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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