecstasy users who complained of psychopathological problems, which they attributed to their past use of Ecstasy, with 20 similar-aged controls. On the TOL task, and Rivermead Behavioral Memory test, the drug-free Ecstasy users showed highly significant impairments compared to the controls. In contrast, performance levels on the other cognitive tasks (Stroop, Golin visual recognition, the Posner task) were similar for the two groups [Milani, 1997]. However, the Ecstasy users

had also used many other illicit psychoactive drugs, which might have contributed to their poor test scores. Furthermore, they had also been selected for testing because they had complained of Ecstasy-related problems, and thus may be considered somewhat atypical or biased as a group (i.e. representing only those who develop problems). Perhaps it should be noted that the other studies in this review did not involve subjects who had complained of drug-related problems, except Krystal et al. [1992]. This was true for the next study, where Dafters et al. [1999] assessed asymptomatic recreational Ecstasy users. Eleven high Ecstasy users (lifetime use >20 tablets), were compared with 12 low Ecstasy users (lifetime use <20 tablets) on a battery of cognitive tests and resting EEG 7 days or more since their last Ecstasy tablet. The high users demonstrated significantly greater EEG alpha amplitude/power and significantly reduced EEG coherence – a measure of synchronization of activity between paired EEG locations. The only cognitive difference between subgroups was on the rule-shift card test, a higher executive task similar to the Wisconsin Card Sort. The high Ecstasy users displayed significantly poorer performance than the low Ecstasy users on this task, and this difference remained even when the use of other illicit drugs was controlled for by partial correlation. There were no significant differences on any of the other measures: National Adult Reading Test (NART, an IQ estimate), Rivermead Behavioral Memory test and a working memory task. However, an important limitation to this study was the absence of a control group. Thus, it is unclear whether the absence of group differences on these other cognitive tasks was because *both* groups were impaired, or because *neither* group was impaired.

Overall, therefore, a number of studies have shown evidence for cognitive problems in drug-free recreational Ecstasy users, and this had been confirmed in a number of further reports from this meeting (see the Discussion paper in this issue). However, 3 of our latest studies have failed to find any significant *group* cognitive impairments in the Ecstasy users. Turner et al. [1998a] contrasted drug-free Ecstasy users and non-user controls on a virtual reality memory task. Each participant followed a standard route around a 'virtual' house, having been asked to find a particular object – which was sited in the final room. Their recall of objects from the various rooms they had passed through was then assessed on a standardized scale. There were no group differences in the recall of most objects, although the recall of some pieces of non-target information was significantly better in the Ecstasy users than non-users. One possible interpretation for this find-

ing was that Ecstasy users displayed wider attentional focus, which facilitated their recall of an incidental (non-target) object; alternatively it may have been a random or type 1 error. This intriguing finding needs to be further studied and/or replicated. Alexis et al. [submitted] compared regular Ecstasy users, novice Ecstasy users and non-user controls on a battery of four cognitive tasks: Warrington recognition memory for words, Warrington Recognition memory for faces, levels of processing and supraspan word recall. No significant group differences emerged on any task. However, inspection of the individual scores revealed occasional poor performance. In particular, the Warrington recognition memory scores for a few Ecstasy users were as low as those described by Spatt et al. [1997] in a case study of an Ecstasy user who had developed severe clinical memory deficits. However, some of our non-user controls also displayed very low Warrington scores, thus emphasizing the variation in cognitive skills across individuals – whether Ecstasy users or not. The third study further confirmed the importance of individual differences. Turner et al. [1999], compared current Ecstasy users (+20 occasions), former Ecstasy users (+20 occasions, but none for at least 1 year) and non-user controls. The cognitive test battery comprised: Wisconsin card sort, Ray-Osterrieth spatial recall, supraspan word recall, verbal fluency and spatial recall. There were no significant decrements in either group of Ecstasy users. However, the former Ecstasy users displayed significantly greater verbal fluency (on one of the three stimulus letters) than the controls; while this also occurred to a lesser (non-significant) extent in the current Ecstasy users. Again, this interesting finding needs replication. Current Ecstasy users did not display any significant task impairments compared to the controls, although their standard errors were higher on every task. This reflected their far wider range of scores, with some Ecstasy users displaying very low task performance. The worst cognitive profile was produced by a current Ecstasy user, who had very low scores on Wisconsin Card Sort and Ray-Osterrieth spatial recall and quite poor word recall (despite near-normal NART: indicating near-average intelligence). However, his drug history was exceptional, with intense use of Ecstasy and many other illicit drugs – often in combination. Milani [1997] described a similar individual who had used enormous amounts of Ecstasy (+2,000 tablets), who also displayed extremely poor cognitive performance. Finally it should be noted that our 3 latest studies (summarized here), were all undertaken in London during late 1997 early 1998. In the post-study debriefings, several participants complained about the poor quality of recent 'Ecstasy' supplies

in London; some commented that good-quality supplies could only be found in Amsterdam. Paradoxically, this may help explain why no significant *group* cognitive impairments had emerged in these studies, with their 'poor-quality' tablets protecting against neurotoxicity (see methodological issues below).

The final source of information regarding cognitive difficulties, are the self-reports from individuals who feel they have developed problems after using Ecstasy. Many of the studies in this review have noted that some of their Ecstasy users had complained of memory problems or concentration difficulties, which they attributed to regular Ecstasy use [Milani, 1997; Morgan, 1998; Parrott et al., 1998; Parrott and Lasky, 1998]. Several case studies describing adverse cognitive sequelae have also been published; the first was outlined earlier [McCann and Ricaurte, 1992], while others were noted by McCann et al. [1996]. More recently, Spatt et al. [1997] presented the neuropsychological test findings from a young female who had experienced an adverse reaction to half an Ecstasy tablet at a rave. She complained of severe memory problems which had continued unabated for the past 9 months, which meant that she was still unable to return to her previous employment or night school study. Warrington recognition memory for words and faces were both very poor (below 5th percentile), while Ray-Osterrieth complex figure recall and word list learning were also highly impaired. However, other cognitive functions were near normal: Boston naming, direct copying of the Ray-Osterrieth figure, verbal fluency and the WAIS intelligence quotient. In our laboratory, the severest case study was a man in his twenties, who had used Ecstasy for 5 years without apparent ill-effects. Then he went on holiday to the Balearics with the specific aim of getting high all the time. After a series of wild nights on MDMA, he woke one morning with the realization that: 'I had fucked my brain up'. Back in the UK, he tried to run his previously successful business, but frequent severe memory lapses made this difficult. On one occasion he greeted some business guests by introducing himself: 'Very pleased to meet you, my name is Tom ... err ... no it is not it's ... err ... William'. Having forgotten his own name, he did not get the contract! No impairments were apparent on an MRI scan, while neuropsychological test results were variable, with poor performance on some tests (Warrington face recognition below the 5th percentile), but not others. One intriguing aspect was that his memory problems waxed and waned; sometimes they were not particularly troublesome, but then they would recur causing marked problems again.

Methodological Problems and Uncertainties

As noted earlier, there are many methodological problems with empirical research in this field. The main problem is that subjects cannot be randomly allocated to drug conditions. Everyone is self-selected, so there may be important a priori differences between those who decide to take Ecstasy, and the far larger numbers who had never taken it (87% of British University students are non-users) [Webb et al., 1996]. However, it is difficult to see why Ecstasy users should display the particular profile of cognitive skills and deficits which has emerged here. Why should their performance on most cognitive tasks be normal, while their scores on tests of memory, higher cognitive processing and impulsiveness are abnormal? Furthermore, while illicit drug takers tend to be more venturesome than non-drug takers, why are only Ecstasy users more impulsive [Morgan, 1998]? It is also difficult to explain the dose-related findings as methodological artefacts. Thus, cognitive problems are generally more evident in heavy Ecstasy users than light users [Dafters, 1999; Parrott and Lasky, 1998]. In a similar fashion, psychiatric problems also tend to be more frequent in the heavy users [Parrott et al., in press; Schifano et al., 1998]. Nevertheless, the non-random distribution of subjects amongst drug conditions remains an enduring methodological problem. Another issue is the uncertain nature of Ecstasy tablets in terms of both purity and strength [Curran, 2000]. Moreover, Ecstasy users tend to use other illicit drugs, including amphetamine, cocaine, cannabis, LSD and magic mushrooms [Morgan, 1999; Parrott et al., in press], while the parallel use of alcohol and nicotine is another confounding factor. These drugs all have strong psychoactive effects, and some have long-term adverse cognitive effects [Angrist, 1987; Schifano, 1996]. Many regular Ecstasy users also follow poor lifestyles, with irregular patterns of sleep and rest. Turner et al. [1998b] found a marked reduction in food intake for 7 days after an Ecstasy tablet. It is widely recognized that good nutrition, together with rest and recuperation, are important for optimal health and efficiency; these factors may therefore contribute to the cognitive problems. All these methodological issues are discussed more fully by Curran [2000].

Table 1. Summary profile of the cognitive deficits and unimpaired cognitive abilities of drug-free Ecstasy (MDMA) users

Memory. Often impaired across a range of tasks: Rivermead Behavioral Memory, immediate word recall, delayed word recall, Ray-Osterrieth spatial recall, Warrington recognition memory. Significantly lower memory task performance levels have been found by several research groups, in comparison with both non-drug users as controls and recreational polydrug users who have never used Ecstasy. Many regular Ecstasy users also complain of memory problems, which they attribute to having used Ecstasy frequently. However, some studies have not found memory decrements.

Higher executive ability. Impairments have been found with the following tasks: Wisconsin Card Sort (or similar) and Tower of London. These tasks are often taken as indices for frontal cortex activity. Again, some studies have not found performance decrements.

Impulsiveness. Studies using the IVE Questionnaire have shown that Ecstasy users are more impulsive than non-users (including polydrug user controls who have never taken MDMA). Impulsiveness scores on the Matching Familiar Figures test are also significantly higher in Ecstasy users.

Most other cognitive functions. Stroop, vigilance, simple reaction time, choice reaction time, Sternberg task, trail making and other simple cognitive tasks. There is little evidence for impairments on these more basic information-processing tasks.

Localized Neural Deficits: A Possible Explanation?

Concern about the recreational use of Ecstasy in humans, stems from the animal data showing long-term neural damage induced by MDMA. Krystal et al. [1992, p. 338] noted: '5-HT innervation of brain regions involved in memory, such as the hippocampus and cerebral cortex appear to be affected by MDMA in animals and primates'. This led to the suggestion that the memory problems in their recreational Ecstasy users may have been caused by reduced serotonin activity in those brain regions. Subsequent findings are largely consistent with this explanation. Thus, if serotonin tracts to the frontal cortex are damaged by MDMA, this could explain the heightened impulsivity and the problems in higher executive processing; while damage to the hippocampus would clearly be consistent with the memory impairments (table 1). Furthermore, if serotonin damage is limited to these particular neural tracts, then it would help explain why many simple cognitive functions are unimpaired. However there is a problem with this model. McCann et al. [1998] reported that serotonin transporters at the syn-

apse were reduced in Ecstasy users, but in *every* brain region studied [McCann et al., 1998]. This raises the question of why other cognitive skills generally seem to be normal [Krystal et al., 1992; Milani, 1997; Morgan, 1998; Parrott et al., 1998; Parrott and Lasky, 1998]. The neuropsychobiological evidence for neurotoxicity, is evaluated in more detail elsewhere [McCann et al., 2000; Ricaurte et al., 2000]; currently the whole issue remains unresolved.

Reduced Cortical Inhibition: An Alternative Possible Explanation?

Another possible explanation for this *particular* pattern of findings, is that it reflects a general reduction in cortical inhibition. This would be consistent with the high impulsiveness found in several studies [Morgan, 1998; Parrott et al., in press; Schifano et al., 1998; Turner et al., submitted]. It could also help explain the TOL performance. Complex problem solving generally benefits from an initial period of reflection, where initial hunches need to be critically analyzed and alternative solutions tested, before the optimal strategy is decided. Any reduction in response inhibition may lead to fast initial responses, but greater error rates. This pattern was evident in drug-free Ecstasy users, on both the TOL task, and Matching Familiar Figures test [Morgan, 1998]. Decreased cortical inhibition might also help explain the memory deficits. The storage of new information is known to be optimal under low cortical arousal, when interference from competing information is at a low level [Folkard, 1980]. Any reduction in cortical inhibition will lead to greater interference from competing information, and thus poorer storage. In contrast, many basic information processing skills (eg. simple/choice reaction time), would probably be largely unaffected by any changes in cortical inhibition. Finally, a decrease in cortical inhibition may also lead to various psychiatric/behavioural problems; in particular, those characterized by behavioural disinhibition and/or cortical overload. Several types of psychiatric problem have been described in Ecstasy users: paranoid ideation and hallucinations, aggression, obsessionality, phobias and impaired eating behaviours, including carbohydrate craving [Parrott et al., in press; Schifano et al., 1996, 1998]. These types of psychiatric disorder are all consistent with impaired cortical control, although the exact nature of any emergent problem will presumably reflect pre-morbid tendencies and sensitivities. This whole area is reviewed by Schifano [2000] in this issue.

Overall Summary and Recommendations for Future Research

Drug-free Ecstasy users often display cognitive deficits, but these seem to be limited to a few specific functions. Memory problems were the first to be reported, and have now been confirmed in several studies from different research groups [Krystal et al., 1992; Milani, 1997; Morgan, 1999; Parrott, 1997; Parrott and Lasky, 1998]. Memory problems are also noted by Ecstasy users attending medical-psychiatric clinics or drug addiction centres [Schifano et al., 1998; Spatt et al., 1997]. The second area which seems to be affected is impulsivity, which has been shown to be increased in several studies; moreover it does not seem to be a general characteristic of all recreational drug users, but is more specific to Ecstasy users [Morgan, 1998]. The third area is difficulty in higher cognitive tasks involving strategy and planning, such as TOL and Wisconsin card sort [Dafters, 1999; Milani, 1997; Turner et al., 1999]. However, in each of the above areas, there does seem to be considerable individual variation, with some users displaying poor cognitive performance, while others show normal task performance. Moreover, some studies have found no group differences between the Ecstasy users and controls. This individual variation is confirmed in the subjective reports, since while some regular Ecstasy users complain of cognitive problems, many others do not.

Future research will need to address several important issues. Firstly, it will need to obtain better data on past histories of psychoactive drug use. One suggestion might be to use hair analysis [Curran, 2000]. However, despite the sophistication and objectivity of hair analysis as a pro-

cedure, it cannot readily solve this problem. It cannot provide full data on past dosage, tablet purity, regularity of use, drug combinations, nor cover many previous years. Thus, self-reported drug histories will probably remain the optimal form of data. But this raises the question of how these individual drug histories should be analyzed; how can these complex and unique patterns of past illicit drug use be reduced to a manageable set of variables? Secondly, future studies should involve more comprehensive test batteries, in order to provide more detailed information on the particular cognitive functions which are impaired in Ecstasy users, as well as those which are not. They also need to investigate whether there is a direct relationship between the changes in impulsivity and cognitive performance. A third topic of importance is individual differences. Why do some individuals seem to develop MDMA-related problems, while others do not? Are there pre-existing differences in personality, serotonin/dopamine functioning and/or genetic markers which can be used to identify the most susceptible individuals? Finally, longitudinal research is probably the next major advance. This might involve screening high-risk groups (e.g. 18-year-olds commencing university) who can then be regularly monitored over time. At each assessment point, detailed drug histories and psychological task assessments could be given. Any changes in psychobiological functioning could then be related to intervening patterns of drug use. The overall aim would be to elucidate whether particular patterns of drug usage were related to changes in health or psychological well-being. These prospective studies should be long-term, since one worrying possibility is that the neurobiological changes will manifest as increasing clinical/cognitive problems with age.

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