Neuropsychobiology

Neuropsychobiology 2000;42:42–48

'Is MDMA a Human Neurotoxin?': Diverse Views from the Discussants

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Key Words
MDMA · Neurotoxin

Abstract
Every discussant at the Novartis symposium was invited to submit a 250-word abstract, giving their views upon the question: 'Is MDMA a human neurotoxin?'. These abstracts are presented here. They illustrate a wide range of viewpoints and opinions, as might be expected from experts in such diverse fields: animal neuroscience, human cognitive testing, police pathology laboratory, psychotherapeutic institute and psychiatric hospital. Some abstracts emphasized the methodological weaknesses of the human empirical data: the uncertain nature of 'Ecstasy' tablets, the reliance on self-report data, and the contributory factors of heat, dancing/exertion, poor diet and other illicit drugs. These factors may lead to psychobiological changes, which could be misinterpreted as neural damage. The absence of gliosis in animal models was also noted, which led to suggestions that there might be alternative interpretations for the neural changes which have been observed in rats and monkeys. Others noted the absence of neural/behavioural change following a single Ecstasy tablet, or commented upon the therapeutic benefits of MDMA in a quiet supportive environment. Nevertheless, novel studies from England, Germany, Italy, the Netherlands, Scotland and Wales confirmed and extended the range of cognitive, behavioural, EEG and neurological deficits, displayed by drug-free Ecstasy users. Moreover, these deficits often remained when other illicit drug use was statistically controlled. In conclusion: If MDMA neurotoxicity in humans is a myth, then it is a myth with a heavy serotonergic component.

Introduction

Thirty MDMA specialists were invited to this Novartis symposium. They comprised authorities from Europe, the US and Australia, with expertise in various aspects of MDMA/Ecstasy use. Some of these invited discussants are animal neuroscientists, studying the effects of MDMA and other ring-substituted amphetamine derivatives upon neural functioning. Others are involved with recreational drug users, assessing the integrity of their behavioural, psychophysiological and neurological functions when drug free. Several specialists are based at university hospi-

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tals or psychiatric clinics, investigating the acute and chronic consequences of illicit drug use. Others work in police laboratories, and are concerned with the exact nature of the Ecstasy samples which clubbers and dancers purchased and consume. Some are outreach workers, who visited clubs and raves in order to encourage safer patterns of drug-related behaviours, Finally, several are advocates of MDMA use for psychotherapy; they had been involved in MDMA trials during the mid-1980s, before it was scheduled as a drug of abuse. Their experiences with MDMA were often quite different, with older individuals having administered single tablets to facilitate psychotherapeutic insights, in quiet and relaxed surroundings – quite different from the hot and sweaty conditions of today's Ecstasy users.

The wording of the invitation to submit an abstract for this special issue of *Neuropsychobiology* was as follows: 'Every discussant is invited to submit a 200- to 250-word abstract, outlining their position on the topic: "Ecstasy (MDMA): a human neurotoxin?". We hope that these contributions will encompass a range of disparate views and opinions. We would like you to present your personal views on the question, possibly briefly noting the work you are currently engaged in. Thus some abstracts may relate to animal laboratory research, others to human studies, others to field work with dancers/clubbers. Other contributors may wish to highlight particular methodological issues which need to be addressed, or debate the wider implications of the topic for society ... Please write your own subtitle – catchy or otherwise.' Abstracts were received from 15 discussants, 2 as co-authors. They are presented (with minimal editing), in alphabetical order below.

Abstracts

How to Find Evidence of MDMA's Neurotoxicity

Richard Dafters
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The emphasis of previous MDMA research on either short-term physiological responses, such as hyperthermia and hyperkinesis, or on long-term histopathological changes may mask important areas of overlap and possible novel diagnostic techniques which do not clearly fall into these categories. For example, recent animal research in our laboratory has shown that doses of MDMA which are known to produce large but transient hyperthermic responses may have long-lasting effects on the organism's thermoregulatory mechanisms, which are revealed as exaggerated thermic responses to an environmental heat-stress test 14 weeks after drug administrations. Similarly, although many of the 'transient' phenomena associated with MDMA use are thought to derive from autonomic nervous system responses or via the hypothalamo-pituitary-adrenocortical axis, very little attention has been overtly directed at possible long-term autonomic indices of toxicity, such as altered measures of heart rate variation. Finally, it is only recently that attention has focused on functional brain imaging techniques. Not all of these techniques are as expensive or difficult to administer as PET and fMRI. Recent studies in our laboratory have shown that quantitative EEG techniques with modern dense-mapping electrode arrays, which are both economic and extremely simple to use, can reveal differences in brain function correlated with prior recreational use of MDMA. In conclusion, researchers need to guard against methodological inertia, and should be aware of new techniques which, in combination with more refined cognitive tests, may prove to be valuable indicators of MDMA's neurotoxicity.

Methodological and Ethical Considerations Regarding MDMA Neurotoxicity

Helen Fox
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The research regarding the neurotoxicity of MDMA remains incongruous due to immense methodological problems. Within the field of animal research, immunostaining data is often unsupported by quantitative data corresponding to 5-HT levels, decreases in 5-HT have (as yet) not been found to relate to corresponding increase in gliosis, and doses given to animals often far exceed those of recreational levels. In human studies, control and MDMA user groups are never fully matched, and generally differ in potentially important aspects. While attempts to obtain (pre-Ecstasy) baseline data raise difficult ethical and practical issues, these criticisms are not meant to disparage research in general, or to deny the fact that MDMA may well be neurotoxic at certain dosages, but rather to highlight the fact that any conclusions drawn should be interpreted with these factors in mind. Furthermore, the tendency for results, supporting the null hypothesis to remain undisclosed [Schmidt, 1996], can only help contribute to biased reporting by the tabloid press. For these reasons, caution should also be taken when relating neurotoxicity findings to functional impairments in humans. The functional significance of a single dose (neurotoxic ... or not?), is also unclear. Although neurotoxicity has been found to be dose-dependent, and recent research has also deficits in executive functioning tasks, delayed verbal racall [Morgan, 1998, 1999] and in free recall [Parrott, 1997], the fact remains that there are many long-term users who do not reveal signs of either cognitive impairments or psychosocial problems. A study

just completed at the University of East London has requested participants to give a subjective account of their experiences regarding depression, anxiety and eating disorders, prior to taking MDMA in order to assess the interaction of these variables with regards to cognitive and attentional impairments. Again, this is not to suggest that long-term problems may not be directly linked to MDMA, but rather urges researchers to emphasize more strongly these other possible factors when reporting data.

Is a Single Dose of MDMA Neurotoxic to Humans?

Alex Gamma
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Although a matter of serious concern at this workshop, it is still unclear, due to lack of direct evidence, whether a single dose of MDMA can cause serotonergic damage in humans. Animal studies show that MDMA neurotoxicity is dose dependent, and reductions in radiolabelled serotonin (5-HT) nerve terminals are not usually found after single low doses approaching typical human doses. A relevant recent human study by McCann et al. found a 25% global decrease in 5-HT transporter binding in human MDMA users (with an average use of 228 doses), which correlated linearly with the extent of previous MDMA use. From this linear relationship it can be inferred that exposure to a single dose of MDMA would reduce 5-HT transporter density by 0.1%, which would be undetectable within the normal variance of 5-HT transporter density and could therefore not be considered as abnormal. This study, together with the available animal data, therefore suggests that one or even a few single doses of MDMA do not produce functionally relevant damage to 5-HT neurons in human beings.

Risk Factors for the Development of Neurotoxic Brain Damage in Ecstasy Users

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There is increasing evidence from the literature that regular Ecstasy use may cause neurotoxic brain damage in humans. In my opinion, there is still no convincing evidence that a single ingestion or sporadic use of Ecstasy bears the same risks. However, some individuals may be more vulnerable than others and develop long-term adverse effects after consumption of relatively small cumulative doses. An important aim of future research should be to identify specific risk behaviours and high-risk groups for the development of neurotoxic effects. The patterns of abuse should be analysed properly, including detailed information not only on the duration of regular use and the estimated cumulative dose, but also on the average dose in one night. As Ecstasy users are mostly polydrug users, the issue of adequate control groups is important. Finally, the metabolizer status of users (ultra-fast, slow metabolizers) should be studied. Recently, we completed a study with 28 Ecstasy users who reported regular use of Ecstasy and cannabis, but no other psychotropic drugs. The last use of Ecstasy had been on average 3 weeks prior to the study. Two matched control groups, a non-user and a cannabis-user group, were included. Ecstasy users performed worse on memory and problem-solving tests, and exhibited differences in information processing (auditory evoked event-related potentials) compared to both control groups. Moreover, low performance on memory tasks was associated with heavier use of Ecstasy. These yet unpublished data underline the dangers of regular Ecstasy use.

Potential Benefits of MDMA from Medical Use versus Potential Toxicity from Abuse

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Data were presented only on recreational users of MDMA without control data on subjects before taking MDMA or without abuse of drugs that effect neuropsychological function. Recreational use/abuse is in contrast to research/therapeutic administration, which involves lower doses, less frequency, drug purity, no sleep interruption, medical screening and lower body temperature without physical exertion from dancing. Lower body temperature in animals reduces 5-HT neurotoxicity [Broening et al., 1995]. In two previous articles, subjects reported benefits from MDMA in a medical setting, including reduction in psychological problems; improvement in interpersonal relationships, self-esteem and mood; and a decreased use of addicting substances [Greer and Tolbert, 1986, 1998]. One cancer patient experienced a dramatic reduction in pain that lasted for weeks, and a child of a Holocaust survivor reported a decrease in depression and negative attitudes for years, both after a single session [Greer and Tolbert, 1998]. There are many valuable therapeutic agents that can, when taken excessively, cause adverse consequences. Such consequences resulting from recreational abuse should not make us blind to the fact that administration of pure material in a medical context may incur no negative sequelae.

MDMA Neurotoxicity Research: Methodological Concerns

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Considerable media attention has been given recently to investigators purporting to demonstrate neurotoxic brain damage in humans who had self-administered large amounts of the polymorphous drug Ecstasy. Attempts to extrapolate these findings to single-dose effects of MDMA, however, fall far short of certitude. Methodologi-

cal flaws in both animal and human studies call into question data interpretation attempting to prove the MDMA neurotoxicity hypothesis. Although animals given large dosages of MDMA appear to undergo persistent reorganization of terminal 5-HT axons, evidence for functional sequelae has been scant. The failure to demonstrate gliosis, the classic marker for neurotoxic brain injury, raises further doubt of the validity of this model of brain 'damage'. Interpretations of human data also contain severe methodological limitations. All subjects were heavy users of the street drug Ecstasy, a term encompassing a variety of substances other than MDMA, including ketamine. Furthermore, these Ecstasy-MDMA subjects also had histories of considerable cocaine and methamphetamine use, while controls not using MDMA were often highly-motivated graduated students free of other drugs as well. Although demonstrations of cognitive deficits and suspect personality traits have been variable, little can be concluded because of the variety of drugs used and the poorly matched controls. There is a pressing need to conduct prospective human research with MDMA. Unfortunately, public apprehension fueled by sensationalist and often inadequately informed media have constricted scientific dialogue. Pressing public health concerns of long-term effects on an increasing percentage of European and American youth remain unanswered. Persistent interest in MDMA's possible therapeutic role must also be addressed. MDMA's potential to cause harm as well as its capacity to facilitate healing when used under optimal conditions can only be answered using well-controlled prospective research designs [Grob and Poland, 1998].

Cognitive, Psychophysiological and Personality Studies of MDMA in Long-Term Users

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We investigated the cognitive effects of MDMA in 36 subjects (24 males, mean age 24 years) with a significant history of predominant MDMA use (mean 4.3 years, cumulative mean total 235 tablets, range 12–2,600), who were compared with 19 controls. The MDMA users had not taken the drug or any other psychoactive drugs for some days before (mean 79 days, range 2–400). Auditory evoked potentials were investigated in a subsample (n = 21), to test for serotonergic depletion as indexed by stimulus intensity dependence. Personality questionnaires included Cloninger's 'neurochemical' dimensions. A multivariate analysis of variance showed significant impairment of MDMA users on tests of learning, recognition and recall and manual dexterity. Compared with normative data, 3 subjects scored below the 2 SD limit on two tests and an additional 8 on one test [Klugman et al., 1999]. Both sides of the brain were implicated, and the patterned deficit profile excluded explanations based on nonspecific factors such as attention and motivation. No relation was found between those deficits identified and history of other drug use including cannabis. The auditory evoked potentials disclosed an augmenting P200 stimulus intensity function which correlated with total tablets taken. The augmenting function as well as a positive correlation with the harm avoidance personality scale were compatible with reduced serotonergic neurotransmission. These results are important in that they identify cognitive deficits in subjects who clearly had a significant history of MDMA use. They support involvement of the serotonergic system, though no relation was found between the electrophysiological and cognitive measures.

Do Validated Biological Measures of Neurotoxicity Really Support the Claim that MDMA Is Neurotoxic to Man?

Madhu Kalia

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It is well established that several pharmacologic agents (e.g. fluoxetine) and MDMA interact with brain 5-HT. These actions have been exploited therapeutically (fluoxetine, antidepressant) or for recreational use in clubbing (MDMA). In order to accurately evaluate the possible effects of these agents on brain structure and function, it is necessary to use standardized and validated biological measures. Merely measuring the degree and duration of depletion of 5-HT and its metabolites is of little value in determining neurotoxicity because those depletions are part of the pharmacologic profile of these agents and are not indicators of 'brain toxicity' or 'brain damage'. Classical, robust, validated biological measures of neurotoxicity include: neurodegeneration and gliosis which are routinely used in evaluating animal and human tissue. Despite the obvious difficulty in directly extrapolating results from these animal studies to man, the value of using tissue from carefully controlled animal studies in determining neurotoxicity cannot be overemphasized. There is no evidence that MDMA or SSRIs like fluoxetine produce neurotoxicity in animals when gliosis is used as a validated measure [O'Callaghan and Miller, 1994]. Furthermore, there is no evidence that perikarya of serotonergic neurons in the raphe nuclei undergo neurodegeneration when call death is used as a validated measure. If 'pruning' of the axon terminals is suspected, then the evaluation of physiological measures such as retrograde transport is recommended. Anterograde transport techniques looking for 'pruning' in few serotonergic axon terminals are useless because this system is ubiquitous and very widely arborized.

Was it MDMA?

L.A. King

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A well-recognized flaw of self-reporting studies is that the identity of the drug consumed is not accurately known. Although MDMA has become synonymous with Ecstasy, the situation is more complex. Whereas many users believe that they are taking MDMA, there have been periods in the UK when methylenedioxyethamphetamine (MDEA) was commoner in street seizures. Other ring-substituted amphetamines such as 2C-B, methylenedioxyamphetamine, phenyl-

butanamine and 4-methylthioamphetamine as well as mixtures (e.g. MDMA + MDEA) are also seen. Ketamine, usually mixed with a stimulant drug such as ephedrine, amphetamine or caffeine, is sold into the same Ecstasy market, and has accounted for up to 10% of Ecstasy seizures in the past few years. All of these various substances are manufactured in the form of well-made tablets of a similar size and often bearing a distinct impression (logo). Capsules and loose powders are extremely rare. The drug content of MDMA tablets is extremely variable. In 1994, the mean MDMA content was close to 100 mg, but by 1997 this had declined to 80 mg. Concern has been raised about toxic contaminants in so-called 'bad batches' of MDMA, but there is no analytical evidence for this. Apart from the active principal(s), Ecstasy tablets contain innocuous fillers and binders such as lactose, cellulose and stearates, as well as traces (<1%) of synthetic impurities.

Psychobiological Risk Factors Involved in Vulnerability to Psychostimulants in Human Adolescents and Animal Models

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Human adolescents show a high tendency to seek for novel sensations, and are frequently involved in recreational use of amphetamine-type stimulants such as MDMA (Ecstasy). In the few human studies, the relationship between MDMA use and individual temperamental features is still unclear. So are the biological and psychological consequences of chronic use. Subjects who had used MDMA for 8 to 20 months showed – following a drug-free period – a combination of dysphoria, aggressiveness and elevated sensation seeking, as well as significantly reduced prolactin and cortisol responses to *d*-fenfluramine. The possibility that such alterations in MDMA individuals are partially related to a premorbid condition, consisting of novelty-seeking behaviour and mood disorders related to a derangement in monoaminergic systems, rather than to substance abuse, cannot be excluded. The role of these psychobiological variables was investigated in an animal model of adolescence. Elevated baseline levels of corticosterone, behavioural arousal and novelty seeking were found in periadolescent mice, which also exhibited, compared to adults, a more marked sensitization of the locomotor response following a repeated and intermittent *d*-amphetamine administration. They were also characterized by a unique hypothalamo-pituitary-adrenocortical axis and behavioural hyporesponsivity to psychological stress and to psychostimulants. The study of such age-related differences could provide a major contribution to the understanding of psychobiological risk factors involved in vulnerability to drugs of abuse in human adolescents.

Ecstasy (MDMA) a Human Neurotoxin?

Margherita Raffaella Milani

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Evidence from studies of recreational Ecstasy users suggests that MDMA produces a wide range of both cognitive and psychiatric impairments. The study I carried out in Italy on 10 MDMA consumers, at the Addiction Treatment Unit in Padova, supports the hypothesis that the drug is associated with long-term cognitive deficits [Milani, 1997]. Data obtained from the neuropsychological tests were consistent with the subjective assessment. There were several limitations to this study. Prospective and controlled researches of MDMA effects on humans are precluded by ethical and legal issues. However, research on animals has revealed long-lasting neurotoxicological effects due to Ecstasy administration. As far as the human brain is concerned, it is not possible to come to any definitive conclusions based on objective experiments. Nevertheless, it is important to point out the main aim of the research in this field: if the purpose is outlining the consequences of recreational use of Ecstasy, we should take in account that, in the real population, Ecstasy consumers are polydrug users. Moreover, we need to consider the environment where people usually take the drug as well as the way they do it. As a conclusion, given the results I obtained from the previously mentioned study and based on personal field work, I argue that the recreational use of Ecstasy together with the style of living that it implies, can be seriously neurotoxic and addictive.

Long-Term Psychological Sequelae of Recreational Use of 'Ecstasy': Controlled Studies in Humans

M.J. Morgan

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Most studies of recreational Ecstasy users have failed to adequately control for their use of other drugs. I have used a design in which the performance of Ecstasy users is compared to that of polydrug users who have used similar quantities of other drugs, but have never taken Ecstasy, as well as with a control group of participants who have never taken any illicit drugs. The results of 8 studies that have employed this design indicate that in many respects the psychological status of Ecstasy users was similar to that of other participants. There were no group differences in state or trait anxiety, mood, anger/aggression, empathy or general health status. There were also no group differences in many measures of cognitive performance including block design, spatial span, verbal fluency and a test of planning ability, although both groups of illicit drug users exhibited higher perceptual aberration, venturesomeness and impulsiveness scores, and tended to be more distractible and initiate responding faster. However, Ecstasy users did exhibit selective deficits in the Wisconsin Card Sort test, committed significantly more errors in a behavioural test of impulsivity, and exhibited marked deficits in immediate an delayed recall performance [Morgan, 1998, 1999]. My recent data also indicate that the memory performance of participants who had not used Ecstasy for at least 6 months was superior to that of those who had used it more recently.

MDMA-Induced Psychopathology: Model Building with Missing Parts?

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Evidence for definite long-term neurotoxic effects of MDMA in humans is inconclusive. Yet despite this, reportage of neurotoxicity and long-term psychopathology is rife. This has arisen because of the compelling animal research, which demonstrates MDMA-induced falls in chemical markers deemed to indicate serotonergic cell loss. In human research, the falls in serotonergic metabolites in CSF, fewer 5-HT sites in PET scans, and psychological changes in impulsivity, cognition/memory and mood, have been used to strengthen the extrapolation from animals. However, the human studies are littered with methodological problems. Comparison/control groups are generally poorly matched on other drug use profiles; many studies do not control for when MDMA was last taken; it is near impossible to discern how much MDMA has been taken, if any, and longitudinal data are missing. With regard to the changes in cognitive function, performance on many tests is unimpaired [Morgan, 1998], or early decrements are not subsequently confirmed [Parrott and Lasky, 1998; Turner et al., 1998a]. Psychological assessment has also largely ignored other potentially confounding effects of MDMA. For example, significant (and often dramatic) reductions in eating behaviour were observed in MDMA users for up to 6 days following weekend drug ingestion [Turner et al., 1998b], and chronic eating disturbances can disrupt cognition [Green et al., 1994]. MDMA-induced disruptions of arousal, sleep/waking or exercise could also interfere with psychological test performance. None of this negates the possibility that MDMA is neurotoxic and psychopathogenic in humans, but these 'anomalies' should be addressed and used to temper any conclusions. More considered statements should be relayed to the ever-hungry media-monster. This last remark is included to plea for researchers to avoid the potentially false construction of Ecstasy psychopathology, since negative media reports can alienate potential MDMA users from volunteering. Some of our participants have questioned our motives for studying MDMA. This is perhaps not surprising in 'zero tolerance' cultures, such as exist in the UK and USA. Thus, when the headline-grabbing hypothesis 'Is MDMA neurotoxic in humans?' is presented as fact, 'MDMA *is* neurotoxic in humans', unqualified by uncertainties, many non-psychopathologized MDMA users may be dissuaded from participating in research. This could jeopardize the chances of accurately answering the question of whether or not this drug is dangerous to all.

Memory Impairment and Diminished Serotonergic Function in Users of 'Ecstasy'

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Administration of MDMA or 'Ecstasy' to animals in doses similar to those used by humans results in long-term damage to serotonergic cerebral neurones. The serotonergic system in involved in mood, cognition and impulse regulation. This (unpublished/submitted) study was designed to investigate if there is an association between past use of Ecstasy and decreased mood, cognitive performance and serotonergic function in humans. We performed a cross-sectional study in three groups of regular visitors of rave parties: two groups of Ecstasy users with moderate and high recreational use of Ecstasy, and a control group who had never used Ecstasy. Moderate users had used Ecstasy on between 12 and 48 separate occasions during the past 2 years, and high users on 48 occasions or more. Regular use of alcohol or drugs other than cannabis led to exclusion. Cognitive performance was assessed by measuring reaction time, direct recall, working memory and information processing. For serotonergic function, the cortisol and prolactin responses to *d*-fenfluramine were measured in a placebo-controlled, cross-over challenge study, at least 1 week after Ecstasy was last used. The use of other illicit drugs, as well as education, depression, anxiety and impulsivity were carefully controlled for using a regression model. The groups were representative samples of the general population of visitors of rave parties. The Ecstasy users and control subjects had comparable demographic variables amd measures of personality and behaviour. Ecstasy users showed significant impairment of memory and prolonged reaction times. In general, more complex tasks were affected stronger. Cortisol release after *d*-fenfluramine administration was significantly reduced in both groups of Ecstasy users compared with the controls. Ecstasy users had higher scores on depression and anxiety scales. Correction of the finding for the likely confounding variables, including recent exposure to Ecstasy, psychosocial profiles and previous use of other drugs did not provide an alternative explanation. These results suggest that prolonged use of Ecstasy may be associated with impairment of memory and serotonergic function. These findings are compatible with neurotoxicity of Ecstasy, as shown in animals.

Overview

Many of the above abstracts emphasized the methodological weaknesses of the human empirical data: the uncertain nature of 'Ecstasy' tablets, the heavy reliance on self-report data, and the contributory factors of heat, dancing/exertion and other illicit drugs. Thus, recreational drug users differ from non-users in many ways, with lifestyles which might be more exciting, but less healthy. Dancing all night, consuming illicit drugs, poor diet, inadequate rest and recuperation can all have adverse consequences. This raises the question of whether it is these related lifestyle factors which lead to psychobiological deficits, which are misinterpreted as neurotoxicity. Other

abstracts commented upon the absence of gliosis in animal models, and questioned whether the neural changes which have been observed in rats and monkeys should be termed neurotoxicity. However, alternative explanatory models for these neural changes do need to be proposed. If they are not a reflection of neurotoxicity, then what exactly do they indicate? (see Kalia for instance). Other contributors have noted the absence of neural/behavioural changes following a single Ecstasy tablet or have suggested psychotherapeutic benefits with MDMA, when administered in quiet reflective environments. But although these are important issues, it is insufficient to simply point out the existence of methodological problems, and state that no conclusions can therefore be offered. Scientific evidence in many topics of practical concern is replete with methodological uncertainties, but scientists still have to weigh up all the evidence – and offer their best estimates for what it all means! This is where the laboratory animal data is so crucial, since without this placebo-controlled double-blind hard scientific evidence for neural damage, it is unlikely that MDMA-induced neurotoxicity in humans would even be suspected.

This leads to the increasing body of evidence for behavioural, psychophysiological and neurological deficits in recreational Ecstasy users. The published evidence for this was outlined in the symposium presentations (earlier papers in this issue), while more recent (largely unpublished) data, from England, Germany, Holland, Italy, Scotland and Wales is summarized in several of the abstracts. Every single study – by Dafters, Gouzoulis-Meyfrank, Gruzelier, Laviola, Milani, Morgan and Verkes – found *some* psychobiological deficits in recreational Ecstasy users. Moreover, these deficits remained even when potentially confounding factors, such as other illicit drug use, were statistically controlled. Not one study reported unimpaired psychobiological functioning! These recent findings (Verkes' findings only emerged the week before the symposium) obviously need to be peer reviewed and published. But they seem to confirm and extend the range of cognitive, psychophysiological and neurological deficits displayed by drug-free Ecstasy users. Furthermore, these deficits are largely restricted to psychobiological functions with serotonergic innervation. Perhaps the famous quotation by Kety [1974] about the genetics of schizophrenia could be paraphrased here: 'If schizophrenia is a myth, it is a myth with a heavy genetic component'. Thus, to offer a simple answer the question investigated during Novartis Foundation symposium:

If MDMA neurotoxicity in humans is a myth, it is a myth with a heavy serotonergic component.

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