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Controversy and Methodological Issues

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Abstract

The controversy over possible MDMA-induced serotonergic neurotoxicity in human recreational Ecstasy users is critically examined in light of recent research findings. Although the designs of such studies have improved considerably since the 1990s, the evidence to date remains equivocal for a number of reasons, including (1) inconsistent findings on the existence and reversibility of persistent Ecstasy-related serotonergic and cognitive deficits; (2) lack of clear association between changes in brain imaging measures and functional deficits attributed to MDMA-induced neurotoxicity; (3) the contribution of concomitant cannabis or other drug use to both brain imaging abnormalities and cognitive deficits; (4) methodological shortcomings such as failure to adequately match samples of Ecstasy users and controls; (5) the questionable relevance of animal models of MDMA-induced neurotoxicity to typical human patterns of Ecstasy use; and (6) the potential role of inherent pre-drug deficits in serotonergic systems, impulse control and executive cognitive function that may predispose to excessive use of drugs including Ecstasy. Given the retrospective nature of nearly all studies of Ecstasy users to date, the controversy over whether MDMA has ever caused neurotoxicity or cognitive deficit in human Ecstasy users is likely to continue for some time without resolution.

KEYWORDS: Ecstasy, neurotoxicity, serotonin, cognition

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Ecstasy is the popular term for the serotonin-releasing agent 3,4-methylenedioxy-

methamphetamine (MDMA), a widely abused illicit drug with mixed stimulant and mild

hallucinogenic actions. According to the 2001 National Drug Strategy Household Survey, 20% of

Australians aged 20-29 have used Ecstasy, a significant increase since the previous (1998) survey.

The widespread use of Ecstasy by young Australian adults naturally raises concern over the health

consequences of such behaviour. Ecstasy is commonly taken at dance clubs or "rave" venues where

the mild hallucinogenic effect of the drug enhances the subjective impact of the music and social

environment. In contrast to such well-known "recreational" use, some researchers and clinicians in

the U.S. and Europe have quietly supported limited therapeutic applications of MDMA (eg., for

cancer-related anxiety, post-traumatic stress disorder, severe depression, Parkinsonism; see

Holland, 2001), and the FDA has recently granted approval for clinical trials of the drug (Check,

2004). Although MDMA-induced fatalities are extremely rare (Cole & Sumnall, 2003), public fears

about MDMA-induced brain damage and persistent cognitive dysfunction have been triggered by

widely publicised research suggesting that (1) MDMA can cause lasting disruptions to the

serotonergic system, and (2) Ecstasy use is commonly associated with deficient cognitive and

memory performance. The possibility of cumulative brain damage as the drug is used repeatedly or

heavily over time presents an alarming prospect. However, the following critical review of the

recent research literature on this controversial topic suggests that such alarm may be unwarranted.

MDMA-Induced Neurotoxicity: A Summary of the Evidence

In animal studies using rodents and primates, repeated high doses of MDMA caused signs of

lasting damage to serotonergic axons in regions such as the prefrontal cortex and hippocampus (eg.,

Battaglia et al., 1991; Callahan, Cord & Ricaurte, 2001; Ricaurte et al, 1988; Sabol et al., 1996).

Long-term recovery appears to be only partial, with abnormal patterns of reinnervation and

incomplete restoration of forebrain serotonin levels (Hatzidimitriou, McCann & Ricaurte, 1999).

MDMA stimulates release of serotonin and also blocks reuptake of other monoamines (Parrott, 2001), however the acute serotonin-releasing action appears to be largely responsible for the unique "entactogenic" psychological effects of the drug (Liechti & Vollenweider, 2001). Although adverse reactions to typical doses of Ecstasy are relatively rare in human Ecstasy users (Gowing et al., 2002), the research findings in animals of serotonergic neurotoxicity induced by MDMA in brain regions such as the hippocampus and prefrontal cortex are disturbing given the central role of these areas in memory and executive cognitive functioning in humans and the involvement of the serotonin system in regulation of mood and impulse control. Thus since the initial work on animals, a substantial number of studies of human recreational Ecstasy users have reported significantly poorer verbal and/or visual memory (eg., Back-Madruga et al., 2003; Bhattachary & Powell, 2001; Bolla, McCann & Ricaurte, 1998; Fox, Parrott & Turner, 2001; Fox, Toplis & Parrott, 2001; Fox et al., 2002; Gouzoulis-Mayfrank et al., 2003; Hanson & Luciana, 2004; McCann et al., 1999; Morgan, 1999; Morgan et al., 2002; Parrott et al., 1998; Reneman, 2000; Reneman et al., 2001), prospective or everyday memory (Heffernan et al., 2001; Rodgers et al., 2001; Zakzanis, Young & Campbell, 2003) and/or executive cognitive functioning (eg., Bhattachary & Powell, 2002; Halpern et al., 2004; Hanson & Luciana, 2004; Heffernan et al., 2001; Morgan et al., 2002; Thomasius et al., 2003; Wareing, Fisk & Murphy, 2000; Zakanis & Young, 2001a) in Ecstasy users compared to controls, with some studies reporting differences on measures of mood, psychopathology and impulsivity as well (eg., Moeller et al., 2002; Morgan et al., 2002; Thomasius et al., 2003; Wareing et al., 2000). Moreover, brain imaging studies of human Ecstasy users have reported deficiencies in cerebral metabolism (Obrocki et al., 2002), serotonin transporter densities (McCann et al., 1998; Reneman et al., 2001) and N-acetylaspartate/creatine ratios (Reneman et al., 2002) in heavy Ecstasy users compared to controls, interpreted as reflecting cumulative MDMA-induced damage to the serotonergic system (also see Gouzoulis-Mayfrank, Dauman & Sass, 2002).

Although the evidence summarised above would seem to present a solid case for neurotoxic effects of MDMA and corresponding adverse functional consequences in human Ecstasy users,

such conclusions are questionable for a number of reasons. These include inconsistent findings on the existence and reversibility of persistent Ecstasy-related serotonergic and cognitive deficits; lack of clear association between changes in brain imaging measures and functional deficits attributed to MDMA-induced neurotoxicity; the contribution of concomitant cannabis or other drug use to both brain imaging abnormalities and cognitive deficits; methodological shortcomings, such as failure to adequately match samples of Ecstasy users and controls; the questionable relevance of animal models of MDMA-induced neurotoxicity to typical human patterns of Ecstasy use; and the potential role of inherent pre-drug deficits in serotonergic systems, impulse control and executive cognitive function that may predispose to excessive use of drugs including Ecstasy. These issues are reviewed below.

Are Ecstasy-Associated Deficits Reversible?

One unresolved issue is the degree of reversibility of the reported deficits. Most earlier brain imaging studies compared recently (1-2 weeks) abstinent Ecstasy users to non-user controls, leaving open the question of long-term improvement or recovery. More recent brain imaging studies that compared recently abstinent current users of Ecstasy versus long-term abstinent former users have reported strong evidence for reversibility of the deficiencies in serotonin transporter densities commonly observed in recently abstinent users (Buchert et al., 2003; Reneman et al., 2001; Thomasius et al., 2003), suggesting that such deficiencies are attributable to short-term functional down-regulation rather than neurotoxicity. Serotonergic deficits (including reduction in serotonin transporter densities) are also well-known effects of antidepressant therapy with tricyclics and SSRIs (Grob, 2000), and may reflect brain changes associated with the therapeutic effects of such drugs rather than neurotoxicity. Nevertheless, despite the apparent reversibility of the reduction in serotonin transporter densities in recent users compared to former Ecstasy users and non-user controls, verbal memory was impaired in both recent and former users in the Reneman et al. brain imaging study. Similarly, both recent and former Ecstasy users were impaired on indices of executive cognitive functioning compared to controls in a study by Wareing at al. (2000), and

Ecstasy users scored higher on anxiety than controls. Morgan et al. (2002) found elevated psychopathology and impulsivity scores, and poorer executive cognitive and verbal recall performance on some (but not all) measures, in both recent and former users compared to controls. A combination of reversible and irreversible deficits in memory performance was indicated in a study of recent users, former users and non-user controls by Bhattachary and Powell (2001). In the Thomasius et al. brain imaging study, both recent and former Ecstasy users scored higher on depression and other measures of psychopathology than non-user controls, and former users exhibited poorer verbal memory performance than controls, again suggesting that functional deficits may not be fully reversible despite the apparent reversibility of Ecstasy-related differences on brain imaging measures. The poorer memory performance of former but not recent users compared to controls as reported by Thomasius et al. could be attributable to differences in overall lifetime drug use between the Ecstasy user samples, given that former Ecstasy users reported considerably higher use of cannabis than recent Ecstasy users and both polydrug user and non-user controls. This raises another problem: the possible contribution of cannabis or other drug use to the observed deficits in Ecstasy users (see below).

Are Cognitive Deficits of Ecstasy Users Due to Serotonergic Neurotoxicity?

Recent findings cited above appear to suggest that memory and executive cognitive performance measures reveal more subtle and enduring deficits than are currently detectable with brain imaging techniques. In any case the methods that have been used to image serotonergic axon terminals in brain imaging studies of Ecstasy users have been extensively criticised (see Kish, 2002, on the issue of specificity of ligands used to measure serotonin transporter densities). More importantly, research on nonhuman primates has generally found that MDMA-induced serotonergic neurotoxicity is not associated with decrements in memory performance even when 50-99% of brain serotonin is permanently depleted (Taffe et al., 2002; Winsauer et al., 2002). The diet drug fenfluramine produces the same signs of serotonergic neurotoxicity in animals as MDMA (Bowyer et al., 2003), yet has been administered to 25,000,000 people over several decades with no evidence

of any associated deficits (Grob, 2000). Thus perhaps a more plausible interpretation of the many reports of memory and cognitive deficits associated with Ecstasy use is that they are not due to MDMA-induced neurotoxicity, a conclusion reached in a recent review by Cole and Sumnall (2003). Certain psychopathological characteristics (eg., obsessive-compulsiveness, impulsivity, anxiety, depression) also appear to distinguish both recent and former Ecstasy users from non-user controls in some of the studies cited above. But a significant problem with many studies reporting brain abnormalities or functional deficits in Ecstasy users is that comparison of Ecstasy users to illicit-drug-naive controls was likely confounded by use of other drugs - especially cannabis, as Ecstasy users tend to use cannabis as well, often extensively.

The Cannabis Confound

A recent physiological study (Gouzoulis-Mayfrank et al., 2002) found that the prolactin response to fenfluramine challenge, an index of serotonergic system functioning, was more affected by past cannabis use than by Ecstasy use, an unexpected result. More importantly, heavy cannabis use has recently been shown to be associated with executive cognitive dysfunction and deficits on tests of visual and verbal memory that were previously found to differentiate Ecstasy users from controls; the cannabis-related deficits persisted for at least one month of abstinence (Bolla et al., 2002). The recent findings by Bolla et al., as well as an earlier report of slowly reversible adverse effects of cannabis on verbal memory (Pope et al., 2001), suggest that at least some of the widely reported deficits in memory and executive cognitive performance in Ecstasy users - especially heavy users (who also tend to be heavy users of cannabis) - might be attributable to heavy use of cannabis rather than Ecstasy. Some recent studies that have attempted to control for cannabis use in Ecstasy users have indeed reported that certain indices of memory impairment, executive cognitive dysfunction or psychopathology were more strongly related to use of cannabis than Ecstasy (Barker & Lyvers, 2002; Croft et al., 2001b; Dafters et al., 2004; Daumann et al., 2001; Morgan et al., 2002; Simon & Mattick, 2002), whereas other studies have indicated that Ecstasy use contributes to some memory and executive cognitive deficits as well as certain psychopathology measures

independently of cannabis or other drug use (Fox et al., 2001ab, 2002; Heffernan et al., 2001; Morgan et al., 2002; Rodgers et al., 2001). For example, Morgan et al. found that most indices of psychopathology related more strongly to cannabis use than Ecstasy use, with the exception of obsessive-compulsiveness, anxiety, somatization and overall symptom severity, which were more strongly related to Ecstasy use; poorer immediate and delayed verbal memory and executive cognitive dysfunction were related to Ecstasy use but not cannabis use. By contrast, Barker and Lyvers (2002) found that immediate and delayed verbal recall and immediate and delayed logical memory test scores were all significantly worse in Ecstasy users than polydrug user controls until level of prior cannabis use was controlled by covariate analysis, in which case the association of Ecstasy use with memory impairment disappeared entirely; measures of various forms of psychopathology and executive cognitive functioning failed to distinguish Ecstasy users from polydrug controls. Further work by Lyvers, Barker and Bradnam (2003) found that after controlling for cannabis use, Ecstasy users scored worse than controls only on obsessive-compulsiveness and phobic anxiety, both of which have been linked to serotonergic dysfunction (Gurtman et al., 2002; Hollander et al., 1992). A single, small-scale longitudinal study of Ecstasy users (Zakzanis & Young, 2001b) found that memory performance worsened after one year of continued Ecstasy use, but use of various other illicit drugs also increased over the same period, calling into question any conclusions about the effect of Ecstasy use on memory. The relative contribution of Ecstasy versus cannabis or other drug use to reported memory and cognitive deficits or psychopathology in Ecstasy users remains unresolved (eg., see recent meta-analysis of Ecstasy vs. cannabis effects on memory by Verbaten, 2003).

Premorbid Factors Associated with Drug Use

A further, and perhaps more serious problem with retrospective studies of drug users is that pre-drug deficiencies in brain serotonergic functioning may constitute an inherent risk factor for alcohol or illicit drug abuse as well as for impulsivity, depression, obsessive-compulsive disorder, and executive cognitive dysfunction (eg., Cloninger, 1987; Conrod, Peterson & Pihl, 1997;

Giancola et al., 1996; Higley & Linnoila, 1997; LeMarquand et al., 1998; Lyvers, 2000; Nielsen et al., 1998; Pihl et al., 1995; Tarter, Moss & Vanyukov, 1995; Virkkunen & Linnoila, 1997). Thus reported differences between Ecstasy or other drug users and non-substance-abusing controls on various measures, especially indices of executive cognitive functioning and impulsivity, may reflect pre-drug traits rather than effects of Ecstasy or other drug use, particularly when heavy users are examined (Croft et al., 2001a; Kish, 2002). Croft et al. attempted to address this issue in a physiological study. They reported differences between Ecstasy users and cannabis users on an EEG measure (intensity dependence of auditory evoked potentials) that they considered to be sensitive to serotonergic system functioning; the presumed serotonergic deficit was related to total Ecstasy consumption but not frequency of use, which Croft et al. tentatively interpreted as consistent with MDMA-induced serotonergic neurotoxicity rather than premorbid characteristics (such as depression) that might have promoted frequent self-medication. However, the increased risk of drug abuse associated with deficient pre-drug serotonergic functioning is generally not attributed to self-medication tendencies but rather to personality traits such as impulsivity and disinhibition, which can promote bingeing behaviour that could easily account for the relationship reported by Croft et al. (see Lyvers, 2000). Further, as noted above, most recent research comparing Ecstasy users to Ecstasy-naive cannabis or polydrug users on indices of memory, executive cognitive functioning and psychopathology has yielded mixed findings. Only if Ecstasy users consistently show signs of enduring brain dysfunction or poor memory or cognitive performance that clearly differentiates them from other substance abusers - especially when level of use of other drugs such as cannabis, methamphetamine or alcohol is carefully matched or otherwise controlled - can the case for functional neurotoxic sequelae of recreational Ecstasy use become tenable. In the absence of any such evidence, the apparent association between heavy use of Ecstasy and cognitive impairment is most plausibly attributable to pre-drug traits associated with an increased risk of substance abuse. This argument also applies to similar recent reports of enduring deficits associated with heavy cannabis use (Bolla et al., 2002; Pope et al., 2003).

Other Methodological Problems

A common methodological criticism of research on recreational Ecstasy users concerns the retrospective nature of the reports of "MDMA" use by participants in such studies (Cole & Sumnall, 2003; Curran, 2000; Grob, 2000; Hurley, Reneman & Taber, 2002). The actual content of pills sold as "Ecstasy" on the black market has been reported to vary, with some samples containing neither MDMA nor the similar drug MDEA but dissimilar drugs such as methamphetamine (known to be neurotoxic in high doses; Ricaurte et al., 2003), ketamine (an NMDA antagonist which can be neurotoxic in laboratory animals; Olney et al., 1991) or the over-the-counter cough suppressant dextromethorphan (which in large doses is hallucinogenic and probably neurotoxic like other NMDA antagonists). Thus any deficits exhibited by Ecstasy users may be attributable to the enduring effects of other neurotoxins sold as MDMA, rather than MDMA itself. However, recent analyses of large seizures of Ecstasy in the UK have indicated that all samples did contain effective doses of MDMA (Cole et al., 2002), and a recent analysis of blood and urine samples from "rave" party attendees in Australia revealed that all participants who said they had taken "Ecstasy" showed high levels of MDMA (Irvine et al., 2003). A recent review (Parrott, 2004) concluded that illicit samples of Ecstasy now contain effective doses of MDMA in 90-100% of cases. Thus it is likely that at least some recent samples of Ecstasy users included a significant proportion who had been exposed to effective (and even possibly neurotoxic) doses of MDMA rather than, or perhaps in addition to, other potentially neurotoxic substances. Other methodological criticisms of research on Ecstasy users include the confounding influence of unequal gender ratios and other demographic differences (such as education level) between user and control groups in many studies. Females have been reported to have 25% lower serotonin transporter densities than males irrespective of drug use (Kish, 2002; Mann et al., 2000), and show a different brain response to MDMA than males (Liechti, Gamma & Vollenweider, 2001), thus brain imaging and other investigations of the serotonin system in Ecstasy users should aim to achieve gender balance between user and control groups. Age, education level and general "premorbid" intelligence (eg., as estimated by reading

scores; Barker & Lyvers, 2002) should also be matched between groups, as should alcohol intake given the abundant evidence of brain shrinkage and cognitive decline associated with chronic heavy alcohol abuse (see Lyvers, 2000).

Are Animal Models Relevant?

A final contentious issue concerns the assumption that animal models of MDMA-induced serotonergic neurotoxicity are actually relevant to typical human use of Ecstasy. This assumption can be questioned given the necessity of administering extremely high repeated doses to rats or primates over a short time interval in order to induce neurotoxicity – cumulative doses that are considerably higher than those taken by human Ecstasy users even after considering interspecies scaling of doses (Aghajanian & Lieberman, 2001; Cole et al., 2002; Grob, 2000). Exposure to neurotoxic dosing regimens may only occur in the most extreme users of Ecstasy, if at all; hence recent and former Ecstasy users should be carefully assessed on the extent of their recent or past Ecstasy use, taking into account factors such as the highest dose taken, the typical dose taken, the number of doses taken per occasion, and the number of prior occasions of Ecstasy use. Although the dose of MDMA per Ecstasy tablet varies widely, this approach would nevertheless help evaluate whether any observed Ecstasy-related deficits might plausibly reflect either cumulative or supra-threshold, high-dose exposure to the drug's potential neurotoxic effect as indicated by animal studies.

Conclusion: Do We Want Ecstasy to Cause Brain Damage?

Recently a widely publicised claim of severe dopaminergic neurotoxicity induced by MDMA in primates (Ricaurte et al, 2002) was retracted (to the authors' credit) when the researchers discovered that the vial supposedly containing MDMA was actually methamphetamine, which is known to be neurotoxic to dopamine neurons at the extremely high doses administered as "MDMA" in the study (the effective dose of methamphetamine is considerably lower than that of MDMA). Subsequent experiments using actual MDMA revealed no signs of dopaminergic neurotoxicity in primates even at very high doses (Ricaurte et al., 2003). Other claims of Ecstasy-induced

Parkinsonism have been convincingly refuted (Kish et al., 2000; Kish, 2003). At present the controversy concerning possible neurotoxic sequelae of recreational MDMA/Ecstasy use is limited to the drug's purported actions on the serotonin system as revealed by high-dose studies in animals, but the Ricaurte et al. mislabelling incident has arguably cast a shadow over all prior claims of Ecstasy-induced brain damage. The fact that the prestigious journal *Science* rushed to publish Ricaurte et al.'s highly implausible initial report has been attributed to the widespread desire of researchers and government agencies to find scientific reasons to condemn Ecstasy use (*Nature* Editorial, 2003). Claims of Ecstasy-induced brain damage have all too often been uncritically reported in the popular media and by various "experts" in an effort to generate alarm or scare young people away from using or trying Ecstasy. Past experience with claims of "reefer madness" suggests that such an approach to preventing illicit drug use only serves to undermine the credibility of the relevant authorities, a case of "crying wolf" that may later backfire. For this reason, claims of MDMA-induced neurotoxicity and associated cognitive deficits or other problems in Ecstasy users must be carefully and dispassionately scrutinized. At present, the accumulated evidence for such claims is not compelling.

On purely scientific grounds the ideal investigation of the neurotoxic potential of MDMA in humans would administer various doses of the drug to Ecstasy-naive volunteers, with brain and behavioral changes measured at various times following MDMA exposure in order to assess their reversibility. A preliminary brain imaging study by Vollenweider, Jones and Baggott (2001) administered a moderate dose of MDMA (1.5-1.7 mg/kg) to Ecstasy-naive volunteers and found no changes in serotonin transporter densities (using PET) from pre-drug baseline to one month after MDMA administration. A related study found no changes in memory and cognitive performance at one month post-MDMA treatment (Ludewig et al., 2003). The research was conducted in Switzerland where restrictions on administration of illicit drugs to humans for research purposes are less stringent than in most other countries. However, the sample size was small and limited to males, and dosing regimens shown to be neurotoxic in nonhuman primates were not used. More

recently, limited clinical trials of MDMA for post-traumatic stress disorder and for anxiety in

terminal cancer patients have been approved in the U.S. (Check, 2004). Nevertheless, given the

legal and ethical issues involved in administering MDMA to humans, studies of retrospectively

self-reported Ecstasy use will continue to be the most common approach for investigating Ecstasy's

possible long-term effects in humans. Unfortunately, for reasons outlined above, the collective

research findings arising from such work are likely to remain equivocal, provoking much discussion

and debate but little insight into the nature of any observed differences between users and non-users

of Ecstasy.

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