Sorted: Ecstasy



JON COLE, HARRY SUMNALL *and* **CHARLES GROB**

argue that the long-term effects of Ecstasy use are far from clear, and that psychologists are muddying the waters.

ECSTASY use and raves are a cultural phenomenon. Their impact upon the 'Chemical Generation' is believed by some to be the defining moment of the late 1980s and early 1990s. Picking up on this the media, always fascinated by illegal drug use, have sensationalised the negative effects of Ecstasy. The media can perhaps be forgiven for this: sensationalism sells. But what about psychologists, as scientists? Are we also guilty of jumping to conclusions when the research is in fact plagued by experimental confounds?

Everyone's taking... What?

All-night dancing with the aid of stimulant drugs is not new. It has been known since the emergence of cocaine in 1920s London, and has continued throughout most of the 20th century. The major difference today is the sheer numbers that are using Ecstasy and other 'dance drugs'. Recent surveys of young people's drug use has indicated that in the UK about 10 per cent of young adults aged between 15 and 29 have tried Ecstasy (e.g. Ramsey *et al*., 1999), although this figure jumps to around 90 per cent when the respondents are attending raves or nightclubs regularly (e.g. Bean *et al*., 1997).

Ecstasy is the colloquial name for the entactogen MDMA (see box). It became a drug of abuse in the early 1980s in several areas of the US. In the mid- to late-1980s MDMA crossed the Atlantic and became part of the of illegal drug scene.

As with all illegal drugs, purity became an important issue – now it is difficult to know for certain exactly what Ecstasy is. Ecstasy tablets are sold under brand names, such as White Dove or Mitsubishi, which refer to imprints stamped on the tablet. Manufacturers of Ecstasy constantly change their brand names because fraudulent copies rapidly follow the emergence of a new design. This has led to a plethora of designs and a corresponding problem in estimating the purity of Ecstasy tablets without a full chemical analysis.

Other drugs have masqueraded as MDMA (the most common being other entactogens), and other drugs have been mixed to produce an MDMA-like effect, such as ketamine and ephedrine. Some tablets contain either no active ingredients at all or legal drugs, such as pain killers. It is difficult in this context for anyone to know with any certainty the actual drug intake of an Ecstasy user.

Acute effects of Ecstasy use

Ecstasy has a high public profile due to the media coverage of deaths that have been associated with its use. The Office of National Statistics reports that in the UK between 1993 and 1997 there were 72 deaths due to Ecstasy. During the same period there were 158 deaths from amphetamines. In contrast, every year around 50,000 people die as result of their alcohol use and around 120,000 as a result of smoking. While every death from the use of drugs is an avoidable tragedy, the perceived 'safety' of Ecstasy has encouraged its use among young people.

If the statistics from the UK and the US are compared, the toxicological effects of MDMA become convoluted. The fatalities recorded for MDMA intoxication differ radically in both symptomatology and number between the US and the UK. In the former, if MDMA is found in the bloodstream after death then it is recorded as a cause of death, even if the primary cause was something entirely different, such as carbon monoxide poisoning or a fall (e.g. Dowling, 1990). Even with this very broad inclusion criterion, the number of recorded fatalities due to MDMA is very low. In the UK, however, the picture is entirely different, as the majority of cases can be directly attributed to the use of MDMA or related drugs.

The most profound adverse reaction to MDMA is hyperthermia – with body temperatures reaching as high as 44ºC – usually followed by multiple organ failure. The overwhelming majority of these adverse reactions have occurred at the weekend after using Ecstasy in raves or nightclubs, leading to the use of the term 'Saturday Night Fever' by staff at accident and emergency departments (Williams *et al*., 1998).

WHAT IS ECSTASY?

The entactogen 3,4-methylenedioxymethamphetamine (MDMA) is commonly referred to as Ecstasy. MDMA was patented in 1914 by Merck but was never made commercially available. Entactogens are drugs that have been used medicinally to aid the psychotherapeutic process by enabling patients to access and deal with repressed painful emotional issues. In 1977, however, the Home Office listed MDMA as a Class A drug and placed it in Schedule 1 of the Misuse of Drugs Act 1971, indicating that it had no medicinal uses.

facts and fiction

Harm-reduction literature in the 1990s advocated methods of reducing body temperature and replacing fluids lost through sweating. While this advice has undoubtedly reduced the incidence of overheating after taking Ecstasy, it has created a new problem. Misinterpretation of this advice by intoxicated users has led to a number of adverse reactions to unrestricted water intake. Too much water can lead to swelling of the brain and in some cases death.

Is Ecstasy a neurotoxin?

Recently attention has moved away from the acute toxicity of Ecstasy. MDMA has been found to produce long-term changes in the structure and function of the brains of various species. These changes involve the neurotransmitter serotonin, and are typically characterised as degeneration of the fibres emerging from serotonergic cell bodies. The cell bodies themselves are unaffected. This has led to the classification of MDMA as a neurotoxin.

As the serotonergic cell bodies are spared and actually regenerate these fibres, some have questioned whether this classification is appropriate. These researchers advocate that a true neurotoxic effect involves the robust and well-validated biological measures of cell-body degeneration, changes that are not present after MDMA administration (e.g. O'Callaghan & Miller, 1993).

Some also argue that the doses required to produce the long-term changes in the serotonergic system far exceed those used by recreational users. Most experiments looking at long-term changes in rats use a minimum of 40 mg/kg of MDMA administered as 10mg/kg injections over six hours at two-hour intervals (e.g. Fischer *et al*., 1995). Primate studies typically use a total of 40mg/kg administered as 5mg/kg injections over four consecutive days at 12-hour intervals (e.g. Fischer *et al*., 1995). In both cases the dosing pattern is not typical of recreational Ecstasy users (who normally take about 1.9 mg/kg orally).

There is also strong evidence that injection of MDMA is two to three times more neurotoxic than oral administration in the primate (Ricaurte *et al.*, 1988). For example, squirrel monkeys given 2.5 mg/kg of MDMA orally every two weeks for four months did not show reduced serotonergic function (Ricaurte, cited in Vollenweider *et al.*, 1999).

But what about humans?

The potential for neurotoxic effects of MDMA has led some researchers to investigate the long-term effects of Ecstasy in recreational drug users. The findings from these studies have been avidly reported by the media, particularly in magazines and programmes aimed at young people. There are many websites by Ecstasy users that report the results of such studies, suggesting that the users themselves are interested in their outcomes.

The general consensus in the media appears to be that Ecstasy causes long-term damage to recreational users (e.g. *Mixmag*, February 1997; *The Face*, June 1998; *The Guardian*, 16 May 2000). However, on closer inspection, there are methodological problems with these studies that preclude such a cause-and-effect relationship to be demonstrated unequivocally.

Sampling Most studies looking at the long-term effects of Ecstasy use similar recruitment methods, with the most widely used being the 'snowball technique'. This involves getting participants to advertise the study to their peers: in particular their Ecstasy-using peers. In practice, this normally equates with a largely student-based population, as recruitment tends to occur in and around universities as part of final-year projects or doctoral theses. One can question whether these samples represent the population as a whole, as they are both self-selected and exclusive, largely consisting of people who have attained a certain academic level.

Given the high media profile of the long-term effects of Ecstasy, one must also question whether the participants are coming forward to confirm their fears about any adverse reactions that they may have suffered. In some studies there are even differences in the backgrounds between the Ecstasy users and their control group, for instance the control group displays a higher level of education. A more extreme example is the use of Ecstasy users from the UK in studies conducted in the US. As it is not reported in the relevant study where the participants actually came from, there is the possibility of cross-cultural contamination of the results (McCann *et al.*, 1998a; 1998b). These inherent differences may have influenced the results obtained; for instance, participants with higher educational attainment are bound to obtain better scores on cognitive tests.

Lifestyle factors The typical design of a study investigating the long-term effects of Ecstasy is to compare a group of users to a group of non-users at a single time point and usually within three weeks of using Ecstasy. But Ecstasy users form a distinct subculture of individuals who attend raves and use dance drugs to aid their experience. Within this subculture it is very difficult to identify individuals who have *not* used Ecstasy, and there are therefore lifestyle factors that may explain the results.

One of the most common side-effects reported by this group of users is sleep disturbance, typically characterised by insomnia and accompanied by fatigue and exhaustion. This is possibly a result of

WEBLINKS

Multidisciplinary Association for Psychedelic Studies: *www.maps.org*

Erowid (information about psychoactive plants and chemicals): *www.erowid.org*

John Cole's website: *www.liv.ac.uk/psychology/deptinfo/staffprofile/jcole.html*

staying awake all night and dancing while under the influence of Ecstasy and other drugs, although similar results have been obtained from clinical studies that involved administering MDMA during the day (e.g. Vollenweider *et al*., 1998). Airline stewardesses exposed to repeated circadian disruption in a similar fashion to Ecstasy users report similar symptoms and have altered cognitive abilities (e.g. Cho *et al*., 2000). As the majority of the dance drugs are anorectic, another common side-effect is a reduced appetite and weight loss.

Both of these major side-effects would not be experienced by non-drug-using controls and represent non-drug-related differences between the groups. Also, controls who have used drugs other than Ecstasy may appear to control for non-Ecstasy drug use – but in fact they would be in a similar position to the non-drug-using controls (in that they have often not attended raves and been up all night dancing).

Psychopathology Two broad types of psychopathology are associated with Ecstasy use in both case reports and surveys: panic attacks, anxiety, and psychotic reactions associated with acute intoxication; and depression associated with long-term use. But the majority of the community-based studies have failed to find a definitive cause-and-effect relationship between Ecstasy use and psychopathology, as these disorders are also found in non-Ecstasy users (e.g. Schifano *et al.*, 1998).

It is also known that most adult psychopathology begins to emerge during adolescence – when Ecstasy use in the UK also usually starts. Therefore it is impossible to accurately determine from retrospective self-reports whether the drug use preceded the onset of symptomatology. When users regularly read media reports of Ecstasy causing psychopathology, it is highly possible that their causal attributions may distort the temporal relationship between drug use and symptoms.

Polydrug use The concept of the 'Ecstasy user' implies that there exists a population of drug users that exclusively use Ecstasy regularly, and that any observed effects in this population are due solely to the effects of MDMA. But epidemiological surveys of drug use among young people have routinely failed to identify such a group. To date there has only been a single study on the long-term effects of Ecstasy where the participants only used Ecstasy and no other drugs that could account for the observed results (Gerra *et al.*, 1998). This suggests that this group is not typical of recreational Ecstasy users.

The overwhelming majority of studies sample from a population that uses a variety of drugs, sometimes simultaneously. Some of these drugs, such as amphetamines and cannabis, are known to produce very similar long-term effects as those reported for Ecstasy. No study published to date has actually quantified the amount of MDMA or other drugs consumed by its participants. Very few studies even urine test on the test day to check that their participants are drug-free.

While some researchers have attempted to statistically control for this confound (e.g. Morgan, 1998), others have simply renamed their sample as 'MDMA polydrug abusers' (e.g. Parrott *et al.*, 2000). The former approach goes some way to addressing the issue of whether other drugs are causing the effect. But as it is known that some drugs have effects when combined it is plausible that simultaneous drug use may be the causal agent – this type of analysis would not detect this. The latter approach is logically flawed as the participants are polydrug users and therefore any of the drugs consumed could account for the observed effects – some authors even concede this in their papers (e.g. Parrott *et al.*, 2000).

Lifetime use Some authors have attempted to correlate the scores of Ecstasy users on a variety of psychological tests with the lifetime dose of MDMA. This is based upon the number of self-reported exposures to Ecstasy assuming that each tablet contains 100mg of MDMA (e.g. Bolla *et al.*, 1998). But one study found that there was huge variation in the quantity of MDMA (19–140mg) within a single brand of tablet (White Dove) and that other tablets contained no MDMA at all (Sherlock *et al*., 1999).

This indicates that attempting to quantify the amount of MDMA consumed based upon the self-reported use of Ecstasy tablets is inaccurate. Any calculations based on this are fundamentally flawed. In some studies using this technique the observed effects are only statistically significant when the lifetime dose of MDMA is manipulated as an independent variable (e.g. Bolla *et al.*, 1998; Grob, 2000).

A more extreme example of how the measurement of Ecstasy use can produce unrealistic results is the study by Wareing *et al.* (2000). Based on the reported average usage of Ecstasy tablets in this study, we calculate that the Ecstasy users had taken on average around 1300 tablets. The reported pattern of use suggests that they had been using up to four tablets of Ecstasy every four days for around four years. This pattern of drug use is not normal for recreational drug users. As these users are spending a significant proportion of their time intoxicated with Ecstasy and other drugs it is hardly surprising that they are showing cognitive deficits.

Animal studies In studies using laboratory animals it is possible to ascertain the dose-dependent effects of MDMA on the brain and behaviour of participants using a cross-sectional design.

Two groups of 'participants' can be obtained where the experimenter knows both their experiential and genetic backgrounds. As both groups are exposed to the same environment, the observed effects of the treatment can be used to determine a cause-and-effect relationship with a high degree of certainty.

Such animal studies have routinely failed to find changes in the behaviour of MDMA-treated animals, even when there was an 80 per cent drop in the markers for serotonergic function and using tests which are sensitive to other serotonergic neurotoxins (e.g. Seiden *et al.*, 1993). Some studies have found that in some tests behavioural deficits do appear, but these studies tend to be in the minority (e.g. Marston *et al.*, 1999). When challenged with drugs the performance of the MDMA-treated animals is found to be different. This suggests that there are underlying neurochemical changes in the brain that don't affect normal behaviour. It remains to be determined what this will actually mean for users of Ecstasy.

So are the long-term effects of Ecstasy 'iatrogenic'?

The pressure to publish positive results has meant that some papers minimise the impact of data that suggest Ecstasy exposure is not having any long-term effects. In these papers there are numerous tests run on the participants, but only the ones that work are reported in detail, while negative data are ignored (e.g. Wareing *et al.*, 2000) or only reported as meeting abstracts (e.g. Morgan, 1998). This suggests that hypotheses concerning the long-term effects of Ecstasy are not being uniformly substantiated and lends support to the idea that Ecstasy is not causing long-term effects associated with a loss of serotonin.

The public health implications of potential MDMA-induced neurotoxicity are undoubtedly important. It is essential that the long-term effects of MDMA on recreational drug users are discovered. On the other hand, telling the 'Chemical Generation' that they are brain-damaged when they are not creates a public health problem. Effective harm reduction relies on accurate information being delivered to the user by a credible source. Misinterpretation of harm reduction information about Ecstasy has already had fatal consequences, and it is important that this is not repeated.

The methodological problems outlined above indicate that the existing studies are a long way from determining a cause-and-effect relationship between Ecstasy use and long-term problems. This has not stopped researchers from publishing papers with titles stating a causal relationship between MDMA and their results (e.g. Bolla *et al.*, 1998; Wareing *et al.*, 2000).

Iatrogenic disorders are defined by the *New Webster's Dictionary* as 'caused by the mannerisms or treatment of a physician, an imaginary illness of the patient brought about by the physician'. We are concerned that the long-term effects of Ecstasy could be iatrogenic because researchers and the media are discussing a hypothesised cause-and-effect relationship as if it were fact. Owing to the presence of confounds, there are possibly alternative explanations for the observed effects. In addition these effects are not supported by animal experiments, where a cause-and-effect relationship could potentially be reliably determined.

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Throwing the baby out with the bath water?

Peer commentary by **MICHAEL MORGAN**.

GENERALLY, I agree with many of the points made in the article by Cole *et al.* and believe that it provides a valuable critique of the field. It offers a particularly timely criticism of some of the overly simplistic assumptions held by some researchers, and many in the media, about the causal relationship between recreational Ecstasy use and associated persistent psychological problems. I have made many of the same points in my publications and have argued that prospective, longitudinal studies are necessary to definitively determine the persistent effects of Ecstasy on human behaviour (e.g. Morgan, 1999, 2000).

The article also echoes many of my own concerns about the methodological difficulties that arise from the fact that controlled laboratory studies of the effects of repeated administration of Ecstasy are precluded for legal and ethical reasons. However, I am concerned that the authors may also be 'throwing out the baby with the bath water' when they suggest that Ecstasy is not damaging to the brain and that associated deficits in neuropsychological performance are attributable to some form of autosuggestion.

The article provides an accurate summary of the history, epidemiology, and acute toxicity and pharmacology of recreational Ecstasy use, and I agree with the authors that the media have tended to sensationalise the relatively small number of deaths associated with its use. I also agree that is not appropriate to quantify the amount of MDMA consumed based on self-reported use of Ecstasy tablets. Elsewhere I have discussed many of the methodological shortcomings of human Ecstasy studies including those relating to inadequate sampling, overreliance on self-reported drug consumption, difficulties with drug purity, and the fact that most Ecstasy users are polydrug users (Morgan, 2000).

On the other hand, I feel that this article may have overstated the significance of some of these methodological problems and that it is too dismissive of attempts by investigators to cater for them. For example, in all of my studies I have employed a polydrug control group, and a variety of statistical techniques (e.g. Morgan, 1998, 1999) to control for the past use of other illicit drugs by Ecstasy users.

We have recently found that heavy Ecstasy users exhibited elevated scores on measures of anxiety, phobic anxiety, interpersonal sensitivity, paranoid ideation, depression, somatisation, obsessive-compulsive tendencies, and altered appetite and restless sleep. But further regression analyses indicated that these forms of psychopathology were primarily predicted by the extent of past cannabis use, rather than past Ecstasy use (Morgan *et al.*, 2002). Thus, our conclusion that 'psychopathology in regular Ecstasy users may be more associated with their polydrug use generally, rather than with their Ecstasy use' is consistent with the view of Cole *et al.* that 'the majority of the community-based studies have failed to find a definitive cause-and effect relationship between Ecstasy use and psychopathology'.

There are a couple of specific points of contention, however. I disagree with the rather sweeping statement that only positive findings are reported in detail and that 'negative data are…only reported as meeting abstracts'. We and other investigators have reported negative as well as positive findings in peer-reviewed publications.

I also disagree with the statement that 'the doses required to produce the long-term changes in the serotonergic system far exceed those used by recreational users', for two reasons. First, the authors may have underestimated the typical consumption patterns of regular Ecstasy users. Some recreational Ecstasy users report taking up to 15 ecstasy tablets in a weekend, and in my most recent study participants consumed an average of about two tablets of Ecstasy in a single session and had occasionally used up to four tablets. Using their own criteria, this would translate into doses of 2.8–5.6mg/kg which are similar to the dose of MDMA (5mg/kg) that has been found to produce depletion of CNS serotonin in non-human primates (Ricaurte *et al.*, 1988). Furthermore, the authors have failed to take into account principles of interspecies scaling (e.g. Ricaurte *et al.*, 2000). When such principles are applied, a dose of 5mg/kg of MDMA in a monkey is equivalent in an adult human to about 1.4mg/kg, or approximately one tablet of Ecstasy.

The main point that I take issue with, however, is that the article tends to ignore the overwhelming evidence that regular Ecstasy users suffer from impulsive behaviour and deficits in verbal memory performance, and that these deficits are specifically associated with past use of Ecstasy (e.g. Morgan 1998, 1999; Morgan *et al.*, 2002). The latter view is further supported by the results of our most recent study. We report that regression analyses

indicated that these cognitive deficits were only predicted by measures of past consumption of Ecstasy – and not by measures of consumption of any other illicit drug (Morgan *et al.*, 2002).

I accept the authors' point that lifestyle factors associated with Ecstasy use (such as repeated exposure to dehydration and hot environments) may contribute to the neuropsychological deficits associated with Ecstasy use and thus should be the subject of further research. However, all of the available evidence suggests that these factors are only likely to play a modulating role in the neurotoxic effects of Ecstasy. Furthermore, I (Morgan, 1999, 2000), and other investigators (Bolla *et al.*, 1998; Semple *et al.*, 1999; Gouzoulis-Mayfrank *et al.*, 2000), have found statistically significant dose–response relations between the extent of exposure to Ecstasy and impairment of memory performance. This is most consistent with a persistent pharmacological effect.

Finally, I do not believe that it is possible that impulsive behaviour and deficits in verbal memory performance in Ecstasy users are 'iatrogenic' disorders induced by some form of autosuggestion. It seems highly implausible to me that samples of Ecstasy users could be sufficiently suggestible and sophisticated enough to feign such selective neuropsychological deficits and appear cognitively unimpaired in all other respects. Furthermore, there is evidence that Ecstasy users may be unaware of such deficits. Recreational Ecstasy users have been reported to exhibit deficits in delayed recall compared with cannabis users and drug-naive controls, although they did not differ in their subjective reports of cognitive failures (Rodgers, 2000).

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'Danger' remains

Peer commentary by **RODNEY J. CROFT**.

AS pointed out by Cole, Sumnall and Grob, there are a number of limitations that plague the field of Ecstasy research. However, I view these as a cause of interpretational difficulties. I would argue that even given these limitations, we are in a strong position to judge the chronic use of Ecstasy as harmful to humans.

It is important to note here that I am not arguing for the unequivocal cause-and-effect relationship that Cole *et al*. deem necessary (as Descartes reminds us, we could always be being deceived by a malignant demon). Rather I am claiming that the difficulties cited by the authors need not lead the researcher to complete scepticism. We *are* in a position to reach reasonable conclusions about the harm that Ecstasy may cause in humans.

For example, the authors claim that because we are unable to obtain accurate drug-use histories, results based on such information are logically flawed. I agree that it is unlikely that participants will accurately describe their drug-use history, but the question that we should be asking is 'In what manner does this affect our results?' The main way is that it will make them more conservative because of an increase in error variance (participants may not know how much Ecstasy they consumed or may not remember accurately). That is, it will *decrease* the chance of concluding that there are relations between Ecstasy use and impairment.

We may of course stretch this scepticism further and postulate other confounding factors, such as a bias predisposing people with such impairments to estimate their use as larger than those without these impairments (this would make a relation between reporting bias and impairment appear to be a relation between Ecstasy use and impairment). Although logically this is a possibility, there are an infinite number of such possibilities. Unless we are to withhold our advice to the Ecstasy user indefinitely while we test the infinite possibilities, we must ask instead whether there is good reason to believe these other possibilities to be true. To answer this we should look to science and rational argument, and I am not aware that either realm has produced strong reasons to treat such possibilities as confounds.

Similarly, although the possibility that psychopathology may precede Ecstasy use rather than being caused by it is important and makes interpretation difficult, there is other evidence that we may look to. For instance, we do know that:

- Ecstasy impairs serotonergic neurone integrity in rats (e.g. Commins *et al*., 1987) and non-human primates (e.g. Ricaurte *et al*., 1988);

best message

- chronic Ecstasy users have decreased serotonin function (McCann *et al*., 1998);
- serotonin enhancement is related to most clinically efficacious antidepressants (Owens & Nemeroff, 1994);
- users experience a transient form of depression a few days after Ecstasy use (Curran & Travill, 1997); and
- chronic Ecstasy users report more depression than controls (Gamma *et al*., 2000).

Thus although, on logical grounds, we cannot discount the alternative possibility suggested by Cole *et al*., there is considerable converging evidence that the psychopathology observed in chronic Ecstasy users may be caused by Ecstasy.

Although I find the authors' scepticism too extreme, I would stress that my discontent is only in degree. I believe that their caution is of paramount importance in Ecstasy research, and that such research should do all that is feasible to rule out such possibilities. The authors' concern, for example, that other drugs may have been confounding Ecstasy research, has recently been shown to be warranted (Croft, MacKay *et al*., 2001). In that study we found the 'expected' cognitive deficits in Ecstasy users relative to controls. However, as Ecstasy users typically also use a considerable quantity of cannabis, we compared them with cannabis users as well and found that the cannabis users exhibited the same deficits as the Ecstasy users. In other words, we did not find any cognitive deficits in the Ecstasy users that were not also observed in the cannabis users, suggesting that Ecstasy may not be directly related to the reported cognitive deficits.

However, the above study addressed cognitive impairment only and therefore should not be treated as a demonstration of a general problem for Ecstasy research. For instance, we recently found that Ecstasy users exhibited decreased serotonin function relative to both controls and cannabis users (Croft, Klugman *et al*., 2001), which suggests that serotonin impairment in Ecstasy users is not merely a result of cannabis use. Further, in support of the view that this impairment was caused by the Ecstasy and was not merely a premorbid group characteristic, this serotonin decrease was proportional to reported lifetime use of the drug and was independent of frequency of use. These results are consistent with the demonstrations that Ecstasy impairs serotonin neurone integrity in non-humans (e.g. Commins *et al*., 1987; Ricaurte *et al*., 1988) and of diminished serotonin function in recreational users (McCann *et al*., 1998). But they are not consistent with the thesis that Ecstasy-related serotonin impairment is merely imaginary.

'…there is strong converging evidence that Ecstasy does cause impairment: that it is not merely iatrogenic'

To conclude, there is strong converging evidence that Ecstasy does cause impairment: that it is not merely iatrogenic. Although conclusions drawn from such evidence cannot be infallible, I believe that the strength of this evidence makes 'danger' the most reasonable message for the researcher to be broadcasting.

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Very real, very damaging

Peer commentary by **ANDY PARROTT**.

AN increasing number of publications have described psychobiological problems in recreational Ecstasy users, including memory deficits, altered sleep, eating disorders, loss of sexual interest and various psychiatric disorders. Cole, Sumnall and Grob suggest that these problems are either iatrogenic (caused by the physician), imaginary, or reflect confounding factors. In this article I will argue that the deficits are very real and cannot be explained away as artefacts. Furthermore, I will outline how MDMA may be causing these problems by damaging serotonergic neural pathways in the brain.

Ecstasy users and non-users are self-selected groups, so there are many potentially confounding factors such as differences in IQ/intelligence, sleep loss, and other drug use (Curran, 2000). The first studies to find memory deficits did indeed suffer from several methodological limitations (e.g. Krystal *et al.*, 1992; Parrott *et al.*, 1998).

However, the later, more sophisticated studies have confirmed these memory deficits, even after controlling for potentially confounding factors. Verkes *et al.* (2001) compared three groups of Dutch ravers/clubbers who all displayed irregular circadian rhythms. Memory scores for the Ecstasy users were significantly lower than for non-user controls, and remained impaired after education, alcohol, cannabis use, and other factors, were controlled by covariance. Morgan (1999) found significant memory deficits, both in comparison with non-users, and with polydrug users who had never taken MDMA. Zakzanis and Young (2001) prospectively assessed Ecstasy users on two occasions one year apart. They controlled for sleep loss by ensuring that the abstinent participants had 'at least seven nights of 7 to 9 hours of continuous sleep' before being tested. Over the year, performance deteriorated significantly on several of the memory tasks, with the degree of worsening positively correlated with the amount of Ecstasy/MDMA taken that year.

Cannabis is an important confounding factor, but the memory deficits generally remain when it has been controlled. Gouzoulis-Mayfrank *et al.* (2000) compared moderate users of Ecstasy with a cannabis control group matched with the Ecstasy group on past cannabis use, and non-user controls. There were no significant cognitive differences between the cannabis group and the non-user controls, whereas the Ecstasy group showed significant deficits on tasks involving memory, learning, and higher intelligence. The Ecstasy users were not, however, impaired on tasks of alertness or attention. Rodgers (2000) found cognitive deficits in regular cannabis users, but significantly worse performance in Ecstasy/cannabis users compared with cannabis users on the delayed recall tasks. Croft *et al.* (2001) found no significant differences between cannabis users and Ecstasy/cannabis users, although each group was more significantly impaired than non-user controls. However the study had unequal sample sizes (11 Ecstasy users, 32 controls), and the small Ecstasy group seems to have contained a mixture of low and high users. Heffernan *et al.* (2001) found significantly impaired self-rated prospective memory in regular Ecstasy users, even after covarying for other drug use. Rodgers *et al.* (2001) undertook a web-based study of 490 participants, and found that everyday memory problems were related to cannabis use, whereas long-term prospective memory deficits were related to past Ecstasy use.

Several studies have found the memory and learning problems are worse in heavy than in light Ecstasy users (Fox, Parrott *et al.*, 2001; Fox, Turner, *et al.*, 2001; Morgan, 2000), with memory problems being reported by 19 per cent of novice Ecstasy users, 52 per cent of moderate Ecstasy users, and 73 per cent of heavy Ecstasy users (Parrott *et al.*, 2002). So overall these selective memory/learning deficits are a robust empirical phenomenon, and have been demonstrated by numerous research groups on at least 18 different memory tasks (see Parrott, 2001).

Laboratory animal research shows that MDMA is a selective neurotoxin, destroying the axon terminals that arise from serotonin cell bodies in the brain stem. Repeated doses of MDMA cause the cumulative loss of serotonergic axon terminals in the cerebral cortex (Ricaurte *et al.*, 2000), and there is increasing evidence for serotonergic neural damage in humans. Studies employing PET, SPECT, and more indirect procedures, have demonstrated reduced serotonin activity in abstinent recreational Ecstasy users (e.g. Verkes *et al.*, 2001). Bolla *et al.* (1998) found a positive association between the serotonergic loss and memory deficits, and Reneman *et al.* (2000) found a positive correlation between serotonergic receptor binding and verbal-learning deficits.

Serotonin is important for a wide range of psychobiological and psychiatric functions: memory, sleep, eating, sex, depression, obsessive compulsive behaviour and anxiety. There have been many published case studies of psychiatric casualties (e.g. McCann *et al.*, 2000; Schifano, 2000). In some cases a predisposition was exacerbated by MDMA, but often there were no known predisposing factors (Soar *et al.*, 2001). Non-clinical surveys of 'normal' young adults, have found raised psychiatric symptom profiles in light and heavy Ecstasy polydrug users (Parrott *et al.*, 2000, 2001). Lifetime

Ecstasy consumption correlates significantly with symptoms of phobic anxiety, psychoticism, general anxiety, and total negative feelings (Milani *et al.*, 2000).

Huether *et al.* (1997) proposed an explanatory model for how MDMA may be causing these problems. An acute dose of MDMA produces 'a massive and prolonged stimulation of serotonin release', which generates the intense feelings of pleasure. In laboratory animals the neurotransmitter release is boosted by high ambient temperatures, which may explain why Ecstasy users favour hot and crowded conditions (Parrott, 2001). The sustained serotonin overactivity severely overstresses the energy metabolism within the pre-synaptic terminal, and this may be the process underlying its destruction (Huether *et al.*, 1997). MDMA also impairs hypothalamic temperature regulation, which is why Ecstasy users overheat when dancing and need 'chill-out' rooms (Parrott, 2001). Serotonin neurotoxicity in laboratory animals is increased by high environmental temperature (Huether *et al.*, 1997), and it is likely that the overheating of recreational Ecstasy users contributes to their neuronal damage.

Cole *et al*. also suggests that many individuals 'use dance drugs to aid their experience'. We empirically investigated this hypothesis, but found that positive moods, sociability, life contentment, and positive psychobiology (e.g. good sex, enjoyment of music) were similar across all drug user and non-drug user groups (Parrott *et al*., 2001). In a prospective study of dance clubbers, Ecstasy users and non-users all reported good moods on the Saturday night (Parrott & Lasky, 1998). However, two days later the recovering Ecstasy users reported significantly higher depression and less sociability, so that over the whole week their average moods were slightly worse than for non-users (Parrott, 2001).

As with most recreational psychoactive drugs, the short-term benefits are heavily outweighed by longer-term negative consequences. And the more drug taken, the worse the long-term effects: we were recently approached by a former very heavy user who had not taken Ecstasy for seven years, but was still experiencing severe sleep problems, phobic anxiety, severe depression, and sexual impotence. In moderate regular users, the cognitive deficits are often independent of awareness or recognition of them (Fox, Parrott *et al.*, 2001).

To summarise, the suggestion of Cole *et al.* that that the problems are iatrogenic or caused by the physician is just bizarre and lacking in supportive evidence. The suggestion that they may be due to confounding factors is a more important criticism, although cognitive deficits remain even when these factors have been statistically controlled. The notion that these deficits are imaginary is negated by the brain-scan literature, the consistency of the human functional deficits, and the extensive animal data. Far from being imaginary, these Ecstasy-related problems are unfortunately very real.

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Where are the casualties?

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THE British Crime Survey indicates that around two million people in the UK have used Ecstasy. If exposure to Ecstasy causes brain damage then we have a very serious public health problem. But there is no credible evidence that the NHS is overrun with Ecstasy casualties. As both Parrott and Morgan state, Ecstasy users may be unaware that they have any problems until they take part in studies. We believe that impairment equates with a clinical problem. Therefore unimpaired individuals are being told by the media that they are brain-damaged and have psychological problems. We believe that this quite neatly fits our definition of an iatrogenic disorder. We are not suggesting that the differences are due to autosuggestion, just that these differences are not clinically significant but are being reported as if they are.

The sole theory put forward for the observed results is that MDMA is a neurotoxin. None of our colleagues questioned the fact that animal studies routinely fail to demonstrate any functional effect of MDMA exposure. Why is it so easy to demonstrate differences in humans but not animals? The animal studies do not have the same confounds. We can demonstrate unequivocally that MDMA-induced neurotoxicity was the causal agent in reliable behavioural or cognitive changes – yet we fail to observe such changes. This suggests that MDMA-induced neurotoxicity does not cause cognitive or psychological impairment.

Parrott has provided us with a review of the relevant data, but there are a number of problems with his comments:

Neurotoxicity The available evidence does not support the energy exhaustion model of serotonin neurotoxicity. Drug treatments predicted by this theory to reduce neurotoxicity actually increase it (Hervías *et al*., 2000). MDMA injected directly into the brain does not cause neurotoxicity, as the theory predicts (Paris & Cunningham, 1991).

Also, it is the case that MDMA-induced neurotoxicity is altered by increased temperature – but over a third of animals die when administered MDMA at the temperatures required to increase neurotoxicity. This would suggest a much higher number of human fatalities if Parrott's theory is correct.

Finally, although the notion of 'light' versus 'heavy' users has entered common usage, we still are not in a position to map directly from animal studies to human use. This means that we have no idea whether human users are using neurotoxic doses of MDMA. Interspecies dose scaling is a controversial area, and was subject to a recent debate in *Neuropsychopharmacology*. The calculation is made even more complex by the unknown and continually changing content of 'street' Ecstasy.

Why do people take it? Contrary to what Parrott suggests, Ecstasy users frequent hot, crowded environments because nightclubs pack large numbers of them into small spaces with inadequate ventilation, not because it alters the effect of their Ecstasy. Also, in a recent survey, 91 per cent of users reported that they used Ecstasy to help them keep going on a night out with friends and 80 per cent to enhance an activity, such as listening to music (Boys *et al.*, 2001).

'...these differences are not clinically significant but are being reported as if they are'

Cognitive deficits The cognitive deficits and psychological problems that Parrott describes are also seen in users of cocaine, alcohol and cannabis. None of these drugs is considered a serotonergic neurotoxin. His theory cannot account for these data. And if serotonin is implicated in so many functions, why are verbal memory deficits the only consistent finding?

Psychopathology and brain imaging In the brain-imaging studies, people with a psychiatric problem were excluded. Any observed differences cannot be the cause of psychiatric problems if the subjects did not have any. This argues against the notion that Ecstasy users are at greater risk of developing psychiatric problems. Several of our studies have failed to find any psychiatric problems in Ecstasy users.

The brain-imaging studies have also been heavily criticised in the literature for numerous methodological problems. The authors of these papers have stated that their results should be interpreted cautiously because of this.

Our colleagues have all agreed that the Ecstasy literature is plagued with a large number of confounds. The question is how these confounds affect our interpretation of the data. There is a large body of data demonstrating consistent differences, and we are not disputing this fact. We simply do not feel comfortable with the notion that millions of young people are being told that they are brain-damaged based upon confounded data. Alternative explanations exist and they need to be tested.

We are not the only ones unconvinced that acute doses of MDMA cause neurotoxic damage and long-term harm. The US Food and Drug Administration has recently approved a clinical trial using MDMA in the treatment of post-traumatic stress disorder. There is another similar trial going on in Spain and one planned in Israel. MDMA has been given to human volunteers in the UK, US, Spain, Germany, Switzerland and Holland. These studies have so far failed to cause psychiatric problems or cognitive difficulties in their participants, and suggest that ethics committees do not regard the drug as a major risk.

But no one should underestimate the dangers of illegally using controlled drugs. There is the very real possibility that Ecstasy use will cause long-term changes in the brain. However, the animal data demonstrate that simplistic theories based on MDMA-induced neurotoxicity are inadequate. Research should move beyond description and start to provide mechanisms for the observed differences. Only then can we effectively warn drug users about the long-term consequences of their drug use.

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