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Neurotoxicity of methylenedioxyamphetamines (MDMA; ecstasy) in humans: how strong is the evidence for persistent brain damage?

E. Gouzoulis-Mayfrank & J. Daumann

Department of Psychiatry and Psychotherapy, University of Cologne, Germany

ABSTRACT

Background The popular dance drug ecstasy (3,4-methylenedioxymethamphetamine: MDMA and some analogues) causes selective and persistent neurotoxic damage of central serotonergic neurones in laboratory animals. Serotonin plays a role in numerous functional systems in the central nervous system (CNS). Consequently, various abnormalities including psychiatric, vegetative, neuroendocrine and cognitive disorders could be expected in humans following MDMA-induced neurotoxic brain damage. **Aims** In recent years, the question of ecstasy-induced neurotoxicity and possible functional sequelae has been addressed in several studies with drug users. The aim of this paper was to review this literature and weigh the strength of the evidence for persistent brain damage in ecstasy users. **Methods** We used Medline to view all available publications on 'ecstasy' or 'MDMA'. All available studies dealing with ecstasy users entered this analysis. **Findings and conclusions** Despite large methodological problems the bulk of evidence suggests residual alterations of serotonergic transmission in MDMA users, although at least partial restitution may occur after long-term abstinence. However, functional sequelae may persist even after longer periods of abstinence. To date, the most consistent findings associate subtle cognitive, particularly memory, impairments with heavy ecstasy use. However, the evidence cannot be considered definite and the issues of possible pre-existing traits or the effects of polydrug use are not resolved. **Recommendations** Questions about the neurotoxic effects of ecstasy on the brain remain highly topical in light of its popularity among young people. More longitudinal and prospective studies are clearly needed in order to obtain a better understanding of the possible long-term sequelae of ecstasy use in humans.

Keywords Ecstasy, MDMA, memory, neurotoxicity, serotonin.

Correspondence to: E. Gouzoulis-Mayfrank, Department of Psychiatry and Psychotherapy, University of Cologne, Kerpener Strasse 62, D-50924 Cologne, Germany. E-mail: e.gouzoulis@uni-koeln.de
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INTRODUCTION

The ring-substituted amphetamine derivative 3,4-methylenedioxymethamphetamine (MDMA) is a popular recreational drug best known by its street name, ecstasy. MDMA and some analogues are used mainly by young people aged 18–30 years and are particularly popular among visitors of raves and disco clubs. In recent epidemiological surveys in Europe and the United states 4.7–13% of young adults reported use of MDMA at least once in their life-time with evidence of abuse of or dependence on MDMA in 15–20% of these users (e.g. [1–4]). The prevalence of MDMA use among ravers was found to be as high as 50% or even 80% [5,6]. Estimates suggest that in the United Kingdom alone 500 000 young people take ecstasy every weekend [2].

An ecstasy tablet will usually contain 70–120 mg of MDMA, but sometimes the concentration is higher or lower. Occasionally tablets will contain similarly acting analogues such as 3,4-methylenedioxyamphetamine (MDA) and 3,4-methylenedioxyethylamphetamine (MDEA), or stimulant amphetamines, and more rarely substances from different classes [7]. The psychological effects of MDMA and its congerers MDA and MDEA last about 3–5 hours and include relaxation, euphoria, lessening of anxiety, feelings of closeness to and empathy for other people, and openness to communication. This psychological profile has been called 'entactogenic', a term

which derives from the Latin root *tactus* (touch) and the Greek roots *en* (inside) and *general* (to produce) and has the connotation of 'inducing a feeling of touch with the world within' [8]. Due to these entactogenic effects MDMA has been considered as a possible adjunct to psychotherapy, because it could help to overcome anxiety and defence mechanisms and could therefore enhance or speed up the therapeutic process [8,9]. However, MDMA and the other 'entactogens' (MDA and MDEA) also have stimulant-like effects and this aspect is likely to be the driver for their widespread use in the dance scene. Finally, they also alter perception and may occasionally induce marked hallucinogenic effects [10]. Thus, the psychotropic profile of ecstasy is complex. This is not surprising in view of the chemical/structural similarity of the entactogens to both stimulant amphetamines and phenethylamine hallucinogens, such as mescaline [11].

The acute pharmacology of MDMA has been studied widely in experimental animals and includes direct and indirect aminergic and serotonergic mechanisms [2]. Among other actions, MDMA binds to all presynaptic monoamine transporters, most strongly to the serotonin transporter (SERT), and induces rapid and powerful release of serotonin (5-HT) and dopamine (DA) from presynaptic terminals. These actions are crucial for both the acute psychological and the physiological effects of ecstasy, which include rising of blood pressure and heart rate, nausea, sweating, tremor, jaw clenching, bruxism and modest rise of body temperature. Every year there are several well-documented fatalities including cases with severe hyperthermia, rhabdomyolysis, disseminated intravascular coagulation and multi-organ failure, and cases with intracranial bleeding or cerebral infarction arising possibly from increased blood pressure or angiitis. Considering the widespread use of ecstasy these acute, dramatic complications from its use are thankfully relatively rare [12]. However, another important danger may be associated with the use of MDMA and MDMA-like drugs, particularly when taken repeatedly and in high doses. Animal studies evidence clearly that MDMA is neurotoxic and will cause persistent alterations in the brain serotonin system when given in high doses. The important question is whether similar changes may occur in humans. Current evidence is alarming, but not conclusive. In this paper, we will review the literature focusing on human studies and will outline future research perspectives.

ECSTASY IS NEUROTOXIC—EVIDENCE FROM ANIMAL STUDIES AND POSSIBLE RELEVANCE FOR HUMANS

Several studies in different laboratories and with different species demonstrate long-term alterations in brain serotonin systems following high and repeated doses of MDMA and MDA. The alterations include depletion of 5-HT and its major metabolite 5-HIAA, reduced [^{3}H]paroxetine binding reflecting reduced density of SERT and reduced serotonergic axonal density in brain tissue (e.g. [13,14]). When reviewing these studies, it is important to note that the bodies of the serotonergic neurones lie tightly together in the raphe nuclei of the brain stem, and their long axons project to virtually every area in the central nervous system. However, some regions such as the hippocampus, the basal ganglia, the thalamus, the substantia nigra, the amygdala and the primary sensory cortex show particularly dense serotonergic innervation [15].

All but one species tested so far, including non-human primates, have confirmed the pattern of selective neurotoxicity for serotonergic axons, with the only exception of mice that exhibit neurotoxic alterations of serotonergic and dopaminergic axons (for review see [2]). Neurotoxicity is clearly dose-dependent. In rats 5-HT depletion was demonstrated 7 days post-treatment after a single high dose of MDMA [10 mg intraperitoneally (i.p.)] and after multiple closely spaced moderate doses of MDMA (4 mg i.p. twice-daily for 4 days, resulting in a 40% loss of cortical 5-HT), but not after a single moderate dose (4 mg i.p.) or multiple largely spaced moderate doses of MDMA (4 mg i.p. daily for 4 days or 4 mg i.p. twice-weekly for 8 weeks) [16]. Two weeks after multiple very closely spaced high doses of MDMA (4×10 mg i.p. at 2-hourly intervals), 40–80% reductions of 5-HT and 40–60% reductions of SERT binding were demonstrated depending on the brain region examined [17]. The rate of recovery was shown to be region-dependent. This probably corresponds to the very different distances that must be covered in the process of reinnervation by re-growing axons, from their origin in the serotonergic cell bodies in the raphe nuclei of the brain stem to the different terminal areas of the brain. In rats, full recovery was shown in most studies and most brain regions after 1 year, but some individual studies reported only partial recovery in the hippocampus and some cortical areas and hyperinnervation in the hypothalamus. In non-human primates, sensitivity to the neurotoxic effects of MDMA was shown to be more pronounced than in rodents, resulting in higher rates of 5-HT depletion with smaller doses of MDMA and persisting hypoinnervation patterns in most neocortical regions and the hippocampus for as long as 7 years post-treatment [13,17,18]. Two weeks after multiple closely spaced moderate doses of MDMA (5 mg i.p. twice-daily for 4 days) the reductions in 5-HT axon density were about 80–95% in the cortex and striatum and 7 years post-treatment; they were still about 35–75% in the same areas [18].

Although a large amount of research has been performed, the precise mechanism of neurotoxicity resulting

from MDMA is not entirely understood (for review see [2]). It seems that a metabolite initially produced peripherally, and not MDMA itself, is responsible for the long-term neurotoxic effects on 5-HT systems because central injections of MDMA, even in large doses, fail to induce long-term neurotoxicity although they do induce acute release of 5-HT. The neurotoxic metabolite is probably taken up into the 5-HT neurone terminals via the SERT. Its further metabolism results in increased generation of free radicals, exhaustion of the antioxidant capacity of the brain tissue and induction of oxidative stress, which is believed to be a key factor in MDMA related neurotoxicity [2]. Hyperthermia enhances the formation of free radicals and both hyperthermia and high ambient temperatures enhance the neurotoxic effects of MDMA. In line with these mechanisms, 5-HT uptake inhibitors, radical trapping agents, antioxidants and several drugs with hypothermic effects (partially) protect against MDMA-induced neurotoxicity. In addition, some role of dopamine in 5-HT neurotoxicity from MDMA is supported by some data, but this issue still remains controversial [2].

Interestingly, the long-term functional abnormalities seen in laboratory animals after neurotoxic MDMA regimens have been only subtle. This may correspond to a complex role of the neuromodulator 5-HT in 'fine tuning' and stabilising neural transmission in cerebral networks [19,20]. Broadly speaking, 5-HT appears to play important roles in several functional systems such as cognition, stimulus processing, psychological wellbeing, sleep control, vegetative and neuroendocrine functions, without it being critical for the essential functioning of any of these domains. Thus, unlike animals with neurotoxic lesions of the dopaminergic system that are clearly parkinsonian, the behaviour of MDMA-treated rats and monkeys with clear neurotoxic lesions of the serotonergic system cannot be distinguished easily from control animals [21–23]. In general, although 5-HT is involved in most brain functions, it is a 'soft modulator'of other neurotransmitters and neuropeptides and as such, removal of 5-HT usually does not induce a pronounced phenotype. Nevertheless, some studies using specialized behavioural test methods and pharmacological challenges reported subtle functional disturbances such as increased anxiety and poor memory performance in MDMA-treated rodents and monkeys [22–30]. However, other studies reported normal or back-to-normal performance within 2–3 weeks following MDMA treatment [31–33], and studies using behavioural tests for the assessment of anxiety and risk-taking behaviour yielded conflicting results [28,29,34,35]. These data strongly suggest that even if ecstasy users are indeed suffering neurotoxic damage of their serotonergic systems, the functional consequences may be subtle and detectable only through demanding behavioural tests or after pharmacological probes. We should, however, emphasize that even a relatively subtle dysfunction in important cognitive and psychological/emotional domains may have a serious impact on the development of young people in both social and educational/occupational terms.

The key question is whether the animal data are relevant for humans. In studies with primates even single doses of MDMA were found to elicit some degree of serotonergic depletion lasting over a few weeks [2]. However, the lowest MDMA dose which was shown to produce long-term neurotoxic effects that persisted over months and years has been 5 mg/kg twice daily over 4 days, i.e. 40 mg/kg overall in 4 days [13,17,18]. Compared to that, the typical dose of a recreational weekend user, with one to two pills of 75–125 mg MDMA or analogue every 1–4 weeks, is clearly lower [7,36,37]. However, according to some formulae for interspecies scaling the typical recreational MDMA doses might well correspond to doses commonly given to animals in experimental studies [2]. On the other hand, humans ingest the drug orally while in experimental animals the drug is administered via subcutaneous or intraperitoneal injection, and these parenteral routes of administration have been shown to result in higher acute plasma levels of MDMA and to produce more pronounced long-term neurotoxic effects [38]. Finally, one study with rodents replicated older findings of neurotoxic effects after relatively closely spaced MDMA doses (e.g. twice daily over 4 days), but failed to demonstrate neurotoxicity after more widely spaced regimens (once daily for 4 days or twice weekly for 8 weeks) [16]; these latter regimens may well correspond better to the use patterns of typical recreational users. Nevertheless, users typically take MDMA over some years and this may result in long-term cumulative neurotoxic effects. Interestingly, the only study which looked at the effects of self-administration of MDMA in primates over a period as long as 18 months did show 5-HT depletions in the order of 25–50% in various cortical and subcortical regions [39]. These decrements in 5-HT content did not reach statistical significance, due possibly to the small sample in this study ($n = 3$). Nevertheless, if the results are upheld in further studies, they are clearly alarming [39]. In addition, some heavy MDMA users take MDMA more frequently than just at weekends, and they tend to take higher amounts of up to 10 pills per session (e.g. [40]). This pattern results in doses at least as high as those administered in studies with experimental animals. Although these heavy users are a minority, given the widespread use of MDMA their absolute number is large. Furthermore, the widespread parallel use of alcohol and other neurotoxic stimulants (amphetamines and cocaine) may act synergistically and enhance the neurotoxic effects of MDMA. Finally, the neurotoxic effects of MDMA may also be enhanced under the typical conditions associated with

MDMA use such as hot, overcrowded surroundings and long periods of dancing leading to further increases in body temperature [2,41,42]. In conclusion, it is possible that the animal data demonstrating MDMA induced neurotoxicity are indeed relevant for humans and that ecstasy users may be exposing themselves to the risk of neurotoxic brain damage.

STUDIES WITH USER POPULATIONS

Brain morphology and global activity

In principle, it is rather unlikely that neurotoxic damage confined to the serotonergic system will be visible in routine brain imaging procedures in terms of loss of brain volume or atrophy or that it will manifest itself as an alteration of global cerebral activity in positron and single photon emission tomography (PET and SPECT) or electroencephalographic (EEG) studies. However, serotonin is not only a neurotransmitter or neuromodulator in neuronal tissues; it also exerts powerful vasoconstrict actions on small brain vessels [43], has neurotrophic effects on brain tissue not confined to the period of brain maturation [44] and has been shown to stimulate neurogenesis in the hippocampus throughout adulthood [45].

Although routine structural MRI, perfusion and diffusion MRI, SPECT with ^{133}Xe and ^{99m}Tc-HMPAO and $H_2{}^{15}O$ PET were all shown to be normal in ecstasy users [46–49], one study reported an association between longer periods of MDMA use and decreased global brain volume [46] and another study [50] demonstrated reduced grey matter density in several cortical regions. In addition, recent studies with MR spectroscopy reported higher concentration of the glia marker myoinositole with heavier use of MDMA [51], dose-dependent reductions of N-acetylaspartate levels (NAA/Cr and NAA/Cho ratios) in the frontal cortex of MDMA users [52] and a tendency towards lower NAA/Cr ratios in the hippocampus of MDMA users compared to controls [53]. These findings could be related to neurotoxic damage and glial proliferation indicating a repair mechanism. In addition, another small pilot study reported a high diffusion coefficient (ADC) and high regional cerebral blood volume (rCBV) in the globus pallidus, a brain area that is particularly rich in serotonin. This finding could be related to vasodilatation due to low serotonergic tone following degeneration of serotonergic axons [48]. Finally, lower metabolic activity (PET) was found in the basal ganglia and amygdala of 93 ecstasy users compared to controls [54], and higher β- and α-, lower δ-activity and lower coherence of brain activity between different electrode positions was found to be associated with heavier patterns of MDMA use [55,56]. These latter findings may well be the result of MDMA neurotoxicity, although alternative interpretations are clearly conceivable.

Central serotonergic parameters

Reduced 5-HT concentration would be the expected outcome of widespread neurotoxic damage of serotonergic axon terminals in the brain tissue of MDMA users. As the 5-HT concentration cannot be measured *in vivo* in human brains, we may use the concentration of the major metabolite of 5-HT, 5-HIAA, in cerebrospinal fluid (CSF) as a proxy for the concentration in the brain. An early study on a small number of ecstasy users reported normal levels of 5-HIAA in the CSF [57]. Since then several studies with larger samples have shown reduced concentrations of 5-HIAA in cerebrospinal fluid of ecstasy users compared to control groups [58–61]. However, only one study [59] reported a correlation between the 5-HIAA concentration and the extent of earlier ecstasy use. The absence of this correlation in the majority of studies means that we cannot disprove the alternative hypothesis of a relatively low serotonergic tone prior to ecstasy exposure.

Recent improvements in nuclear medicine technology, e.g. PET and SPECT using suitable ligands, make the *in vivo* examination of brain tissue receptors and/or binding sites feasible today. In particular the serotonin transporter (SERT) is currently considered as the most suitable marker for presynaptic serotonergic damage. An early PET study with the SERT ligand [^{11}C](+)McN5652 on 14 ecstasy users [62] demonstrated a dose-dependent reduction in its binding, both globally and in most cortical and subcortical brain regions examined. A further study on 10 ecstasy users [63] using SPECT and the SERT ligand β-CIT also demonstrated reduced cortical SERT availability. However, correlations between the SERT availability results, cumulative ecstasy consumption and length of abstinence periods led the researchers to assume a temporary occupation or down-regulation of the binding site rather than structural neurotoxic damage [63]. Since then there has been some debate on the validity of SPECT and PET techniques with SERT ligands in measuring MDMA-related neurotoxicity and on additional subject-related methodological problems of these early studies [64–66]. Nevertheless, more recent studies with refined methods [67] and larger samples (up to 61 current and former users in Thomasius *et al.* [68] confirmed reduced SERT availability at least in female current users with a relatively heavy use pattern (> 50 pills) [68–72]. All in all, alterations were less pronounced in male users, and were absent in former users following abstinence from MDMA use of at least 12 months. These more recent data indicate that women may be more susceptible to MDMA-induced alterations of the serotonergic system than men and, in addition, they suggest at least some degree of

recovery of the assumed serotonergic lesion following prolonged abstinence from ecstasy.

Interestingly, another SPECT study with the 5-HT_{2A} receptor ligand [^{123}I]-R91150 demonstrated reduced cortical binding in current ecstasy users with short-term abstinence and increased binding in former users who had not used ecstasy for an average of 5 months [73]. This pattern is in line with animal data showing temporary (up to 1 month) down-regulation of postsynaptic 5-HT2 receptors resulting from high synaptic 5-HT concentration after administration of MDMA, and long-lasting up-regulation of the same postsynaptic receptors following widespread presynaptic damage of serotonergic neurones leading to 5-HT depletion [74,75]. Hence, unlike the SERT data, postsynaptic receptor data suggest alterations persisting over long periods of time in abstinent MDMA users.

In summary, CSF and PET and SPECT ligand studies have yielded some evidence for long-term alterations in brain serotonergic systems after MDMA use. This evidence is alarming but not conclusive, with some data pointing to at least a partial recovery after prolonged abstinence. In any case, the changes in human brain are not as pronounced as to be visible as reduction of brain volume or atrophy with routine imaging methods. Neither was a clear picture of neurotoxic damage evident when measuring global and regional brain activity with nuclear medicine or EEG methods. Despite these mitigations, the risks posed by ecstasy and/or MDMA should not be underestimated; it is conceivable that even subtle residual changes in the serotonergic system could be functionally important and may contribute to clinical or subclinical alterations of psychological well-being and/or the behaviour of ecstasy users.

Serotonin-related functions

Psychiatric disorders and personality traits

A low serotonergic tone has been widely associated with psychological disturbances, particularly with depression, suicidality, aggressiveness and impulsiveness. There are several anecdotal reports of depressive syndromes, anxiety and psychotic episodes associated with ecstasy use [76] and high psychiatric comorbidity was established in studies with large samples of ecstasy experienced polydrug users [77,78]. A causal link between these disorders and ecstasy may exist at least in a predisposed subgroup of users. However, due to the widespread use of ecstasy and the parallel use of other substances no firm conclusion can be drawn from these reports. Moreover, results from a prospective-longitudinal investigation on a large representative sample of adolescents and young adults ($n = 2462$) over 4 years confirmed a high psychiatric comorbidity in MDMA users, but demonstrated that the use of ecstasy started, in most cases, after the onset of the comorbid disorder [79].

Several studies used standardized psychometric instruments and demonstrated higher scores for impulsiveness, depressive mood, emotional instability, anxiety, novelty seeking, hostility/aggression and an overall heightened level of psychological distress in mostly polydrug ecstasy users compared to control groups [56,80–88]. However, results have not been entirely consistent; for example, one study reported reduced impulsiveness and aggression compared to the control group [60]. Two studies [85,89] suggested a link between high scores and heavy parallel cannabis use. Moreover, in a recent study with a longitudinal design and a follow-up period of 18 months increases in self-rated psychopathology were associated with continued cannabis rather than continued ecstasy use [90]. Finally, in recent studies with relatively large samples of 234, 61 and 50 polydrug ecstasy users and controls using other drugs only, elevated psychopathology appeared to be associated with polydrug use in general and not specifically with ecstasy use [68,91,92].

All in all, it is still unclear whether the frequently reported emotional instability and impulsive features and/or the overall high level of psychological distress result from ecstasy use or from the combined use of several substances or whether, alternatively, these are factors predisposing to a general affinity to drugs. Interestingly, a recent combined SPECT and psychometric study established decreased SERT availability only in current MDMA users, but elevated depression scores in current and former users [93]. In this study higher depression scores were associated with higher life-time MDMA dose, but there was no association of psychometric scores with SERT availability [93]. Finally, another recent study suggests an interaction between genetic factors and the effects of MDMA use on mood (high depression scores only in ecstasy users carrying the s allele of the SERT encoding gene but not in users with the ll genotype) [94]. These findings underline the complexity of the issue and are in line with animal data showing different long-term effects of MDMA on anxiety in rats depending on the level of their baseline anxiety and only a loose association between the neurotoxic effects of MDMA and its long-term impact on anxiety-related behaviour [2,28,29,95].

Sleep and vegetative functions

The importance of 5-HT for the regulation of sleep, circadian rhythms and vegatative functions is undisputed, but the mechanisms and effects are insufficiently explained [96]. In animal experiments, widespread lesions in the serotonergic system lead to marked reduc-

tion in both non-rapid eye movement (REM) and REM sleep [80]. Contrary to this, human studies with substances affecting the serotonergic system showed less dramatic effects and an inconsistent picture [80]. In a poll of 500 users of ecstasy and other drugs, 38% reported sleep problems [97]. However, this study did not differentiate between long-term and acute and lingering effects of the drug for a few days after the use. To our knowledge, there have been only two sleep EEG studies on polyvalent ecstasy users and they have reported contradictory findings: the first study [98] reported a small reduction in sleep length, due solely to a reduction in light sleep stages. The more recent study [80] reported a lengthening of sleep together with an increase in the proportion of deep sleep and a higher sleep efficiency compared to the control group. In summary, there is no convincing evidence to date of lasting sleep disorders following use of ecstasy. There is also no indication of clinically measurable disorders in vegetative body functions and pain perception.

Neuroendocrine secretion

5-HT stimulates the secretion of prolactin (PRL), growth hormone, ACTH and cortisol via the hypothalamo–pituitary–adrenal axis. When baseline hormone levels are within the normal range pharmacological challenge tests can be used to detect subclinical abnormalities in the regulation of endocrine secretion caused by an imbalance in the 5-HT system. The most frequent method is by administering an indirect 5-HT agonist (e.g. L-tryptophan, fenfluramine), thus increasing the rate of production and/or release of 5-HT, that in turn leads to increased secretion of cortisol and PRL with measurable increase in the concentration of both these hormones in peripheral blood. Occasionally a mixed direct/indirect 5-HT agonist (meta-chlorophenylpiperazin = m-CPP) is administered, thus adding the effect of stimulation of postsynaptic 5-HT receptors. Patients with depression or disorders of impulsivity—both conditions associated with a low serotonergic tone—have exhibited weakened hormonal response to indirect 5-HT agonists in several studies [99–101]. Accordingly, if ecstasy users were suffering from neurotoxicity induced 5-HT depletion we would expect to find weak hormonal responses in challenge tests with indirect 5-HT agonists.

Three studies with polydrug ecstasy users by the same group of researchers yielded contradictory results: the first study showed a slightly reduced PRL response to L-tryptophan and the second study showed a normal response [60,102]. Surprisingly, in their latest investigation [103] the authors observed a weaker instead of the anticipated increased hormonal response to the mixed agonist m-CPP (the anticipated increased hormonal response should result from postsynaptic denervation sensitivity following presynaptic serotonergic damage). Studies with D-fenfluramine have been more consistent: one study [86] reported reduced cortisol response and slightly reduced PRL response to the challenge. The most clear results come from a group of Italian researchers [83,84]: the authors were able to recruit a small but carefully chosen group of pure ecstasy users and examine them after a 3-week abstinence period and again after 12 weeks of abstinence. Reduced PRL and cortisol responses to D-fenfluramine were measured after 3 weeks of abstinence. The cortisol response was back to normal after 12 weeks of abstinence, whereas the PRL response remained unchanged at the low level, and was associated with a longer duration of earlier ecstasy use [84]. A further study with small groups [104] also reported weakened or reduced PRL response to D-fenfluramine; this was, however, linked to the extent of parallel use of cannabis rather than ecstasy.

All in all, there is still only limited evidence of the long-term effects of ecstasy use on the endocrine system. Some of the inconsistencies between studies may derive from the use of different challenges with different pharmacological effects. However, one methodologically sound study with longitudinal design [84] does suggest long-lasting dysregulation of neuroendocrine secretion that may well result from ecstasy use.

Central processing of sensory stimuli

5-HT appears to be involved in the fine tuning of sensory and information processing. Interestingly, recent studies suggest that electrophysiological measures of sensory processing may be used to obtain an indirect indication of central neurotransmitter malfunctions. One method makes use of the intensity dependence of early cortical components of sensory evoked potentials, with a strong dependence (more robust increase of the amplitude with more intense stimuli) indicating a low serotonergic innervation tone and vice versa [105–107]. To date two cross-sectional studies have established an increased intensity dependence of auditory evoked potentials in ecstasy users compared to control groups [108,109]. The link with ecstasy use has, however, been less clear and only one of the two studies showed an association of the intensity dependence with the extent of previous ecstasy use [109].

Another method relates to the plasticity of the startle reflex, a primitive motor response to sudden intense sensory stimuli, with the primary reflex pathway being located in the brain stem. The startle reflex exhibits a high degree of plasticity and 5-HT is involved in the fundamental phenomena of habituation, sensitization and prepulse inhibition (PPI) of this reflex [110]. To date, one study reported blunted PPI of the startle reflex in MDMA users [111], but another study found no significant dif-

ferences in habituation and PPI between MDMA users and controls [112]. In the latter investigation sensitization of the startle reflex was stronger in heavy MDMA users compared to moderate users and non-users; however, the degree of sensitization was associated with a younger age at the onset of MDMA (and other drug) use rather than longer duration or heavier pattern of use. All in all, it is unclear whether the electrophysiological findings result from the use of MDMA, or whether they possibly reflect pre-existing traits that might predispose to drug use.

Cognition

Although our understanding of the role of serotonin in cognitive processes is incomplete, there are indications that serotonergic neurotransmission may particularly interfere with an individual's cognitive style (impulsive versus systematic cognition) as well as with memory and learning processes [113,114].

Simple measurements of psychomotor speed and attention (simple and choice reaction tasks, visual scanning) taken in exploratory studies were generally normal in ecstasy users. Some studies reported poorer performance of ecstasy users versus control groups in complex attention, problem solving and tests of frontal executive functions [e.g. Wisconsin Card Sorting Test, WCST and other 'frontal' tests] as well as elevated cognitive impulsivity, i.e. a non-systematic cognitive style [55,61,81,115–118]. However, results have been inconsistent and many other studies reported undisturbed performance of ecstasy users in similar tests [86,119–122]. In addition, some investigations reported deficits in short-term or working memory (WM) in ecstasy users [55,61,81,86,89,116,119,121–127] including samples of former MDMA users with an abstinence period of at least 6 months [89,125,128]. Recent studies indicate that the WM deficits are attributable to deficits in the central executive function of WM [124,128], but again, other studies reported normal WM performance [88,117,118,127,129,130].

To date, the most consistent finding in ecstasy users is that of subtle deficits in episodic memory and learning abilities. Numerous cross-sectional studies reported impairments of learning and memory performance [59,88,89,119,120,127,130–138], and only a small minority of studies reported no differences between ecstasy users and controls [55,124,139] or small and insignificant differences after adjusting for possible confounds [117]. In general, poor memory was associated with a heavier pattern of ecstasy use, although a minority of studies reported an association of memory deficits with the extent of the parallel use of cannabis or the combination of ecstasy and cannabis rather than the use of ecstasy alone [119,138,140–143]. Although most ecstasy users do not suffer cognitive impairment of clinically relevant proportion and even heavy users appear at first mostly unimpaired in their every day life [119,143], several cases with severe deficits have also been reported [144,145]. Interestingly, in a small pilot study with MR spectroscopy the weak memory performance of eight ecstasy users was linked to a low N-acetylaspartate/creatin ratio in the prefrontal cortex, which may be viewed as a measure of neurotoxic damage [146]. These data are in line with recent animal studies which demonstrated subtle impairments of memory performance in MDMA-treated rodents and monkeys [19–24,27]. Moreover, there is concern that the cognitive deficits of ecstasy users—although subtle and mostly subclinical—might help to accelerate the normal brain ageing process and so contribute later on to early age-related cognitive impairment [14,80,139,143].

However, and although the evidence in favour of memory impairment emerging from cross-sectional studies in ecstasy users is relatively strong, recent investigations with larger samples of current and former users and the first longitudinal studies have yielded puzzling and conflicting data. Reneman *et al.* [70] reported deficient memory performance in 22 current and 16 former MDMA users, although serotonin transporter (SERT) availability was reduced only in current users. The authors concluded that neurotoxic effects may be reversible, but effects on memory function may be long-lasting. However, alternative interpretations of these data are also conceivable. Another study with 30 current and 31 former ecstasy users with an abstinence period of at least 5 months reported poorer verbal memory compared to non-user controls only in the former users, but not in the current users, although—in line with the study by Reneman *et al.* [70]—SERT availability was reduced only in the current users, but not in the former users [68]. The authors argued that memory impairments may have been aggravated after abstinence. However, the unimpaired performance of current users and the PET data, which suggest recovery of the assumed neurotoxic lesion following abstinence, are not in favour of this interpretation [68]. Interestingly, a study with experimental tryptophan augmentation/depletion also reported poor memory and altered tryptophan metabolism in former MDMA users with an abstinence period of at least 12 months, but not in the current users [147]. The authors speculated that these findings might reflect consequences of MDMA use that emerge after abstention but also considered an alternative interpretation of premorbid differences in serotonergic neurotransmission of those who stop using the drug compared to continuing users [147]. Finally, a small

longitudinal study with 15 ecstasy users reported memory decline after continued use over 12 months [148], but a larger longitudinal study with 38 ecstasy users reported no memory decline after continued use and no improvement after abstinence over 18 months [149].

If memory problems in ecstasy users were caused by neurotoxicity then we would normally expect the neurotoxic effect and its functional consequences to increase with continued use and (partly) recover after prolonged abstinence. Hence, the data from the most recent longitudinal study [149] may be interpreted as evidence against neurotoxicity related memory decline in ecstasy users. Consequently, these results may imply that a factor other than ecstasy use may be responsible for the relatively low memory performance reported in most cross-sectional studies with ecstasy users. This factor might be loosely associated, but not causally related to ecstasy use (e.g. prolonged stress and/or disturbed sleep patterns in regular club attendants). However, it is possible that memory deficits in ecstasy users persist even after 18 months of abstinence because, as shown in primate studies [18], regeneration of serotonergic axons may take very long and may remain incomplete. In addition, the functional consequences of neurotoxic lesions observed following a threshold use of ecstasy may manifest themselves in binary (yes/no) ways. Compensatory neural mechanisms that might develop could possibly explain the absence of deterioration in these functional consequences despite subsequent 'enlargement' of the neurotoxic lesions. This view would be in line both with findings of a dose-dependent memory deficit in cross-sectional studies comparing ecstasy users with control samples and with findings of stable performance in within-subject longitudinal designs with ecstasy users. In conclusion, the linkage between ecstasy use and memory decline cannot be considered proven, nor can it be rejected, at this stage.

Brain activation studies

Recent studies utilizing the functional MRI technique (fMRI) with the bold response looked at brain activation patterns while subjects were engaged with working memory (WM) and memory tasks. All in all, these pilot studies with small samples reported altered activation patterns in MDMA users compared to controls; however, findings have varied between samples and a link with neurotoxic drug effects is difficult to establish. For example, one study reported higher parietal and lower frontal and temporal activation [150], but another study found higher frontal, thalamic and hippocampal activation while performing a WM task [151]. Interestingly, one study reported altered WM activation patterns in a small group of relatively pure MDMA users ($n = 8$), while polydrug ecstasy users did not differ from controls [152]. Moreover, using a longitudinal design the same group found a dose-dependent increase of parietal activation in subjects who continued using MDMA in the follow-up period of 18 months, but not in subjects who abstained from further drug use after the first examination [153]. Finally, ecstasy users showed diminished hippocampal activation during memory retrieval [154] and reduced hippocampal deactivation while performing a demanding WM task [155]. In these small sample studies the neuropsychological performance of ecstasy users was not significantly different from controls. Hence, the alterations in the activation patterns might be viewed as a more sensitive or earlier index of MDMA-related neurotoxicity, but on the other hand they could also be unrelated to drug use.

SUMMARY AND PERSPECTIVES FOR FUTURE RESEARCH

In summary, the data covering neurotoxic effects of ecstasy in humans are still patchy and partly contradictory. CSF, PET and SPECT studies have brought evidence of alterations in the central serotonergic system of MDMA users. However, SERT availability was shown to be normal in former users with abstinence periods of 5 months or more, suggesting at least a partial recovery. A large number of cross-sectional studies on psychological functioning, neurocognition, neuroendocrine regulation and vegetative functions reported subtle abnormalities in MDMA users that may reflect functional sequelae of long-lasting alterations in serotonergic systems. However, at least in some part, these findings may equally well reflect pre-existing traits of people prone to drug use or sequelae of drug use in general and/or of the associated life-style, as most MDMA users exhibit the common polydrug use pattern and associated behaviours.

Reviewing the literature, we should keep in mind that many studies have significant methodological limitations: some of the earlier investigations have either not captured vital data on the parallel use of other drugs or length of abstinence periods, or the abstinence periods were so short that the recorded effects may well result from the pharmacological effect of short-term depletion of intracellular 5-HT deposits and do not necessarily point to permanent neurotoxic damage (e.g. [123,130,132,156]). Furthermore, many studies have used poorly matched control groups (mostly non-users or polydrug users with overall more moderate use patterns than the polydrug ecstasy users) [56,59,61,80,81,124,133,134,157]. Moreover, there are methodological problems without an obvious solution to date, e.g. questionable reliability of statements by the subjects themselves on their current and earlier con-

sumption habits, difficulties recruiting adequate control groups, uncertainties related to the precise chemical composition of ecstasy tablets, etc. Even elaborate toxicological hair analysis, as performed in some studies [68,139,158,159], offer little benefit over and above the taking of a thorough history of drug use: short hairstyles permit insights into the drug use of the most recent month(s) only; moreover, the adherence of drugs onto hair varies strongly depending on the physical characteristics of the hair and the kind of care applied to it. Nevertheless, without wishing to belittle the importance of these methodological problems, we must point out that the results of studies with relatively careful methodology (e.g. [86,119,143]) (relatively pure ecstasy users, appropriate, well-matched control groups and sufficiently long abstinence periods) are very similar to those of studies with less optimal designs.

Among all functional domains examined so far, the most extensive and consistent findings from cross-sectional studies support a subtle cognitive dysfunction in MDMA users. Several studies support a relative weakening of mnemonic functions compared to control groups with a good correlation between the degree of impairment and the extent of ecstasy use in most cases. Evidence of impairment in central executive functions and increased cognitive impulsiveness is less consistent while other functions such as attention, vigilance and interference appear unaffected. However, a recent well-designed study with large samples reported poor memory performance in former ecstasy users with long-term abstinence, but not in current users [68], and another longitudinal study reported stable memory performance over time (18 months) irrespective of ecstasy use patterns in the follow-up period (continued use or abstinence) [149]. These recent reports challenge the hypothesis of memory dysfunction related to MDMA-induced neurotoxicity without being sufficiently strong to disprove it.

In light of the popularity of ecstasy among young people, questions around its neurotoxic effects on the brain remain highly topical. To date, the message we have to convey to young people in information campaigns is: 'MDMA neurotoxicity for humans is not yet proven, but it is highly likely'. The methodological problems mentioned mean that future research designs will remain a compromise between desirability and practicality. Further longitudinal studies are clearly needed, but may not be sufficient to address every issue. Aspects of polydrug use should be looked at more carefully in future studies with user populations. However, in our view it is critically important for research strategies to evolve gradually towards prospective designs; starting with large cohorts of young people who are not (yet) users, but belong to a risk group for recreational drug use (e.g. attendants of rave parties). Following-up on and re-examining these people over years, recording their drug histories using psychometric instruments and carrying out neuropsychological tests, should hopefully lead to a better understanding of the relation between drug use and subclinical psychological symptoms or neuro-cognitive failures and, also, of questions around progression, persistency and (partial) reversibility of the alterations. One can always debate the ethical aspects of such prospective studies, but we do need to know the answers to the crucial questions around possible long-lasting adverse effects of MDMA on the brain to be able to inform persuasively the many young people at risk.

References

1. Strote J, Lee J E, Wechsler H. Increasing MDMA use among college students: results of a national survey. *J Adolesc Health* 2002;**30**: 64–72.
2. Green AR, Mechan AO, Elliott JM, O'Shea E, Colado MI. The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'). *Pharmacol Rev* 2003;**55**: 463–508.
3. von Sydow K, Lieb R, Pfister H, Hofler M, Wittchen HU. Use, abuse and dependence of ecstasy and related drugs in adolescents and young adults—a transient phenomenon? Results from a longitudinal community study. *Drug Alcohol Depend* 2002;**66**: 147–59.
4. Schuster P, Lieb R, Lamertz C, Wittchen HU. Is the use of ecstasy and hallucinogens increasing? Results from a community study. *Eur Addict Res* 1998;**4**: 75–82.
5. Tossmann P, Boldt S, Tensil MD. The use of drugs within the techno party scene in European metropolitan cities. *Eur Addict Res* 2001;**7**: 2–23.
6. Yacoubian GSJr, Boyle C, Harding CA, Loftus EA. It's a rave new world: estimating the prevalence and perceived harm of ecstasy and other drug use among club rave attendees. *J Drug Educ* 2003;**33**: 187–96.
7. Parrott AC. Is ecstasy MDMA? A review of the proportion of ecstasy tablets containing MDMA, their dosage levels, and the changing perceptions of purity. *Psychopharmacology (Berl)* 2004;**173**: 234–41.
8. Nichols DE. Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: entactogens. *J Psychoact Drugs* 1986;**18**: 305–13.
9. Check E. Psychedelic drugs: the ups and downs of ecstasy. *Nature* 2004;**429**: 126–8.
10. Gouzoulis E, Borchardt D, Hermle L. A case of toxic psychosis induced by 'eve' (3,4-methylenedioxyethylamphetamine). *Arch Gen Psychiatry* 1993;**50**: 75.
11. Gouzoulis-Mayfrank E, Thelen B, Habermeyer E, Kunert HJ, Kovar KA, Lindenblatt H, *et al.* Psychopathological, neuroendocrine and autonomic effects of 3,4-methylenedioxyethylamphetamine (MDE), psilocybin and d-methamphetamine in healthy volunteers: results of an experimental double-blind placebo-controlled study. *Psychopharmacology (Berl)* 1999;**142**: 41–50.
12. Morton, J. Ecstasy: pharmacology and neurotoxicity. *Curr Opin Pharmacol* 2005;**5**: 79–86.
13. Ricaurte GA, Martello AL, Katz JL, Martello MB. Lasting effects of 3,4-methylenedioxymethamphetamine (MDMA) on central serotonergic neurons in nonhuman primates:

neurochemical observations. *J Pharmacol Exp Ther* 1992;**261**: 616–22.
14. Ricaurte GA, McCann UD, Szabo Z, Scheffel U. Toxicodynamics and long-term toxicity of the recreational drug, 3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy'). *Toxicol Lett* 2000;**112–1**: 143–6.
15. Jacobs BL, Azmitia EC. Structure and function of the brain serotonin system. *Physiol Rev* 1992;**72**: 165–229.
16. O'Shea E, Granados R, Esteban B, Colado MI, Green AR. The relationship between the degree of neurodegeneration of rat brain 5-HT nerve terminals and the dose and frequency of administration of MDMA ('ecstasy'). *Neuropharmacology* 1998;**37**: 919–26.
17. Fischer C, Hatzidimitriou G, Wlos J, Katz J, Ricaurte G. Reorganization of ascending 5-HT axon projections in animals previously exposed to the recreational drug (+/–)3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'). *J Neurosci* 1995;**15**: 5476–85.
18. Hatzidimitriou G, McCann UD, Ricaurte GA. Altered serotonin innervation patterns in the forebrain of monkeys treated with (+/–)3,4-methylenedioxymethamphetamine seven years previously: factors influencing abnormal recovery. *J Neurosci* 1999;**19**: 5096–107.
19. Lucki I. The spectrum of behaviors influenced by serotonin. *Biology Psychiatry* 1998;**44**: 151–62.
20. Weiger WA. Serotonergic modulation of behaviour: a phylogenetic overview. *Biol Rev Camb Philosoph Soc* 1997;**72**: 61–95.
21. Slikker WJr, Holson RR, Ali SF, Kolta MG, Paule, MG, Scallet A, *et al.* Behavioral and neurochemical effects of orally administered MDMA in the rodent and nonhuman primate. *Neurotoxicology* 1989;**10**: 529–42.
22. Frederick DL, Paule MG. Effects of MDMA on complex brain function in laboratory animals. *Neurosci Biobehav Rev* 1997;**21**: 67–78.
23. Taffe MA, Davis SA, Yuan J, Schroeder R, Hatzidimitriou G, Parsons LH, *et al.* Cognitive performance of MDMA-treated rhesus monkeys: sensitivity to serotonergic challenge. *Neuropsychopharmacology* 2002;**27**: 993–1005.
24. Marston HM, Reid ME, Lawrence JA, Olverman HJ, Butcher SP. Behavioural analysis of the acute and chronic effects of MDMA treatment in the rat. *Psychopharmacology* 1999;**144**: 67–76.
25. Morley KC, Gallate JE, Hunt GE, Mallet PE, McGregor IS. Increased anxiety and impaired memory in rats 3 months after administration of 3,4-methylenedioxymethamphetamine ('ecstasy'). *Eur J Pharmacol* 2001;**433**: 91–9.
26. Broening HW, Morford LL, Inman-Wood SL, Fukumura M, Vorhees CV. 3,4-methylenedioxymethamphetamine (ecstasy)-induced learning and memory impairments depend on the age of exposure during early development. *J Neurosci* 2001;**21**: 3228–35.
27. Taffe MA, Huitron-Resendiz S, Schroeder R, Parsons LH, Henriksen SJ, Gold LH. MDMA exposure alters cognitive and electrophysiological sensitivity to rapid tryptophan depletion in rhesus monkeys. *Pharmacol Biochem Behav* 2003;**76**: 141–52.
28. McGregor IS, Gurtman CG, Morley KC, Clemens KJ, Blokland A., Li KM, *et al.* Increased anxiety and 'depressive' symptoms months after MDMA ('ecstasy') in rats: drug-induced hyperthermia does not predict long-term outcomes. *Psychopharmacology* 2003;**168**: 465–74.
29. McGregor IS, Van der Clemens KJPG, Li KM, Hunt GE, Chen F, Lawrence AJ. Increased anxiety 3 months after brief exposure to MDMA ('Ecstasy') in rats: association with altered 5-HT transporter and receptor density. *Neuropsychopharmacology* 2003;**28**: 1472–84.
30. Sprague JE, Preston AS, Leifheit M, Woodside B. Hippocampal serotonergic damage induced by MDMA (ecstasy): effects on spatial learning. *Physiol Behav* 2003;**79**: 281–7.
31. Taffe MA, Weed MR, Davis S, Huitron-Resendiz S, Schroeder R, Parsons LH, *et al.* Functional consequences of repeated (+/–)3,4-methylenedioxymethamphetamine (MDMA) treatment in rhesus monkeys. *Neuropsychopharmacology* 2001;**24**: 230–9.
32. Winsauer PJ, McCann UD, Yuan J, Delatte MS, Stevenson MW, Ricaurte GA, *et al.* Effects of fenfluramine, m-CPP and triazolam on repeated-acquisition in squirrel monkeys before and after neurotoxic MDMA administration. *Psychopharmacology* 2002;**159**: 388–96.
33. Timar J, Gyarmati S, Szabo A, Furst S. Behavioural changes in rats treated with a neurotoxic dose regimen of dextrorotatory amphetamine derivatives. *Behav Pharmacol* 2003;**14**: 199–206.
34. Mechan AO, Moran PM, Elliott M, Young AJ, Joseph MH, Green R. A study of the effect of a single neurotoxic dose of 3,4-methylenedioxymethamphetamine (MDMA; 'ecstasy') on the subsequent long-term behaviour of rats in the plus maze and open field. *Psychopharmacology* 2002;**159**: 167–75.
35. Gurtman CG, Morley KC, Li KM, Hunt GE, McGregor IS. Increased anxiety in rats after 3,4-methylenedioxymethamphetamine: association with serotonin depletion. *Eur J Pharmacol* 2002;**20**: 89–96.
36. Sherlock K, Wolff K, Hay AW, Conner M. Analysis of illicit ecstasy tablets: implications for clinical management in the accident and emergency department. *J Accid Emerg Med* 1999;**16**: 194–7.
37. Cole JC, Bailey M, Sumnall HR, Wagstaff GF, King LA. The content of ecstasy tablets: implications for the study of their long-term effects. *Addiction* 2002;**97**: 1531–6.
38. Mechan A, Yuan J, Hatzidimitriou G, Irvine RJ, McCann UD, Ricaurte GA. Pharmacokinetic profile of single and repeated oral doses of MDMA in squirrel monkeys: relationship to lasting effecs on brain serotonin neurons. *Neuropsychopharmacology* 2005;**26**: 1–12.
39. Fantegrossi WE, Woolverton WL, Kilbourn M, Sherman P, Yuan J, Hatzidimitriou G, *et al.* Behavioral and neurochemical consequences of long-term intravenous self-administration of MDMA and its enantiomers by rhesus monkeys. *Neuropsychopharmacology* 2004;**29**: 1270–81.
40. Theune M, Esser W, Druschky KF, Interschick E, Patscheke H. Grand mal series after Ecstasy abuse. *Nervenarzt* 1999;**70**: 1094–7.
41. Colado MI, Granados R, O'Shea E, Esteban B, Green AR. Role of hyperthermia in the protective action of clomethiazole against MDMA ('ecstasy')-induced neurodegeneration, comparison with the novel NMDA channel blocker AR-R15896AR. *Br J Pharmacol* 1998;**124**: 479–84.
42. Parrott AC. MDMA (3,4-methylenedioxymethamphetamine) or ecstasy: the neuropsychobiological implications of taking it at dances and raves. *Neuropsychobiology* 2004;**50**: 329–35.
43. Cohen Z, Bonvento G, Lacombe P, Hamel E. Serotonin in the regulation of brain microcirculation. *Prog Neurobiol* 1996;**50**: 335–62.

44. Azmitia EC. Serotonin neurons, neuroplasticity, and homeostasis of neural tissue. *Neuropsychopharmacology* 1999;**2**: S33–45.
45. Gould E. Serotonin and hippocampal neurogenesis. *Neuropsychopharmacology* 1999;**21**: S46–51.
46. Chang L, Grob CS, Ernst T, Itti L, Mishkin FS, Jose-Melchor R, *et al.* Effect of ecstasy [3,4-methylenedioxymethamphetamine (MDMA)] on cerebral blood flow: a co-registered SPECT and MRI study. *Psychiatr Res* 2000;**98**: 15–28.
47. Gamma A, Buck A, Berthold T, Vollenweider FX. No difference in brain activation during cognitive performance between ecstasy (3,4-methylenedioxymethamphetamine) users and control subjects: a [H2 (15) O]-positron emission tomography study. *J Clin Psychopharmacol* 2001;**21**: 66–71.
48. Reneman L, Majoie CB, Habraken JB, den Heeten GJ. Effects of ecstasy (MDMA) on the brain in abstinent users: initial observations with diffusion and perfusion MR imaging. *Radiology* 2001;**220**: 611–17.
49. Gamma A, Buck A, Berthold T, Hell D, Vollenweider FX. Deviations in mood and personality in 'Ecstacy' (3,4-methylenedioxymethamphetamine) users are not reflected in deviant cerebral blood flow: a [H2,15O]-positron-emission-tomography study. *Eur Neuropsychopharmacol* 1999;**9**: S237.
50. Cowan RL, Lyoo IK, Sung SM, Ahn KH, Kim MJ, Hwang J, *et al.* Reduced cortical gray matter density in human MDMA (Ecstasy) users: a voxel-based morphometry study. *Drug Alcohol Depend* 2003;**72**: 225–35.
51. Chang L, Ernst T, Grob CS, Poland RE. Cerebral (1)H MRS alterations in recreational 3, 4-methylenedioxymethamphetamine (MDMA, 'ecstasy') users. *J Magn Reson Imaging* 1999;**10**:521–6.
52. Reneman L, Majoie CB, Flick H, den Heeten GJ. Reduced N-acetylaspartate levels in the frontal cortex of 3,4-methylenedioxymethamphetamine (Ecstasy) users: preliminary results. *AJNR* 2002;**23**: 231–237.
53. Daumann J, Fischermann T, Pilatus U, Thron A, Moeller-Hartmann W, Gouzoulis-Mayfrank E. Proton magnetic resonance spectroscopy in ecstasy (MDMA) users. *Neurosci Lett* 2004;**362**: 113–16.
54. Buchert R, Obrocki J, Thomasius R, Vaterlein O, Petersen K, Jenicke L, *et al.* Long-term effects of 'ecstasy' abuse on the human brain studied by FDG PET. *Nucleic Med Commun* 2001;**22**: 889–97.
55. Dafters RI, Duffy F, O'Donnell PJ, Bouquet C. Level of use of 3,4-methylenedioxymethamphetamine (MDMA or Ecstasy) in humans correlates with EEG power and coherence. *Psychopharmacology* 1999;**145**: 82–90.
56. Gamma A, Frei E, Lehmann D, Pascual-Marqui RD, Hell D, Vollenweider FX. Mood state and brain electric activity in ecstasy users. *Neuroreport* 2000;**11**: 157–62.
57. Peroutka SJ, Pascoe N, Faull KF. Monoamine metabolites in the cerebrospinal fluid of recreational users of 3,4-methylenediethyloxymethamphetamine (MDMA); 'ecstasy'). *Res Commun Subst Abuse* 1987;**8**: 125–37.
58. Ricaurte GA, Finnegan KT, Irwin I, Langston JW. Aminergic metabolites in cerebrospinal fluid of humans previously exposed to MDMA: preliminary observations. *Ann NY Acad Sci* 1990;**600**: 699–708.
59. Bolla KI, McCann UD, Ricaurte GA. Memory impairment in abstinent MDMA ('Ecstasy') users. *Neurology* 1998;**51**: 1532–7.
60. McCann UD, Ridenour A, Shaham Y, Ricaurte GA. Serotonin neurotoxicity after (+/–)3,4-methylenedioxymethamphetamine (MDMA; 'Ecstasy'): a controlled study in humans. *Neuropsychopharmacology* 1994;**10**: 129–38.
61. McCann UD, Mertl M, Eligulashvili V, Ricaurte GA. Cognitive performance in (+/–)3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') users: a controlled study. *Psychopharmacology* 1999;**143**: 417–25.
62. McCann UD, Szabo Z, Scheffel U, Dannals RF, Ricaurte GA. Positron emission tomographic evidence of toxic effect of MDMA ('Ecstasy') on brain serotonin neurons in human beings. *Lancet* 1998;**35**: 1433–7.
63. Semple DM, Ebmeier KP, Glabus MF, O'Carroll RE, Johnstone E. C. Reduced *in vivo* binding to the serotonin transporter in the cerebral cortex of MDMA ('ecstasy') users. *Br J Psychiatry* 1999;**175**; 63–9.
64. Kish SJ. How strong is the evidence that brain serotonin neurons are damaged in human users of ecstasy? *Pharmacol Biochem Behav* 2002;**71**: 845–55.
65. Reneman L, Booij J, Habraken JB, de Bruin K, Hatzidimitriou G, den Heeten GJ, *et al.* Validity of [123I]beta-CIT SPECT in detecting MDMA-induced serotonergic neurotoxicity. *Synapse* 2002;**46**: 199–205.
66. Szabo Z, McCann UD, Wilson AA, Scheffel U, Owonikoko T, Mathews WB, *et al.* Comparison of (+)-(11) C-McN5652 (11) C-DASB as serotonin transporter radioligands under various experimental conditions. *J Nucleic Med* 2002;**43**: 678–92.
67. McCann UD, Szabo Z, Seckin E, Rosenblatt P, Mathews WB, Ravert HT, *et al.* Quantitative PET studies of the serotonin transporter in MDMA users and controls using [(11)C]McN5652 and [(11)C]DASB. *Neuropsychopharmacology* 2005 [Advance online publication, 20 April].
68. Thomasius R, Petersen K, Buchert R, Andresen B, Zapletalova P, Wartberg L, *et al.* Mood, cognition and serotonin transporter availability in current and former ecstasy (MDMA) users. *Psychopharmacology* 2003;**167**: 85–96.
69. Reneman L, Booij J, de Bruin K, Reitsma JB, de Wolff FA, Gunning WB, *et al.* Effects of dose, sex, and long-term abstention from use on toxic effects of MDMA (ecstasy) on brain serotonin neurons. *Lancet* 2001;**358**: 1864–9.
70. Reneman L, Lavalaye J, Schmand B, de Wolff FA, van Den BW, den Heeten GJ, *et al.* Cortical serotonin transporter density and verbal memory in individuals who stopped using 3,4-methylenedioxymethamphetamine (MDMA or 'ecstasy'): preliminary findings. *Arch Gen Psychiatry* 2001;**58**: 901–6.
71. Buchert R, Thomasius R, Nebeling B, Petersen K, Obrocki J, Jenicke L, *et al.* Long-term effects of 'ecstasy' use on serotonin transporters of the brain investigated by PET. *J Nucleic Med* 2003;**44**: 375–84.
72. Buchert R, Thomasius R, Wilke F, Petersen K, Nebeling B, Obrocki J, *et al.* A voxel-based PET investigation of the long-term effects of 'Ecstasy' consumption on brain serotonin transporters. *Am J Psychiatry* 2004;**161**: 1181–9.
73. Reneman L, Endert E, de Bruin K, Lavalaye J, Feenstra MG, de Wolff FA, *et al.* The acute and chronic effects of MDMA ('ecstasy') on cortical 5-HT2A receptors in rat and human brain. *Neuropsychopharmacology* 2002;**26**: 387–96.
74. Scheffel U, Lever JR, Stathis M, Ricaurte GA. Repeated administration of MDMA causes transient down-regulation of serotonin 5-HT2 receptors. *Neuropharmacology* 1992;**31**: 881–93.

75. Hegadoren KM, Baker GB, Bourin M. 3,4-Methylenedioxy analogues of amphetamine: defining the risks to humans. *Neurosci Biobehav Rev* 1999;**23**: 539–53.
76. Schifano F. Potential human neurotoxicity of MDMA ('Ecstasy'): subjective self-reports, evidence from an Italian drug addiction centre and clinical case studies. *Neuropsychobiology* 2000;**42**: 25–33.
77. Schifano F, Di Furia L, Forza G, Minicuci N, Bricolo R. MDMA ('ecstasy') consumption in the context of polydrug abuse: a report on 150 patients. *Drug Alcohol Depend* 1998;**5**: 85–90.
78. Topp L, Hando J, Dillon P, Roche A, Solowij N. Ecstasy use in Australia: patterns of use and associated harm. *Drug Alcohol Depend* 1999;**55**: 105–15.
79. Lieb R, Schuetz C, Pfister H von Sydow K, Wittchen H. Mental disorders in ecstasy users: a prospective-longitudinal investigation. *Drug Alcohol Depend* 2002;**68**: 195.
80. McCann UD, Eligulashvili V, Ricaurte GA. (+/−)3,4-Methylenedioxymethamphetamine ('Ecstasy')-induced serotonin neurotoxicity: clinical studies. *Neuropsychobiology* 2000;**42**: 11–16.
81. Morgan MJ. Recreational use of 'ecstasy' (MDMA) is associated with elevated impulsivity. *Neuropsychopharmacology* 1998;**19**: 252–64.
82. Parrott AC, Sisk E, Turner JJ. Psychobiological problems in heavy 'ecstasy' (MDMA) polydrug users. *Drug Alcohol Depend* 2000;**60**: 105–10.
83. Gerra G, Zaimovic A, Giucastro G, Maestri D, Monica C, Sartori R, *et al.* Serotonergic function after (+/−)3,4-methylenedioxymethamphetamine ('Ecstasy') in humans. *Int Clin Psychopharmacol* 1998;**13**: 1–9.
84. Gerra G, Zaimovic A, Ferri M, Zambelli U, Timpano M, Neri E, *et al.* Long-lasting effects of (+/−)3,4-methylenedioxymethamphetamine (ecstasy) on serotonin system function in humans. *Biol Psychiatry* 2000;**47**: 127–36.
85. Daumann J, Pelz S, Becker S, Tuchtenhagen F, Gouzoulis-Mayfrank E. Psychological profile of abstinent recreational ecstacy (MDMA) users and significance of concomitant cannabis use. *Hum Psychopharmacol* 2001;**16**: 627–31.
86. Verkes RJ, Gijsman HJ, Pieters MS, Schoemaker RC, de Visser S, Kuijpers M, *et al.* Cognitive performance and serotonergic function in users of ecstasy. *Psychopharmacology* 2001;**153**: 196–202.
87. MacInnes N, Handley SL, Harding GF. Former chronic methylenedioxymethamphetamine (MDMA or ecstasy) users report mild depressive symptoms. *J Psychopharmacol* 2001; **15**, 181–186.
88. McCardle K, Luebbers S, Carter J D, Croft RJ, Stough C. Chronic MDMA (ecstasy) use, cognition and mood. *Psychopharmacology* 2004;**173**: 434–9.
89. Morgan MJ, McFie L, Fleetwood H, Robinson JA. Ecstasy (MDMA): are the psychological problems associated with its use reversed by prolonged abstinence? *Psychopharmacology* 2002;**159**: 294–303.
90. Daumann J, Hensen G, Thimm B, Rezk M, Till B, Gouzoulis-Mayfrank E. Self-reported psychopathological symptoms in recreational ecstasy (MDMA) users are mainly associated with regular cannabis use: further evidence from a combined cross-sectional/longitudinal investigation. *Psychopharmacology* 2004;**173**: 398–404.
91. Parrott C, Milani RM, Parmar R, Turner JD. Recreational ecstasy/MDMA and other drug users from the UK and Italy: psychiatric symptoms and psychobiological problems. *Psychopharmacology* 2001;**159**: 77–82.
92. Roiser JP, Sahakian B J. Relationship between ecstasy use and depression: a study controlling for poly-drug use. *Psychopharmacology* 2004;**173**: 411–17.
93. de Win MM, Reneman L, Reitsma JB, den Heeten GJ, Booij J, van Den BW. Mood disorders and serotonin transporter density in ecstasy users—the influence of long-term abstention, dose, and gender. *Psychopharmacology* 2004;: 376–82.
94. Roiser JP, Cook LJ, Cooper JD, Rubinsztein DC, Sahakian BJ. Association of a functional polymorphism in the serotonin transporter gene with abnormal emotional processing in ecstasy users. *Am J Psychiatry* 2005;**162**: 609–12.
95. Ho YJ, Pawlak C R, Guo L, Schwarting RK. Acute and long-term conesquences of single MDMA administration in relation to individual anxiety levels in the rat. *Behav Brain Res* 2004;**149**: 135–44.
96. Jouvet M. Sleep and serotonin: an unfinished story. *Neuropsychopharmacology* 1999;**21**: S24–7.
97. Cohen RS. () Subjective reports on the effects of the MDMA ('ecstasy') experience in humans. *Prog Neuropsychopharmacol Biol Psychiatry* 1995;**19**:, 1137–45.
98. Allen RP, McCann UD, Ricaurte GA. Persistent effects of (+/−)3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') on human sleep. *Sleep* 1993;**16**: 560–4.
99. Cleare AJ, Murray RM, O'Keane V. Assessment of serotonergic function in major depression using d-fenfluramine: relation to clinical variables and antidepressant response. *Biol Psychiatry* 1998;**44**: 555–61.
100. Correa H, Duval F, Mokrani M, Bailey P, Tremeau F, Staner L, *et al.* Prolactin response to D-fenfluramine and suicidal behavior in depressed patients. *Psychiatr Res* 2000;**93**: 189–99.
101. Evans J, Platts H, Lightman S, Nutt D. Impulsiveness and the prolactin response to d-fenfluramine. *Psychopharmacology* 2000;**149**: 147–52.
102. Price LH, Ricaurte GA, Krystal JH, Heninger GR. Neuroendocrine and mood responses to intravenous 1-tryptophan in 3,4-methylenedioxymethamphetamine (MDMA) users. Preliminary observations. *Arch Gen Psychiatry* 1989;**46**: 20–2.
103. McCann UD, Eligulashvili V, Mertl M, Murphy DL, Ricaurte GA. Altered neuroendocrine and behavioral responses to m-chlorophenylpiperazine in 3,4-methylenedioxymethamphetamine (MDMA) users. *Psychopharmacology* 1999;**147**: 56–65.
104. Gouzoulis-Mayfrank E, Becker S, Pelz S, Tuchtenhagen F, Daumann J. Neuroendocrine abnormalities in recreational ecstasy (MDMA) users: is it ecstasy or cannabis? *Biol Psychiatry* 2002;**51**: 766–9.
105. Carrillo-de-la-Pena MT. ERP augmenting/reducing and sensation seeking: a critical review. *Intl J Psychophysiol* 1992;**12**: 211–20.
106. Hegerl U, Juckel G. Intensity dependence of auditory evoked potentials as an indicator of central serotonergic neurotransmission: a new hypothesis. *Biol Psychiatry* 1993;**33**: 173–87.
107. Juckel G, Schmidt LG, Rommelspacher H, Hegerl U. The Tridimensional Personality Questionnaire and the intensity dependence of auditory evoked dipole source activity. *Biol Psychiatry* 1995;**37**: 311–17.
108. Tuchtenhagen F, Daumann J, Norra C, Gobbele R, Becker S, Pelz S, *et al.* High intensity dependence of auditory evoked dipole source activity indicates decreased seroton-

ergic activity in abstinent ecstasy (MDMA) users. *Neuropsychopharmacology* 2000;**22**: 608–17.
109. Croft RJ, Klugman A, Baldeweg T, Gruzelier JH. Electrophysiological evidence of serotonergic impairment in long-term MDMA ('ecstasy') users. *Am J Psychiatry* 2001;**15**: 1687–92.
110. Geyer MA, Krebs-Thomson K, Braff DL, Swerdlow NR. Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in press. *Psychopharmacology* 2001;**156**: 117–54.
111. Quednow BB, Kuhn KU, Hoenig K, Maier W, Wagner, M. Prepulse inhibition and habituation of acoustic startle response in male MDMA ('ecstasy') users, cannabis users, and healthy controls. *Neuropsychopharmacology* 2004;**29**: 982–90.
112. Heekeren, K., Daumann, J., Geyer, M. A., Gouzoulis-Mayfrank, E. Plasticity of the acoustic startle reflex in currently abstinent ecstasy (MDMA) users. *Psychopharmacology* 2004;**173**: 418–24.
113. Meneses A. 5-HT system and cognition. *Neurosci Biobehav Rev* 1999;**23**: 1111–25.
114. Buhot MC, Martin S, Segu L. Role of serotonin in memory impairment. *Ann Med* 2000;**32**: 210–21.
115. Zakzanis KK, Young DA. Executive function in abstinent MDMA ('ecstasy') users. *Med Sci Monit* 2001;**7**: 1292–8.
116. Fox HC, Parrott AC, Turner JJ. Ecstasy use: cognitive deficits related to dosage rather than self-reported problematic use of the drug. *J Psychopharmacol* 2001;**1**: 273–81.
117. Halpern JH, Pope HG Jr, Sherwood AR, Barry S, Hudson JI, Yurgelun-Todd D. Residual neuropsychological effects of illicit 3,4-methylenedioxymethamphetamine (MDMA) in individuals with minimal exposure to other drugs. *Drug Alcohol Depend* 2004;**75**: 135–47.
118. von Geusau NA, Stalenhoef P, Huizinga M, Snel J, Ridderinkhof KR. Impaired executive function in male MDMA ('ecstasy') users. *Psychopharmacology* 2004;**175**: 331–41.
119. Gouzoulis-Mayfrank E, Daumann J, Tuchtenhagen F, Pelz S, Becker S, Kunert HJ, *et al.* Impaired cognitive performance in drug free users of recreational ecstasy (MDMA). *J Neurol Neurosurg Psychiatry* 2000;**68**: 719–25.
120. Gouzoulis-Mayfrank E, Thimm B Rezk M, Hensen G, Daumann J. Memory impairment suggests hippocampal dysfunction in abstinent ecstasy users. *Prog Neuropsychopharmacol Biol Psychiatry* 2003;**27**: 819–27.
121. Fox HC, McLean A, Turner JJ, Parrott AC, Rogers R, Sahakian BJ. Neuropsychological evidence of a relatively selective profile of temporal dysfunction in drug-free MDMA ('ecstasy') polydrug users. *Psychopharmacology* 2002;**162**: 203–14.
122. Fisk JE, Montgomery C, Murphy P, Wareing M. Evidence for executive deficits among users of MDMA (Ecstasy). *Br J Psychology* 2004;**9**: 457–66.
123. Curran HV, Travill RA. Mood and cognitive effects of +/−3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy'): week-end 'high' followed by mid-week low. *Addiction* 1997;**9**: 821–31.
124. Wareing M, Fisk JE, Murphy PN. Working memory deficits in current and previous users of MDMA ('ecstasy'). *Br J Psychology* 2000;**91**: 181–8.
125. Wareing M, Fisk JE, Murphy P, Montgomery C. Verbal working memory deficits in current and previous users of MDMA. *Hum Psychopharmacology* 2004;**19**: 225–34.
126. Wareing M, Murphy PN, Fisk JE. Visuospatial memory impairments in users of MDMA ('ecstasy'). *Psychopharmacology* 2004;**173**: 391–7.
127. Yip JT, Lee TM. Effect of ecstasy use on neuropsychological function: a study in Hong Kong. *Psychopharmacology* 2005;**179**: 620–8.
128. Wareing M, Fisk JE, Murphy P, Montgomery C. Visuo-spatial working memory deficits in current and former users of MDMA ('ecstasy'). *Hum Psychopharmacol* 2005;**20**: 115–23.
129. Klugman A, Hardy S, Baldeweg T, Gruzelier J. Toxic effect of MDMA on brain serotonin neurons. *Lancet* 1999;**353**: 1269–70.
130. Bhattachary S, Powell JH. Recreational use of 3,4-methylenedioxymethamphetamine (MDMA) or 'ecstasy': evidence for cognitive impairment. *Psychol Med* 2001;**31**: 647–58.
131. Krystal JH, Price LH, Opsahl C, Ricaurte GA, Heninger GR. Chronic 3,4-methylenedioxymethamphetamine (MDMA) use: effects on mood and neuropsychological function? *Am J Drug Alcohol Abuse* 1992;**1**: 331–41.
132. Parrott AC, Lasky J. Ecstasy (MDMA) effects upon mood and cognition: before, during and after a Saturday night dance. *Psychopharmacology* 1998;**139**: 261–8.
133. Morgan MJ. Memory deficits associated with recreational use of 'ecstasy' (MDMA). *Psychopharmacology* 1999;**141**: 30–6.
134. Reneman L, Booij J, Schmand B, van Den BW, Gunning B. Memory disturbances in 'Ecstasy' users are correlated with an altered brain serotonin neurotransmission. *Psychopharmacology* 2000;**148**: 322–4.
135. Rodgers J, Buchanan T, Scholey AB, Heffernan TM, Ling J, Parrott AC. Patterns of drug use and the influence of gender on self-reports of memory ability in ecstasy users: a web-based study. *J Psychopharmacol* 2003;**17**: 389–96.
136. Back-Madruga C, Boone KB, Chang L, Grob CS, Lee A, Nations H, *et al.* Neuropsychological effects of 3,4-methylenedioxymethamphetamine (MDMA or ecstasy) in recreational users. *Clin Neuropsychol* 2003;**17**: 446–59.
137. Hanson KL, Luciana M. Neurocognitive function in users of MDMA: the importance of clinically significant patterns of use. *Psychol Med* 2004;**34**: 229–46.
138. Montgomery C, Fisk JE, Newcombe R. The nature of ecstasy-group related deficits in associative learning. *Psychopharmacology* 2005 [Epub ahead of print, 25 January].
139. Parrott AC. Human research on MDMA (3,4-methylenedioxymethamphetamine) neurotoxicity: cognitive and behavioural indices of change. *Neuropsychobiology* 2000;**42**: 17–24.
140. Croft RJ, Mackay AJ, Mills AT, Gruzelier JG. The relative contributions of ecstasy and cannabis to cognitive impairment. *Psychopharmacology* 2001;**153**: 373–9.
141. Simon NG, Mattick RP. The impact of regular ecstasy use on memory function. *Addiction* 2002;**97**: 1523–9.
142. Dafters RI, Hoshi R, Talbot AC. Contribution of cannabis and MDMA ('ecstasy') to cognitive changes in long-term polydrug users. *Psychopharmacology* 2004;**173**: 405–10.
143. Rodgers J. Cognitive performance amongst recreational users of 'ecstasy'. *Psychopharmacology* 2001;**151**: 19–24.
144. Spatt J, Glawar B, Mamoli B. A pure amnestic syndrome after MDMA ('ecstasy') ingestion. *J Neurol Neurosurg Psychiatry* 1997;**62**: 418–19.

145. Soar K, Parrott AC, Fox HC. Persistent neuropsychological problems after 7 years of abstinence from recreational Ecstasy (MDMA): a case study. *Psychol Rep* 2004;**95**: 192–6.
146. Reneman L, Majoie CB, Schmand B, van Den BW, den Heeten GJ. Prefrontal N-acetylaspartate is strongly associated with memory performance in (abstinent) ecstasy users: preliminary report. *Biol Psychiatry* 2001;**50**: 550–4.
147. Curran HV, Verheyden SL. Altered response to tryptophan supplementation after long-term abstention from MDMA (ecstasy) is highly correlated with human memory function. *Psychopharmacology* 2003;**169**: 91–103.
148. Zakzanis KK, Young DA. Memory impairment in abstinent MDMA ('Ecstasy') users: a longitudinal investigation. *Neurology* 2001;**56**: 966–9.
149. Gouzoulis-Mayfrank E, Fischermann T, Rezk M, Thimm B, Hensen G, Daumann J. Memory performance in polyvalent MDMA (ecstasy) users who continue or discontinue MDMA use. *Drug Alcohol Depend* 2005;**78**: 317–23.
150. Daumann J, Fimm B, Willmes K, Thron A, Gouzoulis-Mayfrank E. Cerebral activation in abstinent ecstasy (MDMA) users during a working memory task: a functional magnetic resonance imaging (fMRI) study. *Brain Res Cogn Brain Res* 2003;**16**: 479–87.
151. Moeller FG, Steinberg JL, Dougherty DM, Narayana PA, Kramer LA, Renshaw PF. Functional MRI study of working memory in MDMA users. *Psychopharmacology* 2004;**177**; 185–94.
152. Daumann J, Schnitker R, Weidemann J, Schnell K, Thron A, Gouzoulis-Mayfrank E. Neural correlates of working memory in pure and polyvalent ecstasy (MDMA) users. *Neuroreport* 2003;**14**: 1983–7.
153. Daumann J, Fischermann T, Heekeren K, Thron A, Gouzoulis-Mayfrank E. Neural mechanisms of working memory in ecstasy (MDMA) users who continue or discontinue ecstasy and amphetamine use: evidence from an 18-month longitudinal functional magnetic resonance imaging study. *Biol Psychiatry* 2004;**56**: 349–55.
154. Daumann J, Fischermann T, Heekeren K, Henke K, Thron A, Gouzoulis-Mayfrank E. Memory-related hippocampal dysfunction in poly-drug ecstasy (3,4-methylenedioxymethamphetamine) users. *Psychopharmacology* 2004 [Epub ahead of print, 15 September].
155. Jacobsen LK, Mencl WE, Pugh KR, Skudlarski P, Krystal JH. Preliminary evidence of hippocampal dysfunction in adolescent MDMA ('ecstasy') users: possible relationship to neurotoxic effects. *Psychopharmacology* 2004;**173**: 383–90.
156. Parrott AC, Lees A, Garnham NJ, Jones M, Wesnes K. Cognitive performance in recreational users of MDMA of 'ecstasy': evidence for memory deficits. *J Psychopharmacol* 1998;**12**: 79–83.
157. Parrott AC. Human research on MDMA (3,4-methylenedioxymethamphetamine) neurotoxicity: cognitive and behavioural indices of change. *Neuropsychobiology* 2000;**42**: 17–24.
158. Rothe M, Pragst F, Spiegel K, Harrach T, Fischer K, Kunkel J. Hair concentrations and self-reported abuse history of 20 amphetamine and ecstasy users. *Forensic Scie Int* 1997;**89**: 111–28.
159. Cooper GA, Allen DL, Scott KS, Oliver JS, Ditton J, Smith ID. Hair analysis: self-reported use of 'speed' and 'ecstasy' compared with laboratory findings. *J Forensic Sci* 2000;**45**: 400–6.