HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2013; **28**: 289–307.
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/hup.2318

SPECIAL ISSUE ON NOVEL PSYCHOACTIVE SUBSTANCES

Human psychobiology of MDMA or 'Ecstasy': an overview of 25 years of empirical research

Andrew C. Parrott[1,2]*

[1]*Department of Psychology, Swansea University, Swansea, South Wales, UK*
[2]*Centre for Human Psychopharmacology, Swinburne University, Melbourne, Australia*

Aims This paper aimed to review how scientific knowledge about the human psychobiology of MDMA has developed over time.
Methods In this paper, the empirical findings from earlier and later studies will be reviewed.
Results When MDMA was a 'novel psychoactive substance', it was not seen as a drug of abuse, as it displayed loss of efficacy. However, recreational users display a unique pattern of increasing doses, deteriorating cost–benefit ratios, and voluntary cessation. MDMA increases body temperature and thermal stress, with cortisol levels increased by 800% in dance clubbers. It can be extremely euphoric, although negative moods are also intensified. MDMA causes apoptosis (programmed cell death) and has been investigated for cancer therapy because of its anti-lymphoma properties. Recreational users show deficits in retrospective memory, prospective memory, higher cognition, problem solving, and social intelligence. Basic cognitive skills remain intact. Neuroimaging studies show reduced serotonin transporter levels across the cerebral cortex, which are associated with neurocognitive impairments. Deficits also occur in sleep architecture, sleep apnoea, complex vision, pain, neurohormones, and psychiatric status. Ecstasy/MDMA use during pregnancy leads to psychomotor impairments in the children.
Conclusions The damaging effects of Ecstasy/MDMA are far more widespread than was realized a few years ago, with new neuropsychobiological deficits still emerging. Copyright © 2013 John Wiley & Sons, Ltd.

KEY WORDS—MDMA; Ecstasy; serotonin; neurotoxicity; SERT; memory

AIMS AND OVERVIEW

The aim of this review is to investigate how our understanding of MDMA has developed since it was first used as a recreational drug over 25 years ago (Shulgin, 1986). The focus throughout will be on empirical research findings (Table 1). The first section will cover basic neurotransmitter effects, followed by changing patterns of recreational usage and a historical analysis of Ecstasy/MDMA purity. Acute MDMA administration can lead to physiological overstimulation and increased core body temperature. In medical terms, acute MDMA can cause potentially fatal disorders, although the emergency treatment of casualties has improved, so that deaths are comparatively rare. Its effects on neurohormones such as cortisol will also be covered, whereas its mood effects are more subtle and complex than was originally thought. The body of this review will cover the longer-term effects of recreational Ecstasy/MDMA on memory, neurocognition, and other psychobiological functions. There will also be coverage on other topics such as chronic tolerance, cost–benefit ratios, drug cessation, serotonergic neurotoxicity, programmed cell death or apoptosis, and usage during pregnancy. Other areas of potential deficit still need to be investigated. The main conclusion from this review is that it can take many years to reveal the neuropsychobiological effects of a novel psychoactive substance.

MDMA: BASIC NEUROCHEMISTRY

The name 3,4-methylenedioxymethamphetamine indicates that MDMA is a ring-substituted methamphetamine derivative. Like the parent compound, it is a powerful central nervous system (CNS) stimulant, with many behavioural similarities to both methamphetamine and amphetamine. However, whereas the prime neurochemical modes of action for the amphetamines are dopaminergic and noradrenergic, MDMA has a particular affinity for the serotonin transporter (SERT). Acute MDMA administration reverses the

*Correspondence to: A. C. Parrott, Professor, Department of Psychology, Swansea University, Swansea, SA2 8PP, UK. E-mail: a.c.parrott@swansea.ac.uk

Received 21 September 2012
Accepted 22 March 2013

Table 1. Increase in empirical knowledge about the neuropsychobiological effects of Ecstasy/MDMA in humans, since its first general use as a recreational drug

Years since 1986	5 years	15 years	25 years
Research publication dates	1991–1992	2001–2002	2011–2012
Acute effects			
Thermal stress and increased body temperature	Individual case reports	First laboratory studies	Placebo-controlled laboratory studies; real-world studies of MDMA using dancers/ravers
Acute hyponatraemia (electrolyte dilution in blood)	Case reports	Further evidence—as part of the acute serotonin syndrome	Cohort studies of dancers/ravers reveal more acute hyponatraemia in women
Deaths	Early reports	Further reports and case studies	Systematic reports on annual death rates. Coroners' reports showing significantly more deaths from MDMA than from amphetamine/ methamphetamine.
Chronic effects			
Retrospective memory deficits	Case studies and first cohort investigation	Several cohort studies, with range of control groups	Extensive empirical evidence, using a wide range of performance tasks
Prospective memory deficits	—	First cohort studies	Extensive empirical evidence, using a wide array of performance measures
Higher cognitive deficits	—	First cohort studies	Extensive evidence, using a wide array of differing neurocognitive tasks and cognitive measures
Evoked potential changes and neurocognitive deficits	—	—	Many cohort studies; changes in brain activity often associated with performance impairments
Psychiatric distress	Individual case studies	Early cohort studies showing deficits	Large cohort studies; prospective studies showing more psychiatric symptoms after initiation and symptom recovery after cessation; initial genetic studies
Sleep impairment	—	Early studies showing deficits	Further empirical evidence for deficits
Sleep apnoea	—	—	One high-quality study; apnoea in young (non-overweight) users
Serotonergic neurotoxicity	Predicted, but no direct empirical evidence	First neuroimaging evidence for deficits	Extensive evidence with improved serotonin transporter markers, also other indices; wide array of neuroimaging measures
Immunocompetence reduced	—	Early studies showing deficits	Further empirical evidence
Oxidative stress increased	—	—	Early empirical evidence
Apoptosis (programmed cell death)	—	—	Anti-lymphoma actions, cultured human cells; potential drug for cancer therapy

normal process of serotonin reuptake and so leads to an efflux of serotonin into the synaptic cleft (Berger *et al*., 1992). Hence, an acute dose of MDMA can release 80% of available serotonin into the synaptic cleft, although it still affects dopamine, noradrenaline, and several other neurotransmitter systems (Green *et al*., 1995; Cadet *et al*., 2007). Hence, neurochemically, MDMA has been described as a messy substance (McDowell and Kleber, 1994).

In laboratory animal studies, repeated dosing with MDMA has been shown to adversely affect the serotonergic neurotransmitter system. Puerta *et al*. (2009) noted that MDMA administration to animal species in the laboratory animals can induce 'a selective damage to serotonergic axon terminals'. This is commonly termed 'serotonergic neurotoxicity', although there is an ongoing debate over the specific nature of these serotonergic changes. In a critical review of the contrasting explanatory models, Biezonski and Meyer (2011) debated whether MDMA causes distal axon terminal loss or other neuroadaptive/neural system changes. They noted a plethora of evidence for the depleting effects of MDMA on serotonin and the SERT, in both laboratory animals and human

DOI: 10.1002/hup

recreational users. This allowed them to conclude that although the underlying mechanisms for these serotonergic changes remained uncertain, MDMA 'can certainly be considered "neurotoxic" in terms of causing serotonergic dysfunction'. Benningfield and Cowan (2013) summarized recent findings on the patterns of 5-hydroxytryptamine (5-HT) receptor change in humans, which further indicated that MDMA was a persistent serotonergic neurotoxin (also: Parrott, 2013).

CHANGING PATTERNS OF RECREATIONAL USAGE OVER 25 YEARS

MDMA was first widely used as a recreational drug around 25 year ago (Shulgin, 1986; Parrott, 2001). Since then, it has been used by minority subgroups of young people under the street name 'Ecstasy' (Schifano 2000; Parrott, 2004a; Mc Cann *et al*., 2008; Degenhardt and Hall, 2009). Population surveys have revealed that it is the third most widely used illegal drug, after cannabis and cocaine. There have been suggestions that its use is pervasive amongst young people, but recreational MDMA has always been a minority activity, with the overwhelming majority of young people never taking it. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 2010) surveyed its use across European countries and found that Ecstasy/MDMA usage was acknowledged by 8.6% of adults in the 16–65 years age range. Amongst those who had taken it, the majority take it just a few times, with regular use being comparatively rare. In a survey of +3000 British university students aged around 18–25 years (Webb *et al*., 1996), 12.9% stated that they had ever taken it, with 5% taking it 'once or twice' and 2.6% reporting 'regular' usage.

In psychosocial terms, Ecstasy/MDMA is mainly taken by dance clubbers and ravers, and here, the percentage of users can be very high—up to 96% in some surveys (Winstock *et al*., 2001). The association with dance clubbing developed in the Balearic Islands during the mid-1980s and has spread to countries worldwide, with usage across Europe, the Americas, Australasia, the Far East, and China (Suy *et al*., 1999; Parrott, 2001; Winstock *et al*., 2001; Zhou *et al*., 2003; Singer *et al*., 2004). However, this association with dancing was not always present. In the first empirical investigation of recreational MDMA users, Peroutka *et al*. (1988) interviewed 100 students at a Californian university campus. The typical dose was a single 125-mg MDMA tablet, which generated tachycardia (increased heart rate), trismus (jaw clenching), bruxism (tooth grinding), and positive moods. Potential candidates for the study were recognized by the research assistant as follows: if they saw a group of students 'walking together, holding hands, and laughing or singing' they were approached because 'they may have ingested MDMA' (Peroutka *et al*., 1988).

ECSTASY/MDMA

An enduring question is whether Ecstasy always contains MDMA. An empirical review revealed some interesting historical changes (Parrott, 2004a). When first introduced, Ecstasy/MDMA was perceived as a drug of high street purity. Renfroe (1986) chromatographically analysed +20 000 recreational drug samples sent to a Californian laboratory between 1972 and 1985. The Ecstasy/MDMA supplies emerged with ratings of high quality; indeed, they were shown to be purer than any other street drug. Renfroe (1986) noted that 'MDMA, when adulterated, only contained its close relative MDA ... amphetamine and methamphetamine samples, on the other hand, were often impure combinations, including a variety of CNS stimulants and sometimes barbiturates, antihistamines, analgesics and/or synthetic opiates'. Other surveys from this period indicated finding high rates of purity (Table 1 in Parrott, 2004a). Impurity became an issue during the mid-1990s, when supplies of the precursor chemicals were restricted by police seizures and demand for Ecstasy tablets outstripped supplies. The Netherlands Drugs Information Monitoring System reported that the highest levels of impurity occurred during mid-1990s (Spruit, 2001). In the late 1990s and early 2000s, the purity of Ecstasy was high again, with rates often around 90% and some surveys indicating 100% purity (Cole *et al*., 2002; Table 3 in Parrott, 2004a, 2004b). However, purity rates for all street drugs can vary. The Netherlands Drugs Information Monitoring System survey reported maximum purity in 2000 and 2004, followed by a reduction in subsequent years (Vogels *et al*., 2009; note that similar reductions were also found with cocaine during this period). There are also empirical reports of high purity. In Parrott *et al*. (2008), every self-rated Ecstasy user had MDMA in their saliva samples, which were collected in a dance club environment. In a larger Australian study, Scholey *et al*. (2011) also found very high concordance ($p = 0.00003$) between self-rated Ecstasy and MDMA presence in hair. More recently, Cathy Montgomery (September 2012, personal communication) described pure 'almost crystalline' MDMA in police seizures from Liverpool, UK; see also Krul *et al*. (2012), for the Netherlands.

DOI: 10.1002/hup

PSYCHOPHYSIOLOGICAL OVERSTIMULATION AND MEDICAL ABREACTIONS

Recreational stimulants such as cocaine, amphetamine, methamphetamine, and MDMA cause sympathomimetic activation (Parrott *et al*., 2004). With MDMA, this general activation is accompanied by elements of the serotonin syndrome: 'Many Ecstasy-using clubbers can be seen to display mild signs of the serotonin syndrome. Hyperactivity, mental confusion, hyperthermia, and trismus (jaw clenching) are typical on-drug experiences for most Ecstasy users' (Parrott, 2002). This overstimulation may reflect the combined effects of sympathomimetic drug with environmental influences, given that dance clubs have loud music, have dynamic light shows, and are often overcrowded. Suy *et al*. (1999) reported that in a large Dutch rave, the disc jockey employed auditory and visual co-stimulation 'to achieve a state of heightened arousal'. Cohen (1998) noted that one American Ecstasy user felt that he or she 'had a stereo inside my body'. In psychophysiological terms, MDMA leads to increased heart rate, heightened blood pressure, and faster breathing, in a quiet medical laboratory (Liechti *et al*., 2001). When taken at dance clubs and raves, the stimulatory effects are often much stronger (Parrott, 2002, 2004b). This can make acute MDMA more dangerous than the other recreational stimulants. Schifano *et al*. (2010) analysed the government data on recreational stimulant deaths in the UK between 1997 and 2007. Over this period, there were 832 deaths related to amphetamine or methamphetamine and 605 deaths related to Ecstasy/MDMA. Many were related to multiple-drug ingestion or 'polydrug' use. However, in the analysis of 'mono-intoxication' fatalities, Schifano *et al*. (2010) found that deaths following Ecstasy use were significantly more represented than deaths following amphetamine/methamphetamine use ($p < 0.007$).

MDMA causes thermal stress and overheating. The majority of recreational Ecstasy/MDMA users report feeling hot, with pronounced sweating and feelings of dehydration (Davison and Parrott, 1997; Topp *et al*., 1999; Parrott *et al*., 2008). An American dance clubber noted that 'It feels like your blood is 115 degrees Fahrenheit' (Cohen, 1998). In a placebo-controlled laboratory study, Freedman *et al*. (2005) confirmed that acute MDMA administration led to a significant increase in core body temperature. A high oral dose of 2.0 mg/kg can generate a group mean peak increase of around 0.7°C in the laboratory (Table 2 in Parrott, 2012a). In dance clubbers, this temperature increase can be even more pronounced. Morefield *et al*. (2009) undertook a field study of party goers who displayed a group mean core body temperature increase of +1.1°C and skin temperature increase of +1.8°C. Many dance clubbers visit the 'chill-out' room to rest and recover, although some continue to dance for prolonged periods (Suy *et al*., 1999) or dance continuously with minimal breaks (Parrott *et al*., 2006).

Some recreational Ecstasy/MDMA users drink an excessive amount of water and develop hyponatraemia, or the dilution of sodium electrolytes in the blood. Rosenson *et al*. (2007) reviewed 1407 cases of MDMA-attributed hyponatraemia in California and found a significant over-representation of women, possibly due to lower mean body weight with higher drug concentrations; this may reflect neurohormonal influences. Van Dijken *et al*. (2013) measured plasma sodium levels at a Dutch rave and found mild hyponatraemia in 25% of female MDMA users, compared with 3% of male users, despite similar pill consumption rates. Greene *et al*. (2009) described various medical problems in 332 patients admitted to one London hospital following acute MDMA reactions. Intriguingly, whereas some were hyperthermic, others had low body temperature or hypothermia. This is because MDMA impairs thermoregulatory control and can therefore induce hypothermia when Ecstasy users find themselves in colder environments (e.g. outside the dance club, Parrott, 2012a). Hall and Henry (2006) reviewed the medical scenarios and treatment options for physicians dealing with MDMA-related medical emergencies: 'Hyperpyrexia and multi-organ failure are now relatively well-known, other serious effects have become apparent more recently. Patients with acute MDMA toxicity may present to doctors working in Anaesthesia, Intensive Care, and Emergency Medicine. A broad knowledge of these pathologies and their treatment is necessary for those working in an acute medicine speciality'.

Despite rapid medical intervention, some disorders are difficult to reverse and deteriorate rapidly, with occasional fatal outcomes (Schifano *et al*., 2003). In an early report, Henry *et al*. (1992) described MDMA-induced fatalities in seven young party goers, whose body temperatures at the intensive care unit ranged between 40°C and 43°C. The causes of death include various forms of organ failure. MDMA induces apoptosis, or programmed cell death, in cultured liver cells (Montiel-Duarte *et al*., 2002), and another form of death is from acute liver failure (Smith *et al*., 2005). Other fatalities result from cardiac arrest, brain seizure, 'rhabdomyolysis' or the destruction of skeletal muscle tissue, and 'disseminated intravascular coagulation' or the failure of blood clotting—which results in uncontrollable bleeding through multiple sites (Henry *et al*., 1992; Hall and Henry, 2006).

DOI: 10.1002/hup

ACUTE MOOD EFFECTS

MDMA has always been recognized as a powerful euphoriant, but its mood effects are actually more complex and variable. The most recent studies have shown that it can also intensify *negative* emotional states (Bedi and de Wit, 2010, 2011; Parrott *et al*., 2011a, 2011b; Kirkpatrick *et al*., 2012). Because MDMA is a general mood enhancer, the specific mood effects elicited may depend on factors such as internal expectations and environmental influences (Parrott, 2007a, 2007b). In historical terms, most focus has been on its positive mood effects, and they can be extremely powerful. In an early survey of Australian users, Solowij *et al*. (1992) noted that most recreational users described feelings of euphoria, intimacy, and personal closeness. In a later survey of British users, Verheyden *et al*. (2003) reported that 91% experienced a *euphoric rush* following Ecstasy. With North American dance clubbers, Cohen (1998) noted positive responses such as feeling like 'floating, flying, highly sensual' and that 'everyone was your friend'. One of the recreational users in Parrott (2010) described its effects as follows: 'Imagine the best feeling you have ever felt, times it by ten and you're still not close to how amazing you feel'. Not all positive experiences are so strong or euphoric, and some novice recreational users have noted that its positive effects were not as strong as they had expected. In Parrott (2010), we empirically investigated this variation by asking different subgroups of users to rate the strength of their on-drug experiences. Novice users who had taken the drug a few times before quitting reported less positive initial experiences than novice users who had continued to take it (Table 2). The positive mood effects of MDMA have been confirmed in placebo-controlled laboratory trials. Cami *et al*. (2000) reported increased feelings of euphoria and stimulation following 75- and 125-mg MDMA. Liechti *et al*. (2001) combined three trials where MDMA (mean 108 mg) was administered to drug-naive participants; significant increases were found on every positive mood scale. Farre *et al*. (2004) similarly found significant increases in feeling high and feeling stimulated. Bedi *et al*. (2010) reported significant increases in feeling loving and friendly.

It is less widely recognized that negative moods are also boosted by MDMA, yet this has been repeatedly found in laboratory and field studies. Liechti *et al*. (2001) reported significant increases in self-rated apprehensiveness, depression, and other negative moods in the relaxing conditions of a medical laboratory; the 'acute adverse effects and sequelae were also more frequent in female than in male subjects'. Tancer and Johanson (2007) reported a significant increase in anxiety. Bedi and de Wit (2011) reported a significant increase in 'feeling anxious' in female volunteers only, following oral doses of 75- and 125-mg MDMA; there was also a significant increase in self-rated 'loneliness' after 75-mg MDMA with both genders. Parrott *et al*. (2011a, 2011b) employed the Positive and Negative Affect Scales and found significant increases in negative moods following 100-mg oral MDMA, whereas on the positive mood factor, there was only a slight gain, which did not approach significance. In contrast, acute methamphetamine led to a significant increase in both positive and negative mood states. Similar findings were described by Kirkpatrick *et al*. (2012).

Negative reactions also occur with recreational Ecstasy/MDMA users, with acute feelings of anxiety, overstimulation, panic, and loss of personal control (Davison and Parrott, 1997; Cohen, 1998). Positive and negative mood changes often develop in the same individual, with feelings of happiness and depression, and extraversion and introversion, during the same Ecstasy/MDMA experience (Liechti *et al*., 2001). To summarize, MDMA is essentially a mood intensifier. By enhancing neurobiological activity across several

Table 2. Positive and negative effects for the first and last Ecstasy experiences, as self-rated by four subgroups of recreational Ecstasy/MDMA users: light former users, light current users, heavy former users, and heavy current users (after O'Sullivan and Parrott, unpublished project; reported in Parrott, 2010)

Dependent variable	Light former users	Light current users	Heavy former users	Heavy current users	ANOVA group effect *F*-value (*df* 3, 60)	Significance level (*p*-value)
Sample size (*N*)	18.0	10.0	22.0	18.0		
Positive effects *first* time	4.9	6.6	8.6	8.8	12.22	<0.001
Positive effects *last* time	3.9	6.2	3.4	4.3	4.40	<0.010
Decline in positive effects: from *first to last* time	−1.0	−0.4	−5.2	−4.5		
Negative effects *first* time	3.6	3.2	3.9	2.9	0.55	Non-significant
Negative effects *last* time	5.8	4.2	5.3	5.0	0.66	Non-significant
Increase in negative effects: from *first to last* time	+2.2	+1.0	+1.4	+2.1		
Cost–benefit ratio *first* time (%)	+36.0	+103.0	+120.0	+203.0		
Cost–benefit ratio *last* time (%)	−33.0	+47.0	−36.0	−14.0		

Self-rating scales: 1–10 (*minimum* to *maximum*).
ANOVA, analysis of variance.

DOI: 10.1002/hup

neurotransmitter and neurohormonal systems, it can intensify a wide range of neuropsychobiological states. Furthermore, as with another serotonergic drug LSD, its mood effects may reflect the environmental situation (Parrott, 2006, 2007). This could help explain why in laboratory studies, the mood reaction can be quite negative (Bedi and de Wit, 2011; Parrott *et al*., 2011a, 2011b; Kirkpatrick *et al*., 2012). Many recreational users also note the importance of positive expectancy for optimizing the on-drug experience (Parrott, 2004b), with one recreational user noting that 'Ecstasy is not a happy drug. It by itself does not do anything. The Ecstasy and joy must come from within you' (Cohen, 1998). The notion of pre-drug mental preparation is also consistent with Hopper *et al*. (2006), who found that cravings for Ecstasy occurred in the period before drug ingestion—but not at other times. Finally, the positive effects of MDMA decline with continued usage (Table 2). With the development of chronic tolerance, continued usage leads to fewer gains but more problems; hence, the drug is taken less frequently over time, followed by voluntary drug cessation. MDMA is somewhat unique as a recreational drug, in that most users quit using it on their own (Parrott, 2005).

CHRONIC TOLERANCE

An understanding of chronic tolerance is crucial for explaining MDMA usage patterns. Tolerance featured strongly in the first experiential descriptions, with Shulgin (1986) noting that 'MDMA does not lend itself to overuse because its most desirable effects diminish with frequency of use'. Greer and Tolbert (1986) similarly commented that its pleasurable effects diminished, and adverse effects increased, when taken repeatedly. They also noted that this property distinguished MDMA from other drugs of abuse. Peroutka *et al*. (1988) found that regular American users reported that the positive effects of MDMA declined with repeated usage, whereas its negative effects increased. In an equivalent survey of 100 Australian users, Solowij *et al*. (1992) similarly commented that its pleasurable effects declined with successive doses. In those early years, most users did not take large amounts, with most users reporting a lifetime usage of less than 10 occasions. They typically took it alone as a monosubstance and had breaks of several weeks between drug sessions to minimize 'drug habituation' (Davison and Parrott, 1997).

Chronic tolerance largely disappeared from conceptual awareness in the 1990s, with none of the following MDMA reviews mentioning it (Green *et al*., 1995; McCann *et al*., 1996; Hegadoren *et al*., 1998; Morgan, 2000; Parrott, 2000; Schifano, 2000). One exception was Steele *et al*. (1994) who briefly noted its occurrence in some individuals. Somewhat later, Kalant (2001) noted that it took years for tolerance and dependence to novel drugs to become acknowledged and that it was best to reserve judgment on MDMA. Chronic tolerance was covered by a single paragraph in Parrott (2001). The main reason for this was the absence of empirical data. However, it still featured in experiential descriptions, with Saunders (1997) noting that 'The experience of the love effect from ecstasy rapidly fades from repeated usage'.

In the early 2000s, several research groups compared novice and more experienced users and generated the first empirical data on chronic tolerance (Parrott, 2005). Fox *et al*. (2001) found that light/novice users took an average of 1.8 tablets per occasion, and moderate users took an average of 2.2 tablets per occasion, whereas heavy lifetime users reported a mean of 3.7 Ecstasy tablets per occasion. The maximum number of tablets per occasion also increased across these subgroups to 3.6, 5.5, and 10.9, respectively. Verkes *et al*. (2001) compared moderate and heavy Ecstasy users and found that the heavier users had a significantly greater lifetime usage of Ecstasy/MDMA and also took significantly more tablets per occasion. Schifano *et al*. (1998) noted that young Ecstasy users who did not report problems were light novice users, whereas those users who complained of MDMA-related problem were more experienced users who had been taking it for longer and took more tablets per occasion. In a large Internet survey, Scholey *et al*. (2004) again reported more intensive Ecstasy/MDMA consumption by the more experienced users.

Bingeing was not reported in the earliest MDMA studies. Peroutka (1989) noted that it was rare to find individuals who took large quantities: 'To my knowledge there are simply no reports of individuals who take frequent and large amounts of MDMA'. Solowij *et al*. (1992) found no evidence for bingeing in a survey of 100 Australian users, whereas Winstock (1991) noted that bingeing was extremely unusual in the UK at that time. The first empirical report of bingeing came from a Scottish study undertaken in 1993–1995. This was published a few years later by Hammersley *et al*. (1999), who revealed two types of Ecstasy/MDMA bingeing: 'stacking', or several tablets all at once, and 'boosting' where successive tablets were taken over that evening—or on successive days. Bingeing mainly occurred in the more experienced users and was also accompanied by erratic patterns of intensive drug usage. Hence, 76% of heavier users

DOI: 10.1002/hup

reported bingeing, whereas it was noted by only 16% of light users. Intensive Ecstasy usage also led to more days off work due to illness, reduced appetite, and episodes of depression (Hammersley *et al*., 1999). By the late 1990s, dosage escalation and bingeing had become more typical of Ecstasy/MDMA usage, as noted in a survey of readers of the dance club magazine 'Mixmag' (Winstock *et al*., 2001). Bingeing could sometimes be extreme, with Topp *et al*. (1999) defining bingeing as taking Ecstasy on a continual basis without sleep for +48 h. This pattern also typifies heavy cocaine users. There have been many case reports of individuals consuming 10–25 tablets in a single session, who demonstrate both tolerance and a wide range of neuropsychobiological problems (Schifano and Magni, 1994; Jansen, 1999; Kopelman *et al*., 2001; Soar *et al*., 2002).

One novel development in the mid-2000s was the 'MDMA bomb'. This comprises MDMA powders wrapped in a twist of cigarette paper and then swallowed. Each bomb may contain around 150–225 mg of MDMA, or the equivalent of two or three Ecstasy tablets. Chronic tolerance also occurs with these bombs, with one user reporting that they 'only used to take one bomb a night', but now takes 'three or more bombs a night' (Parrott, 2010). I am not aware of any research comparing the effects of bombs and tablets. There are also little empirical data on the two other modes of MDMA self-administration, snorting and injecting. Some users snort MDMA powders, in a way similar to nasal cocaine, and this may generate a more intense hit but can cause nasal/facial problems. Some experienced drug users inject MDMA. Topp *et al*. (1999) found that 16% of their sample of 329 recreational users had injected Ecstasy/MDMA. Injecting caused a more rapid hit and was financially cheaper. However, the drawbacks included an acute reaction that was 'too intense to enjoy', worse come down afterwards, and more adverse health consequences. Because of these problems, Topp *et al*. (1999) found that many former injectors had reverted to the oral route.

CORTISOL

Cortisol is important for homeostatic control and everyday well-being. However, this key neurohormone is affected by acute and chronic MDMA. Dumont and Verkes (2006) reviewed laboratory studies of acute neurohormonal reactions to MDMA in humans, and 11 of the 12 studies reported significant increases in cortisol. Harris *et al*. (2002) reported that 0.5-mg/kg MDMA led to a cortisol increase of 100%, whereas 1.5-mg/kg MDMA led to an increase of 150%. Similar increases were evident in most of the other acute-dose laboratory studies (Dumont and Verkes, 2006). The neurohormonal response can be even stronger in recreational users at dance clubs. Parrott *et al*. (2008) monitored a group of 12 Ecstasy users on successive weekends of dance clubbing, once when on MDMA and once when clubbing during abstinence. Saliva tests confirmed MDMA during the on-drug weekend and its absence during the off-drug weekend. Cortisol levels were increased by 800% in the on-MDMA condition but were unchanged during abstinence (Figure 1). A similar 800% increase in cortisol was also found in a follow-up study, with more experienced Ecstasy users at a house party (Parrott *et al*., 2007).

The regular use of MDMA can lead to changes in cortisol reactivity. Gerra *et al*. (1998) reported a significantly reduced cortisol response to a *d*-fenfluramine challenge, in drug-free recreational MDMA users.

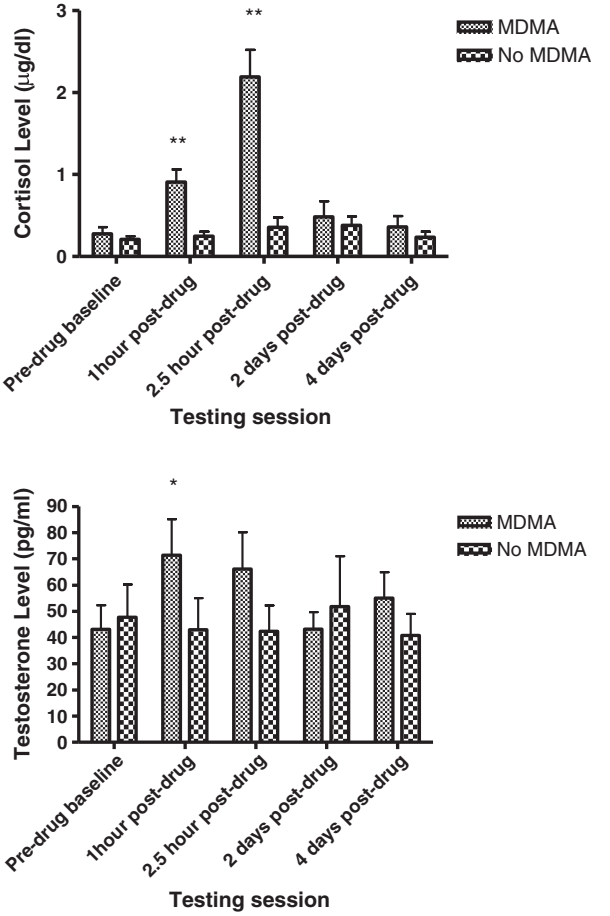

Figure 1. Cortisol and testosterone levels of recreational Ecstasy/MDMA users dance clubbing. Twelve unpaid volunteers were assessed on self-administered MDMA and while abstaining from MDMA, over counterbalanced weekends at the same dance club venue, with the same group of friends. *P*-levels represent paired comparisons with pre-drug baseline (after Parrott *et al*., 2008)

DOI: 10.1002/hup

Verkes *et al*. (2001) reported a reduced cortisol response to a *d*-fenfluramine challenge, in both moderate and heavy Ecstasy users. Gerra *et al*. (2003) reported that baseline cortisol was significantly lower in abstinent Ecstasy users compared with non-user controls and that they displayed reduced cortisol responses to stress. The authors noted that this might indicate a neuroendocrine dysfunction induced by repeated MDMA use. Parrott *et al*. (2012) collected hair samples from recreational drug users and non-users, which were analysed for 3-month cortisol levels. The light Ecstasy/MDMA users from the past 3 months (one to four occasions) showed a slight non-significant elevation of hair cortisol compared with controls. The heavier Ecstasy/MDMA users (more than four occasions) demonstrated significant increases in 3-month cortisol, when compared with both the other groups.

MEMORY DEFICITS

The first psychobiological deficits to be empirically revealed in abstinent Ecstasy users were deficits in retrospective memory (McCann and Ricaurte, 1991). Krystal *et al*. (1992) found mild to moderate levels of impairment on the Wechsler Adult Intelligence Scale memory subscales in a small group of abstinent Ecstasy/MDMA users. Parrott *et al*. (1998) found that two subgroups of novice and moderate ecstasy users had significantly poorer immediate and delayed word recall than non-user controls, whereas other basic cognitive skills were not impaired. Morgan (1999) reported significantly poorer prose recall in abstinent Ecstasy users, compared with both non-user controls and an active polydrug user control group. Other empirical descriptions of impaired memory include a brief prospective study of dance clubbers, before, during, and after weekend drug use (Parrott and Lasky, 1998). Verkes *et al*. (2001) employed a control group of regular ravers who had never taken MDMA, hence providing control for circadian rhythm factors. To summarize the situation in 2001, this was the area of psychobiological deficit with the most extensive amount of empirical evidence, with deficits in many different tasks (Table 2 in Parrott 2001; Bolla *et al*., 1998; Rodgers, 2000).

In subsequent years, there have been many further empirical reports of memory impairments, although not every study has found deficits. Several neurocognitive reviews have each concluded that abstinent Ecstasy/MDMA users show memory deficits. Laws and Kokkalis (2007) calculated the 'effect size' for different types of retrospective memory task, and with short-term memory tasks, there was a moderate-to-large effect size, whereas for longer-term memory tasks, the effect size was somewhat larger (Cohen's $d = -0.87$). Rogers *et al*. (2009) undertook a comprehensive review of over 100 neurocognitive studies, which passed strict acceptance criteria. The most frequently used memory paradigms were the Rey Auditory Verbal Learning Test, Rivermead Paragraph Recall, and digit span forwards and backwards. The main conclusion was that memory deficits in abstinent Ecstasy users were statistically significant in comparison with those in both non-user control groups and polydrug user controls. Most studies in this area are cross-sectional. However, Zakzanis and co-workers undertook a prospective neurocognitive investigation of 15 MDMA users, who were tested at yearly intervals (Zakzanis and Young, 2001; Zakzanis and Campbell, 2006). With Rivermead Paragraph Recall, they showed a significant decline in immediate and delayed recall over the 12 months, whereas on the other memory tasks, there was no decline from baseline. One year later, seven participants were continuing to take MDMA, whereas the other eight had quit. Former users showed unchanged or improved memory performance, whereas continuing users showed either unchanged or further deteriorations in memory performance.

PROSPECTIVE MEMORY DEFICITS

In an earlier review (Parrott, 2001), there was one empirical report describing prospective memory deficits in abstinent Ecstasy/MDMA users (Heffernan *et al*., 2001). Since then, there have been a marked increase in empirical reports, using various assessment procedures. They include complex games that mimic real-world activities, video films requiring pre-planned responses, and 'virtual-reality' prospective memory situations (Montgomery *et al*., 2010). Heffernan *et al*. (2001) found significant prospective memory deficits, which were confirmed in later studies using a range of paradigms. In an Internet survey (Rodgers *et al*., 2003), Ecstasy/MDMA users again reported prospective memory problems. Rendell *et al*. (2007) developed a virtual board game task designed to mimic various prospective memory work-related activities. Moderate lifetime Ecstasy/MDMA users were significantly worse than controls, whereas heavy users were significantly worse than both the other two groups; the deficits remained after controlling for various potential confounders. Montgomery *et al*. (2010) used a virtual-reality prospective memory task modelled around everyday office worker tasks and again found significant deficits in Ecstasy polydrug users compared with polydrug controls. Hadjiefthyvoulou *et al*. (2011a)

DOI: 10.1002/hup

employed an extensive battery of everyday memory tasks, prospective memory tasks, and self-report scales; Ecstasy users showed significantly worse performance than non-user controls and cannabis users. These findings were broadly replicated using the Cambridge Prospective Memory test (Hadjiefthyvoulou *et al*., 2011b). In summary, retrospective memory seems to be particularly sensitive to the adverse effects of recreational Ecstasy/MDMA. This may be because it involves both memory and higher executive control.

HIGHER COGNITIVE DEFICITS

In 2001, the higher cognitive skills of abstinent Ecstasy/MDMA users had hardly been assessed (Parrott, 2001). Since then, many studies have been undertaken, and they have revealed deficits in a range of complex cognitive measures. In one of the earliest studies to employ an extensive neurocognitive test battery, McCann *et al*. (1999) reported normal performance on many of the more basic cognitive tasks, but significant deficits on others, including logical reasoning. The authors noted that these differences were often quite subtle and could only be detected using sensitive cognitive tasks. Fox *et al*. (2001) also employed a different battery of cognitive tasks but also reported normal functioning on several measures, together with significant deficits on others. For instance, deficits were apparent on the Tower of London problem-solving task, which involved higher executive planning. The extent of these deficits was also associated with past lifetime usage, with heavy users taking around 2.5 times longer to solve each problem, when compared with non-user controls. In a follow-up study, Fox *et al*. (2002) administered the Cambridge Automated Neurocognitive Test Battery to abstinent Ecstasy/MDMA users and polydrug controls. The emergent cognitive profiles were compared with past clinical profiles of patients with documented forms of brain damage. The overall Cambridge Automated Neurocognitive Test Battery profiles of abstinent Ecstasy/MDMA users were closest to those of temporal lobe patients.

Reay *et al*. (2006) employed an innovative battery of cognitive tasks and found various deficits including complex decision-taking tasks such as Brixton spatial anticipation. The Ecstasy/MDMA users were significantly impaired on standard questionnaires for psychosocial functioning and higher executive processing. The authors noted that the higher cognitive deficits could help to explain the impairments in emotional understanding and the subtle processes that underlie psychosocial skill. In summary, abstinent Ecstasy/MDMA users have been shown to be impaired on a range of higher cognitive tasks, including measures of executive processing, logical reasoning, problem solving, and emotional intelligence (Fisk *et al*., 2005). It should however be noted that many basic cognitive skills are generally unaffected. Hence, simple reaction time, basic attention, vigilance, and other basic neurocognitive skills are generally not impaired (Parrott *et al*., 1998; Back-Madruga *et al*., 2003), although even some basic working memory tasks may be impaired, when higher information-processing loads are required (Murphy *et al*., 2009).

Neurocognitive performance has also been assessed in Ecstasy/MDMA users with minimal use of other substances. Halpern *et al*. (2004) investigated light/moderate and heavier MDMA users, from Salt Lake City, USA, who were unusual in that they displayed minimal use of other psychoactive drugs. The light MDMA user subgroup showed no significant differences from non-user controls, whereas the heavy user subgroup showed significant deficits on higher cognitive tasks, such as Wisconsin card sort, Stroop interference, and the revised strategies application test. As in many other studies, simpler cognitive task performance skills were not impaired. In a follow-up study, Halpern *et al*. (2011) tested Ecstasy users with mean lifetime usage similar to their previous light/moderate group. The overall analysis revealed minimal cognitive deficits. But when the overall group was split into lighter and heavier users, the latter subgroup demonstrated impairments on various measures, including spatial span forwards, digit span backwards, the revised strategies applications test, and the grooved pegboard test with the non-dominant hand. Whether this reflects a higher loading for executive control with the non-dominant hand remains to be further investigated (Parrott, 2011) In summary, there is an extensive empirical literature showing that MDMA is associated with impairments in various aspects of memory and higher executive processing, whereas performance on simpler cognitive tasks is generally not impaired,

SEROTONERGIC NEUROTOXICITY IN HUMANS

In laboratory animals, it is well established that repeated dosing with MDMA can lead to a pronounced reduction in markers for serotonin across higher brain regions. This was first shown in the mid-1980s, and subsequent research has found that the serotonergic changes can be modulated by factors such as heat and caging the animals in social groups (Huether *et al*., 1997; Green *et al*., 2003; Puerta *et al*., 2009). Ricaurte *et al*. (2000) noted that animal findings led

DOI: 10.1002/hup

to the prediction that similar serotonergic damage might also occur in humans. The first human neuroimaging studies were undertaken in the late 1990s, and they found lower levels of serotonin markers in drug-free MDMA users (McCann *et al*., 1998). Subsequent positron emission tomography, single-photon emission computed tomography, and functional magnetic resonance imaging (fMRI) studies were undertaken by research groups in Germany, the Netherlands, the USA, the UK, and elsewhere. In a review by Reneman *et al*. (2006), it was noted that every study of *heavy* users had found a significant reduction in the density of SERTs in higher brain regions (see also Cowan, 2007). This has been confirmed more recently. Kish *et al*. (2010) compared 49 moderate Ecstasy users with 50 non-user controls, using an extensive list of methodological controls. Significant serotonergic reductions were again clearly apparent, with significantly lower SERT levels in all areas of the cerebral cortex. Furthermore, these serotonergic deficits remained after controlling for every potential confounder they could address. McCann *et al*. (2008) found a similar pattern of serotonergic deficits. Erritzoe *et al*. (2011) reported that MDMA-preferring drug users showed significant decreases in SERT binding potential across several brain regions, with the greatest mean reduction in the neocortex (−56%). In contrast, LSD-preferring drug users did not show any significant changes in SERT. Di Iorio *et al*. (2012) investigated female polydrug MDMA users with comparatively light lifetime usage (group mean: 13.5 occasions). Cortical serotonin 2A receptor binding potential levels were measured, with higher levels predicted as a neuroadaptive response to reduced serotonin activity. The authors found significantly higher levels across various areas of the cerebral cortex, including the occipital–parietal, temporal, and fronto-parietal lobes/regions. Green *et al*. (2012) questioned whether MDMA produced 5-HT neurotoxicity in humans, stating that it was 'our contention that MDMA does not cause neurotoxic damage to 5-HT neurones in the human brain'. However, in an invited commentary (Parrott, 2012b), it was noted that the authors had *explicated* that they had not reviewed the empirical evidence on this topic. Benningfield and Cowan (2013) summarized the most recent empirical findings, which indicated persistent changes to the serotonin system.

BRAIN ACTIVITY AND COGNITIVE PERFORMANCE

A major development in knowledge about the adverse effects of Ecstasy/MDMA has arisen from studies measuring brain activity in parallel with cognitive task performance. In recent years, numerous EEG and neuroimaging studies have been published, and the following comprises just a brief selection of findings. McCann *et al*. (2008) showed that memory task performance was inversely associated with SERT binding levels in various brain regions, including the dorsolateral prefrontal cortex and other areas known to be involved in memory. Kish *et al*. (2010) found that lower memory task performance was associated with SERT binding loss in the insular cortex and hippocampus. Daumann *et al*. (2005) measured episodic memory in an fMRI study and found significantly lower activity levels in the left hippocampus during information retrieval, although functional task performance was not impaired. Roberts *et al*. (2009) recorded fMRI during a face-learning task, with significantly worse performance in abstinent ecstasy/MDMA users compared with controls and abstinent cannabis users. They tended to show different patterns of brain activity, with a mixture of hyperactivity and hypoactivity in different regions. Jacobsen *et al*. (2004) found selective differences in brain activation patterns, along with selective neurocognitive performance deficits, in novice Ecstasy/MDMA users. They suggested that even light usage of MDMA might be associated with dysfunction in the inhibitory circuits in the hippocampus. Karageorgiou *et al*. (2009) undertook fMRI measures during performance of a simple psychomotor task. Although performance scores did not differ between groups, there were a number of group differences in the fMRI measures, along with significant associations between lifetime MDMA exposure and signal magnitude in motor areas of the brain, including the basal ganglia thalamo-cortical circuits. Quednow *et al*. (2004) found that the pre-pulse inhibition of the acoustic startle response was significantly reduced in abstinent MDMA users, whereas cannabis users were similar to controls. Burgess *et al*., (2011), measured evoked response potentials during a recognition memory task. Abstinent Ecstasy/MDMA users showed a significant reduction in the size of the late event-related potential (ERP) over the left parietal lobe, an area known to be important for memory recognition.

SLEEP DEFICITS

Although there have been a few empirical studies on core psychobiological functions such as sleep, the number of investigations is surprisingly limited, and further studies are required. In an early sleep study, Allen *et al*. (1993) found reduced total sleep time, due mainly to reduced Stage 2 non-rapid eye movement

DOI: 10.1002/hup

sleep, in abstinent recreational Ecstasy/MDMA users. In a later study, the same group reported longer sleep times, mainly due to increases in non-rapid eye movement Stages 3 and 4. Jones *et al*. (2008) found changing subjective sleep patterns after weekend Ecstasy use, with reduction in both sleep time and sleep quality during the initial post-drug days and a return to normal sleep after 5 or 6 days of recovery. In a sleep review, McCann and Ricaurte (2007) concluded that abstinent Ecstasy/MDMA users had an increased risk for chronic sleep disturbances. More recently, the same group reported an increased incidence of sleep apnoea, which was significantly associated with lifetime MDMA usage (McCann *et al*., 2009). Because serotonin is involved in the control of breathing, this medical disorder may reflect serotonergic neurotoxicity.

VISUAL DEFICITS

The visual cortex is densely innervated by serotonergic fibres, and Kish *et al*. (2010) found that the occipital lobe of abstinent MDMA users showed a 46% group mean reduction in SERT levels. Rizzo *et al*. (2005) had earlier predicted that MDMA may cause changes in visual ability. However, visual skills and performance have been investigated in only a few empirical studies. Cowan *et al*. (2001) found preliminary evidence for some reduction in visual cortical activation to red and blue photic stimuli, in an early fMRI study. Dickson *et al*. (2009) investigated the magnitude of the visual tilt illusion, which provides an index of lateral inhibition between visual neurones in the primary visual cortex, which is thought to reflect serotonergic activity. Significant impairments were found in the abstinent Ecstasy/MDMA users, with the extent of deficit related to lifetime usage. Murphy *et al*. (2012) undertook a meta-analysis of neurocognitive studies involving visuo-spatial memory tasks and found deficits in the recall of spatial information, recognition of figures, and reproduction of figures. Rizzo *et al*. (2005) found normal performance on basic visual measures such as visual acuity and visual contrast; however, on a more difficult task, which involved the spatial integration of complex visual arrays, performance was significantly impaired. The authors hypothesized that this might adversely affect complex visually skilled tasks such as car driving. This was empirically confirmed by Dastrup *et al*. (2010), who found 'riskier' car driving in abstinent Ecstasy users, due to following a lead vehicle too closely. In a similar acute-dose study, Stough *et al*. (2012) reported that 100-mg MDMA led to several performance impairments in a car-driving simulator, with deficits on higher-order skills with visual components, such as 'safe car following', 'inappropriate braking', and other measures.

ECSTASY/MDMA USE DURING PREGNANCY

Many psychoactive drugs have been shown to damage foetal development; hence, it is important to assess the effects of Ecstasy/MDMA during pregnancy. In retrospective reports, McElhatton *et al*. (1999) noted an increased rate of congenital abnormalities in the children of mothers who had used MDMA during pregnancy. In a prospective investigation, the Drugs and Infancy study monitored 28 mothers who took Ecstasy/MDMA during the first trimester of pregnancy. The polydrug control group comprised 68 mothers who used other recreational drugs while pregnant and included several with previous Ecstasy/MDMA usage. Each neonate was assessed on an extensive psychological test battery on repeated occasions. At the 4-month post-partum session, the two groups were similar on most measures, but the children of the Ecstasy/MDMA mothers had significantly lower 'motor quality' scores (Singer *et al*., 2012a). When assessed at 12 months post-partum, similar deficits were again apparent, with the children of mothers who were regular user of Ecstasy/MDMA during the first trimester again displaying gross psychomotor deficits (Singer *et al*., 2012b).

APOPTOSIS (PROGRAMMED CELL DEATH) AND CANCER TREATMENT

Simantov (2004) commented that MDMA had multiple molecular and neuropharmacological effects and that although its serotonergic/neurotoxic effects had been widely investigated, it displayed many other properties. In particular, MDMA 'induces programmed cell death in cultured human serotonergic cells'. Cadet *et al*. (2007) similarly commented on this programmed cell death, or apoptosis. It was further suggested that it may comprise one of several mechanisms for MDMA-induced neurotoxicity, along with oxidative stress and hyperthermia. Apoptosis has a range of adverse implications for recreational users, as in animal studies, it has been found to destroy liver and retinal cells (Parrott, 2006). Apoptosis may however have some medicinal benefits. In particular, their ability to damage human cells may make MDMA drugs useful for cancer therapy. Wasik *et al*. (2011) noted that 'MDMA/ecstasy is cytotoxic toward lymphoma cells in vitro', although the concentrations mitigated against its practical usage for cancer therapy. Their research attempted to 'redesign

DOI: 10.1002/hup

the designer drug', to separate 'desired anti-lymphoma activity from unwanted psychoactivity and neurotoxicity'. To this end, they tested a series of MDMA analogues. Another medical research group, Riahi *et al.* (2010) used molecular modelling to understand 'the complex formed between MDMA and DNA', to design novel anti-cancer and anti-viral drugs.

PSYCHOTHERAPY WITH MDMA

In the early 1980s, it was suggested that MDMA represented a new class of drugs, the 'entactogens', which facilitated contact with the true self (Nichols, 1986). It was proposed that MDMA might prove useful for psychotherapy, and some informal trials were conducted. Greer and Tolbert (1986) described their therapeutic experiences with 29 clients. Mithoefer *et al.* (2011) described a more recent placebo-controlled trial of post-traumatic stress disorder (PTSD). Both reports concluded that MDMA was safe for human administration and recommended larger double-blind studies. However, in a review of MDMA's potential for psychotherapy, I raised a number of critical issues that needed to be addressed before it could be argued that MDMA might be a safe drug for clinical use (Parrott, 2007a, 2007b). The main proponents for MDMA-assisted therapy have suggested that one or two therapeutic sessions with MDMA will produce long-lasting gains (Doblin, 2002). However, this does not fit with current models of pharmacotherapy (Parrott, 2007a, 2007b), where regular dosing is required to maintain the altered neurotransmitter status (viz. antidepressants or antipsychotics). In neurochemical terms, the effects of MDMA are short lived, only lasting a few hours. For an enduring change, the psychotherapeutic element is essential, and this may be more important than the actual drug effect. Greer and Tolbert (1986) suggested that 'We viewed the effects of MDMA as secondary to the effects of the therapeutic ritual'. Mithoefer *et al.* (2011) embedded their two MDMA-assisted sessions in a series of pre-drug-free and post-drug-free therapy sessions. Another issue was that the acute effects of MDMA can be unpredictable, as both positive and negative psychological materials can be released. Greer and Tolbert (1986) noted that all their clients reported some positive experiences, although negative drug effects were also universal: 'All subjects reported some undesirable experiences during or after their sessions. The longest that any of these symptoms persisted was one week, except in two subjects'. In these latter two clients, the abreactions were longer lasting, with one person needing psychotherapy to counteract their anxiety and panic attacks.

Another issue is the post-MDMA rebound period, when neurochemical depletion may lead to feelings of depression, anger, paranoia, aggression, and other negative sequelae (Curran and Travill, 1997; Parrott and Lasky, 1998; Parrott *et al.*, 2011a, 2011b). Individuals with pre-existing depression may be at particular risk of drug-induced distress during the post-MDMA recovery period. There is also the general inadvisability of using stimulant drugs with psychiatric patients. In a laboratory study involving MDMA administration, Vollenweider *et al.* (1998) excluded individuals with a personal psychiatric history, as certain psychiatric traits might increase the liability for 'prolonged and severe responses to stimulant and hallucinogenic drugs'. Greer and Tolbert (1986) similarly warned against using MDMA in psychiatrically vulnerable individuals: 'There is an indication that MDMA may predispose people to a recurrence of previous psychological disabilities'. Psychotherapy may be safer without the use of stimulant co-drugs. It may also be more robust and enduring over time.

Mithoefer *et al.* (2011) assessed 12 PTSD clients in their MDMA therapy group and eight clients in a placebo therapy group. Although double blind, 19 of the 20 clients correctly guessed their drug condition, whereas the therapists were 'correct in all cases'. Significant post-MDMA therapy gains were found with the post-traumatic stress disorder scale, which was scored by the clinician. There were significantly fewer gains in the PTSD scale with placebo-treated clients. Every client completed the Symptom Check List for self-rated psychiatric symptoms (SCL-90R), although the findings were not presented in the published report. They have however been provided by Doblin (2011; personal communication). There were no significant analysis of variance changes in the SCL-90R anxiety subscale, although both groups showed a general reduction over time (MDMA group: 51.0 at baseline, reducing to 39.7 at 2 months; placebo group: 51.4 at baseline, reducing to 45.1 at 2 months). There was a significant reduction in SCL-90R depression scores, with stronger gains in the MDMA-treated group (MDMA group: 52.4 at baseline, reducing to 38.5 after 2 months; placebo group: 49.5 at baseline, reducing to 42.1 after 2 months). It should be emphasized that these were preliminary findings and the full analysis of the SCL-90R data is still awaited.

Other issues that need to be addressed have been outlined elsewhere (Parrott, 2007a, 2007b). Perhaps the most important is the very misleading message for the general public (at-risk youngsters in particular) that MDMA is safe for human consumption and that MDMA can help solve your personal problems

DOI: 10.1002/hup

(see Parrott, 2008, for a more detailed debate about this aspect of recreational drug use). Furthermore, the potential dangers of using an unpredictable CNS stimulant for *clinical* purposes may be illustrated with two hypothetical scenarios. A Special Air Forces soldier is discharged from the army with post-traumatic stress disorder. His therapist attempts MDMA-assisted therapy, but the drug stimulates the re-emergence of unpleasant war experiences. It induces feelings of aggression, which the soldier manages to control while still in the clinic. However, later that evening, he violently attacks a stranger in the street. Following his arrest, the lawyer argues that this aggressive act had been triggered by the MDMA-assisted therapy session. The second hypothetical case is a female rape victim. After the first MDMA-assisted therapy session, the client feels much better, but the gains do not endure over time. Following a second MDMA-assisted therapy session some time later, again, there is a brief period of symptomatic relief. A third session is requested, but the therapist explains that this cannot be clinically recommended, as the gains were not enduring. The client now seeks out their own illicit supplies of Ecstasy/MDMA. The only time she feels good is when she is on MDMA, and she becomes a habitual user. However, with reducing efficacy and increasing mid-week blues, her chronic anxiety, depression, and low self-esteem steadily worsen. She is hospitalized after an unsuccessful suicide attempt. The family discovers her diary, which is given to the lawyer. In both cases, the therapist is sued, along with the pharmaceutical company that provided the MDMA.

MDMA COMPARED WITH OTHER PSYCHOSOCIAL DRUGS

Nutt *et al*. (2007) attempted to compare the relative dangers of the main types of psychosocial drug, using a series of subjective rating scales. Heroin and cocaine were graded as the two most harmful drugs, whereas Ecstasy/MDMA emerged as one of the least harmful (18th out of 20). Unfortunately, it was unclear how this low harm rating score for Ecstasy/MDMA was given, as they cited no empirical research studies or reviews. Instead, Nutt *et al*. (2007) suggested that: 'for drugs which have only recently become popular e.g. Ecstasy or MDMA, the longer term health and social consequences can only be estimated from animal toxicology at present'. Nutt *et al*. (2007) noted that the most pleasurable drugs tended to be the most problematic, and on the 'intensity of pleasure' scale, heroin and cocaine were given maximum scores of 3.0. In contrast, Ecstasy/MDMA was given an 'intensity of pleasure' score of 1.5, which was lower than cigarette smoking at 2.2. It is unclear why Ecstasy was rated as less pleasurable than smoking a cigarette, although the low pleasure score contributed to its low harm score. Another question concerned drug injections, with Nutt *et al*. (2007) noting that 'The potential for intravenous use is taken into account in the Misuse of Drugs classification and was treated as a separate parameter in our exercise'. Cocaine and heroin were given maximum scores of 3.0, whereas Ecstasy/MDMA was given a score of 0. Again, this did not accord with the empirical literature. In their survey of 329 recreational Ecstasy/MDMA users, Topp *et al*. (1999) reported that 54 (16%) had injected Ecstasy. MDMA injecting may be atypical and only occurs amongst the more experienced Ecstasy users, although this pattern would also describe cocaine. Most cocaine users never inject, and it is only found with experienced users. Hence, the injection score for MDMA should be similar to that for cocaine. Many of the other Ecstasy harm values in Nutt *et al*. (2007) were surprisingly low. With revised values based on the empirical literature, MDMA rises to the fifth most harmful drug (Parrott, 2009b).

There is a paucity of empirical data on the comparative psychobiological effects of different recreational stimulants. Table 3 summarizes the findings from three pilot studies comparing recreational Ecstasy/MDMA and cocaine users. The neurocognitive profiles of the cocaine and ecstasy users were similar, with both drugs showing impairments in comparison with controls (Table 3; after Parrott *et al*., 2011b). The adverse neurocognitive profiles of the Ecstasy/MDMA users were similar to those described earlier, whereas the cognitive deficits of cocaine users were also similar to other findings from recreational cocaine users (Soar *et al*., 2012). The main difference between the two drugs was in post-drug recovery, where Ecstasy/MDMA users reported more pronounced after-effects than did cocaine users (Study 2 in Table 3). The heightened depression was similar to that found in earlier studies (Curran and Travill, 1997; Parrott and Lasky, 1998; Parrott *et al*., 2008). However, the significant feelings of paranoia in the post-Ecstasy recovery period have not been empirically described before. In relation to psychiatric aspects, Williamson *et al*. (1997) found broadly similar patterns of psychiatric distress in recreational users of cocaine, amphetamine, and MDMA.

In a New York residential laboratory study, Kirkpatrick *et al*. (2012) administered oral doses of 20- and 40-mg methamphetamine, 100-mg MDMA, and placebo to experienced recreational stimulant users. The 40-mg methamphetamine and 100-mg MDMA conditions produced similar subjective 'high'

DOI: 10.1002/hup

and 'good drug effect' scores, whereas the 'bad drug effect' rating was significantly increased *only* by MDMA. The negative effects of acute MDMA included blurred vision, difficulty in concentration, confusion, chills, and sweating, whereas these effects were not reported after methamphetamine (Table 2 in Kirkpatrick *et al*., 2012). The authors concluded that 'Single oral doses of methamphetamine and MDMA produced many overlapping, prototypical stimulant effects. Both drugs increased cardiovascular activity and ratings of stimulation and euphoria, while they decreased food intake. The drugs did however produce differences on some measures ... only methamphetamine improved cognitive performance and increased self-reported desire to take the drug again, whereas only MDMA increased negative subjective-effect ratings'. In summary, the closest drugs to Ecstasy/MDMA in terms of basic physiological effects and neuropsychobiological harm scores are other recreational stimulants such as cocaine and methamphetamine (Williamson *et al*., 1997; Kirkpatrick *et al*., 2012; Soar *et al*., 2012). Currently, there is insufficient empirical evidence to compare it with more novel psychoactive substances, such as mephedrone.

FUTURE RESEARCH

One topic of interest is the marked individual differences in reactions to MDMA. It remains unclear why some individuals show strong physiological abreactions to small doses of MDMA, namely, strong serotonin syndrome, medical emergencies, and death, whereas other individuals are more robust. There is also variance in the acute mood reactions, with powerful euphoria in some, moderate mood gains in others, and occasional negative responses. Setting and environment, the extent of dancing/exercise, overheating, and drug stacking/bingeing may be important factors. Gender, expectancy, personality profiles, psychiatric predispositions, and genetic vulnerabilities all need to be further studied. Co-drug use can also modulate the effects of MDMA in subtle but important ways. Although there are some empirical data on all these topics, they all need to be further investigated.

The development of chronic tolerance also needs to be better understood, with considerable individual variation in this phenomenon, similar to those factors influencing the development of neurotoxicity. The bio-energetic stress model proposes that any chronic damage will reflect the accumulation of individual sessions of acute distress (Parrott, 2006). Hence, the extent of metabolic cellular damage will reflect cumulative dosage, bingeing, frequency of use, and environmental co-stimulation (Parrott, 2004, 2009). There may be some potential collaborations between neurotoxicity studies in recreational users and investigations into apoptosis and cell death in oncology (cancer therapy) research. There are also many questions around drug cessation. The cost–benefit ratio may provide a useful model for studying how and why users decide to quit. In psychiatric terms, the ways in which MDMA can heighten psychiatric stress need to be

Table 3. Comparison of neurocognitive performance and self-rated moods in recreational cocaine and Ecstasy/MDMA users: overview of three pilot studies (after Parrott *et al*., 2011a, 2011b)

	Control group	Control/alcohol	Cocaine/MDMA	Cocaine	MDMA
Study 1: by Lauren Evans, memory and cognition					
Dysexecutive Questionnaire (problem score)	22.1		38.2***		37.1**
Consonant updating (correct recall)	3.2		3.1		2.1
Random letter (number generated—two per second)	98.1		83.1***		96.6
Supraspan word recall (total words)	31.1		29.9		27.9
Study 2: by James Howell, self-rated mood states					
Excitement (on drug)		3.6		4.0	4.7*
Paranoia (on drug)		1.5		3.0*	2.5
Clearheadedness (on drug)		3.0		3.1	1.8*
Aggression (on drug)		2.3		3.1	1.5
Overheating (on drug)		2.5		3.5*	3.9**
Depressed (post-drug recovery)		2.1		2.7	3.2*
Paranoia (post-drug recovery)		1.6		2.6*	3.6***
Sociableness (post-drug recovery)		3.7		3.1	2.3**
Clearheadedness (post-drug recovery)		3.8		3.3	2.1**
Study 3: by Rebecca Robart, memory and cognition					
Rivermead Behavioural Memory (info recall)	9.9			9.2	8.9
Auditory verbal learning task (words learned)	9.4			8.0	7.2*
Trail making (task completion time)	15.9			19.9	21.4**

Tukey paired comparison tests with control group (two tailed).
*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

DOI: 10.1002/hup

further studied, with pre-morbid factors a key factor. More generally, EEG and ERP studies have proven very useful in the past few years, and they provide an inexpensive method for research into the brain–behaviour interface. The greatest gain in knowledge is likely to arise from prospective neuroimaging studies on high-risk individuals. Here, the structural measures will need to be complemented by an extensive battery of functional assessments, covering every neuropsychobiological function with a serotonergic component (Table 1).

OVERVIEW

The main lesson from this review is that it can take many years of research to reveal the damaging neuropsychobiological effects of a new psychoactive substance (Table 1). The first reports of psychobiological problems with MDMA were individual case studies of memory deficits, followed by the first group study (Krystal *et al*., 1992). These were confirmed in later cohort studies, and there are now numerous studies in this area (Laws and Kokkalis, 2007; Rogers *et al*., 2009). The first reports of retrospective memory deficits emerged in the early 2000s, and with many subsequent confirmations, this comprises an archetypal disorder for Ecstasy/MDMA users, as it involves both memory and cognitive control (Heffernan *et al*., 2001; Montgomery *et al*., 2010). Another key area of deficit is higher cognitive functioning (Table 1), but again, this has only emerged from research undertaken in the past 10 years (Fox *et al*., 2002; Reay *et al*., 2006). Psychiatric status can also be impaired and was one of the first types of dysfunction to be described. This was not covered in the present article, as it is being reviewed elsewhere (Parrott, in preparation). The following comprises a brief selection of studies showing enhanced psychiatric symptoms and distress (McCann and Ricaurte, 1991; Schifano *et al*., 1998; Parrott *et al*., 2000, 2001; MacInnes *et al*., 2001; Soar *et al*., 2001; Morgan *et al*., 2002; Roiser and Sahakian, 2004; Parrott, 2006; Brière *et al*., 2012). Another key area of growth over the past 15 years has been in neuroimaging and EEG/ERP studies, and they have documented a range of adverse effects on brain functioning (McCann *et al*., 1998, 2008; Kish *et al*., 2010; Burgess *et al*., 2011; Erritzoe *et al*., 2011; Di Iorio *et al*., 2012). Several areas of deficit have only emerged in the past 10 years, for instance vision, pain, meta-cognition, sleep apnoea, and immunocompetence; however, the empirical data on all these functions remain very limited. The hypothalamic–pituitary–adrenal axis, cortisol, oxytocin, and other neurohormones also need to be further studied. Cardiac, hepatic, renal, and lung functioning have hardy been studied, and they all need to be investigated. More fundamentally, basic cellular integrity and core metabolic processing may also be damaged (Parrott, 2006). Finally, there is novel evidence for the adverse effects of Ecstasy/MDMA during pregnancy (Singer *et al*., 2012b).

CONFLICT OF INTEREST

The author has declared no conflict of interest.

REFERENCES

Allen RP, McCann UD, Recourse GA. 1993. Persistent effects of (+/−) 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") on human sleep. *Sleep* **16**: 560–564.

Back-Madruga C, Boone KB, Chang L, *et al*. 2003. Neuropsychological effects of 3,4-methylenedioxymethamphetamine (MDMA or ecstasy) in recreational users. *Clin Neuropsychol* **17**: 446–459.

Bedi G, de Wit H. 2011. Individual differences in acute responses to MDMA in humans: effects of sex and past ecstasy use. *Open Addict Jour* **4**: 6–7.

Bedi G, Hyman D, de Wit H. 2010. Is ecstasy an empathogen? Effects of 3,4-methylenedioxymethamphetamine on prosocial feelings and identification of emotional states in others. *Biol Psychiat* **68**: 1134–1140.

Benningfield MM, Cowan RL. 2013. Brian serotonin function in MDMA (Ecstasy) users: evidence for persisting neurotoxicity. *Neuropsychopharmacology* **38**: 253–255

Berger UV, Gu XF, Azmitia EC. 1992. The substituted amphetamines 3,4 methylenedioxymethamphetamine, methamphetamine, para-chloroamphetamine and fenfluramine induce 5-hydroxytryptamine release via a common mechanism blocked by fluoxetine and cocaine. *Eur Jour Pharmacol* **215**: 153–160.

Biezonski DK, Meyer JS. 2011. The nature of 3, 4-methylenedioxymethamphetamine (MDMA)-induced serotonergic dysfunction: evidence for and against the neurodegeneration hypothesis. *Curr Neuropharmacol* **9**: 84–90.

Bolla KI, McCann UD, Ricaurte GA. 1998. Memory impairment in abstinent MDMA ("Ecstasy") users. *Neurology* **51**: 1532–1537.

Brière FN, Fallu JS, Janosz M, Pagani LS. 2012. Prospective associations between meth/amphetamine (speed) and MDMA (Ecstasy) use and depressive symptoms in secondary school students. *Jour Epidemiol Community Health* **66**: 990–994.

Burgess AP, Venables L, Jones H, Edwards R, Parrott AC. 2011. Event related potential (ERP) evidence for selective impairment of verbal recollection in abstinent recreational methylenedioxymethamphetamine ("Ecstasy")/polydrug users. *Psychopharmacology* **216**: 545–556.

Cadet JL, Krasnova IN, Jayanthi S, Lyles J. 2007. Neurotoxicity of substituted amphetamines: molecular and cellular mechanisms. *Neurotox Res* **11**: 183–202.

Cami J, Farré M, Mas M, *et al*. 2000. Human pharmacology of 3,4-methylenedioxymethamphetamine ("ecstasy"): psychomotor performance and subjective effects. *Jour Clin Psychopharmacol* **20**: 455–466.

Cohen RS. 1998. The Love Drug: Marching to the Beat of Ecstasy. Haworth Medical Press: New York State.

Cole JC, Bailey M, Sumnall HR, Wagstaff GF, King LA. 2002. The contents of ecstasy tablets: implications for the study of their long-term effects. *Addiction* **97**: 1531–1536.

Cowan RL. 2007. Neuroimaging research in human MDMA users: a review. *Psychopharmacology* **189**: 539–556.

Cowan RL, deB Frederick B, Haga E, *et al*. 2001. Visual cortex activation using the fMRI BOLD method in human MDMA (ecstasy) users. In: MDMA/Ecstasy Research: Advances, Challenges, and Future Directions. NIDA Conference, Bethesda, MD, USA, July 2001, Conference Abstract, p. 46.

Curran HV, Travill RA. 1997. Mood and cognitive effects of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"): weekend "high" followed by mid-week "low". *Addiction* **92**: 821–831.

Dastrup E, Lees MN, Bechara A, Dawson JD, Rizzo M. 2010. Risky car following in abstinent users of MDMA. *Accid Anal Prevent* **42**: 867–873.

Daumann J, Fischermann T, Heekeren K, Henke K, Thron A, Gouzoulis-Mayfrank E. 2005. Memory-related hippocampal dysfunction in poly-drug ecstasy (3,4-methylenedioxymethamphetamine) users. *Psychopharmacology* **180**: 607–611.

Davison D, Parrott AC. 1997. Ecstasy in recreational users: self-reported psychological and physiological effects. *Hum Psychopharmacol* **12**: 91–97.

Degenhardt L, Hall W. 2009. The health and psychological effects of "ecstasy" (MDMA) use. NDARC monograph, no. 62, University of New South Wales, Australia.

Di Iorio CR, Watkins TJ, Dietrich MS, *et al*. 2012. Evidence for chronically altered serotonin function in the cerebral cortex of female 3,4-methylenedioxymethamphetamine polydrug users. *Arch Gen Psychiatry* **69**: 399–409.

Dickson C, Bruno R, Brown J. 2009. Investigating the role of serotonin in visual orientation processing using an 'ecstasy' (MDMA)-based research model. *Neuropsychobiology* **60**: 204–212.

Doblin R. 2002. A clinical plan for MDMA (Ecstasy) in the treatment of posttraumatic stress disorder (PTSD): partnering with the FDA. *Jour Psychoact Drugs* **34**: 185–194.

Doblin R. 2011. The use of MDMA for psychotherapy. Breaking Convention Conference, Kent University, UK, April 2011.

Dumont GJ, Verkes RJ. 2006. A review of acute effects of 3,4-methylenedioxymethamphetamine in healthy volunteers. *Jour Psychopharmacol* **20**: 176–187.

EMCDDA. 2010. The European Monitoring Centre for Drugs and Drug Addiction annual report 2010: state of the drugs problem in Europe. Europ Surveill, vol 15.

Erritzoe D, Frokjaer VG, Holst KK, *et al*. 2011. In vivo imaging of cerebral serotonin transporter and serotonin (2A) receptor binding in 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") and hallucinogen users. *Arch Gen Psychiat* **68**: 562–576.

Fisk JE, Montgomery C, Wareing, Murphy PN. 2005. Reasoning deficits in Ecstasy (MDMA) polydrug users. *Psychopharmacology* **181**: 550–559.

Fox H, Parrott AC, Turner JJD. 2001. Ecstasy/MDMA related cognitive deficits: a function of dosage rather than awareness of problems. *Jour Psychopharmacol* **15**: 273–281.

Fox HC, McLean A, Turner JJD, Parrott AC, Rogers R, Sahakian BJ. 2002. Neuropsychological evidence of a relatively selective profile of temporal dysfunction in drug-free MDMA ("ecstasy") polydrug users. *Psychopharmacology* **162**: 203–214.

Freedman RR, Johanson CE, Tancer ME. 2005. Thermoregulatory effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology* **183**: 248–256.

Gerra G, Bassignana S, Zaimovic A, *et al*. 2003. Hypothalamic–pituitary–adrenal axis responses to stress in subjects with 3,4-methylenedioxymethamphetamine ('ecstasy') use high correlation with dopamine receptor sensitivity. *Psychiat Res* **30**: 115–124.

Gerra G, Kaimovic A, Guicastro G, *et al*. 1998. Serotonergic function after 3,4-methylenedioxymethamphetamine. *Internat Clin Psychopharmacol* **13**: 1–9.

Green AR, Cross AJ, Goodwin GM. 1995. Review of the pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA or ecstasy). *Psychopharmacology* **119**: 247–260.

Green AR, Mechan AO, Elliott JM, O'Shea E, Colado MI. 2003. The pharmacology and clinical pharmacology of 3,4-methylenedioxymethamphetamine (MDMA, "ecstasy"). *Pharmacol Revs* **55**: 463–508.

Green AR, King MV, Shortall SE, Fone KCF. 2012. Lost in translation: preclinical studies on 3,4-methylenedioxymethamphetamine provide information on mechanisms of action, but do not allow accurate prediction of adverse events in humans. *Brit Jour Pharmacol* **166**: 1523–1526.

Greene SL, Wood DM, Dargan PI. 2009. Epidemiological and clinical characteristics of acute MDMA related presentations to an inner city London Emergency Department. *Neuropsychobiology* **60**: 214.

Greer G, Tolbert R. 1986. Subjective reports of the effects of MDMA in a clinical setting. *Jour Psychoact Drugs* **18**: 319–327.

Hadjiefthyvoulou F, Fisk JE, Montgomery C, Bridges N. 2011a. Everyday and prospective memory deficits in ecstasy/polydrug users. *J Psychopharmacol* **25**: 453–464.

Hadjiefthyvoulou F, Fisk JE, Montgomery C, Bridges N. 2011b. Prospective memory functioning among ecstasy/polydrug users: evidence from the Cambridge Prospective Memory Test (CAMPROMPT). *Psychopharmacology* **215**: 761–774.

Hall AP, Henry JA. 2006. Acute toxic effects of 'Ecstasy' (MDMA) and related compounds: overview of pathophysiology and clinical management. *Brit Jour Anaesth* **96**: 678–685.

Halpern JH, Pope HG, Sherwood AR, Barry S, Hudson JI, Yurgelun-Todd D. 2004. Residual effects of illicit 3,4-methylenedioxymethamphetamine in individuals with minimal exposure to other drugs. *Drug Alcohol Depend* **75**: 135–147.

Halpern JH, Sherwood AR, Hudson JI, Gruber S, Kozin D, Pope HG. 2011. Residual features of long term ecstasy use with minimal exposure to other drugs. *Addiction* **106**: 777–786.

Hammersley R, Ditton J, Smith I, Short E. 1999. Patterns of ecstasy use by drug users. *Brit Jour Criminol* **39**: 625–647

Harris DS, Baggott M, Mendelson JH, Mendelson JE, Jones RT. 2002. Subjective and hormonal effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology* **162**: 396–405.

Heffernan TM, Jarvis H, Rodgers J, Scholey AB, Ling J. 2001. Prospective memory, everyday cognitive failures, and central executive function in recreational users of ecstasy. *Hum Psychopharmacol* **16**: 607–612.

Hegadoren KM, Baker GB, Bourin M. 1998. 3,4-Methylenedioxy analogues of amphetamine: defining the risks to humans. *Neurosci Biobehav Revs* **23**: 539–553.

Henry JA, Jeffries KJ, Dawling S. 1992. Toxicity and deaths from 3,4-methylenedioxymethamphetamine ("Ecstasy"). *Lancet* **340**: 384–387.

Hopper JW, Su Z, Looby AR, *et al*. 2006. Incidence and patterns of polydrug use and craving for ecstasy in regular ecstasy users: an ecological momentary assessment study. *Drug Alcohol Depend* **85**: 221–235.

Huether G, Zhou D, Ryuther E. 1997. Causes and consequences of the loss of serotonergic presynapses elicited by the consumption of 3,4 methylenedioxymethamphetamine (MDMA, "'ecstasy"') and its congeners. *Jour Neural Transmiss* **104**: 771–794.

Jacobsen LK, Mencl WE, Pugh KR, Skudlarski P, Krystal JH. 2004. Preliminary evidence of hippocampal dysfunction in adolescent MDMA ("ecstasy") users: possible relationship to neurotoxic effects. *Psychopharmacology* **173**: 383–390.

Jansen KLR. 1999. Ecstasy (MDMA) dependence. *Drug Alcohol Depend* **53**: 121–124.

Jones KA, Callan F, Blagrove MT, Parrott AC. 2008. Sleep, energy and self-rated cognition across 7 nights following recreational ecstasy/MDMA use. *Sleep and Hypnosis* **10**: 16–28.

Kalant H. 2001. The pharmacology and toxicology of "ecstasy" (MDMA) and related drugs. *Canad Med Assn Jour* **165**: 17–28.

Karageorgiou J, Dietrich MS, Charboneau EJ, *et al*. 2009. Prior MDMA (Ecstasy) use is associated with increased basal ganglia-thalamocortical circuit activation during motor task performance in humans: an fMRI study. *Neuroimage* **46**: 817–826.

Kirkpatrick MG, Gunderson EW, Perez AY, Haney M, Foltin RW, Hart CL. 2012.A direct comparison of the behavioral and physiological effects of methamphetamine and 3,4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology* **219**: 109–22.

Kish SJ, Lerch J, Furukawa Y, *et al*. 2010. Decreased cerebral cortical serotonin transporter binding in ecstasy users: a positron emission tomography/[(11)C]DASB and structural brain imaging study. *Brain* **133**: 1779–1797.

Kopelman MD, Reed LJ, Marsden P, *et al*. 2001. Amnesic syndrome and severe ataxia following the recreational use of 3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy') and other substances. *Neurocase* **7**: 423–432.

Krul J, Girbes AR, Sanou BT. 2012. Increase in serious ecstasy-related incidents in the Netherlands. *Lancet* **380**: 1385.

Krystal JH, Price LH, Opsahl C, Ricaurte GA, Heninger GR. 1992. Chronic 3,4-methylenedioxymethamphetamine (MDMA) use: effects on

mood and neuropsychological function? *Amer Jour Drug Alcohol Abuse* **18**: 331–341.

Laws KR, Kokkalis J. 2007. Ecstasy (MDMA) and memory function: a meta-analytic update. *Hum Psychopharmacol* **22**: 381–388.

Liechti ME, Gamma A, Vollenweider FX. 2001. Gender differences in the subjective effects of MDMA. *Psychopharmacology* **154**: 161–168.

MacInnes N, Handley SL, Harding GF. 2001. Former chronic methylenedioxymethamphetamine (MDMA or ecstasy) users report mild depressive symptoms. *Jour Psychopharmacol* **15**: 181–186.

McCann UD, Slate SO, Ricaurte GA. 1996. Adverse reactions with 3,4-methelenedioxymethamphetamine (MDMA: 'ecstasy'). *Drug Saf* **15**: 107–115.

Mc Cann UD, Szabo Z, Vranesic M, *et al*. 2008. Positron emission tomographic studies of brain dopamine and serotonin transporters in abstinent (+/−)3,4-methylenedioxymethamphetamine ("ecstasy") users: relationship to cognitive performance. *Psychopharmacology* **200**: 439–450.

McCann UD, Ricaurte GA. 1991. Lasting neuropsychiatric sequelae of (+/−) methylenedioxymethamphetamine ('Ecstasy') in recreational users. *Jour Clin Psychopharmacol* **11**: 302–305.

McCann UD, Ricaurte GA. 2007. Effects of (+/−) 3,4-methylenedioxymethamphetamine (MDMA) on sleep and circadian rhythms. *Scient World Jour* **2**: 231–238.

McCann UD, Szabo Z, Scheffel U, Dannals RF, Ricaurte GA. 1998. Positron emission tomographic evidence of toxic effect of MDMA ("Ecstasy") on brain serotonin neurones in human beings. *Lancet* **352**: 1433–1437.

McCann UD, Mertl M, Eligulashvili V, Ricaurte GA. 1999. Cognitive performance in (+/−)3,4-methylenedioxymethamphetamine (MDMA, "ecstasy") users: a controlled study. *Psychopharmacology* **143**: 417–425.

McCann UD, Sgambati FP, Schwartz AR, Ricaurte GA. 2009. Sleep apnea in young abstinent recreational MDMA ("ecstasy") consumers. *Neurology* **73**: 2011–2017.

McDowell DM, Kleber HD. 1994. MDMA: its history and pharmacology. *Psychiat Annals* **24**: 127–130.

McElhatton PR, Bateman DN, Evans C, Pughe KR, Thomas SH. 1999. Congenital anomalies after prenatal ecstasy exposure. *Lancet* **354**: 1441–1442.

Mithoefer MC, Wagner MT, Mithoefer AT, Jerome L, Doblin R. 2011. The safety and efficacy of +/−3,4-methylenedioxymethamphetamine assisted psychotherapy in subjects with chronic, treatment-resistant posttraumatic stress disorder: the first randomized controlled pilot study. *Jour Psychopharmacol* **25**: 439–452.

Montgomery C, Hatton NP, Fisk JE, Ogden RS, Jansari A. 2010. Assessing the functional significance of ecstasy-related memory deficits using a virtual reality paradigm. *Hum Psychopharmacol* **25**: 318–325.

Montiel-Duarte C, Varela-Rey M, Oses-Prieto JA, *et al*. 2002. 3,4-Methylenedioxymethamphetamine ("Ecstasy") induces apoptosis of cultured rat liver cells. *Biochim Biophys Acta* **1588**: 26–32.

Morefield KM, Keane M, Felgate P, White JM, Irvine RJ. 2009. The acute psychobiological impacts of illicit 3,4-methylenedioxymethamphetamine (MDMA, 'Ecstasy') consumption in recreational environments. *Neuropsychobiology* **60**: 216–217.

Morgan MJ. 1999. Memory deficits associated with recreational use of "ecstasy" (MDMA). *Psychopharmacology* **141**: 30–36.

Morgan MJ. 2000. Ecstasy (MDMA): a review of its possible persistent psychological effects. *Psychopharmacology* **152**: 230–248

Morgan MJ, McFie L, Fleetwood LH, Robinson JA. 2002. Ecstasy (MDMA): are the psychological problems associated with its use reversed by prolonged abstinence? *Psychopharmacology* **159**: 294–303.

Murphy PN, Wareing M, Fisk JE, Montgomery C. 2009. Executive working memory deficits in abstinent ecstasy/MDMA users: a critical review. *Neuropsychobiology* **60**: 159–175.

Murphy PN, Bruno R, Ryland L, *et al*. 2012. The effects of 'ecstasy' (MDMA) on visuospatial memory performance: findings from a systematic review with meta-analyses. *Hum Psychopharmacol* **27**: 113–138.

Nichols DE. 1986. Differences between the mechanism of action of MDMA, MBDB, and the classic hallucinogens. Identification of a new therapeutic class: entactogens. *J Psychoact Drugs* **18**: 305–313.

Nutt D, King la, Saulsbury W, Blakemore C. 2007. Development of a rational scale to assess the harm of drugs of potential misuse. *Lancet* **369**: 1047–1053.

Parrott AC. 2000. Human research on MDMA (3,4-methylenedioxymethamphetamine) neurotoxicity: cognitive and behavioural indices of change. *Neuropsychobiology* **42**: 17–24.

Parrott AC. 2001. Human psychopharmacology of Ecstasy (MDMA): a review of fifteen years of empirical research. *Hum Psychopharmacol* **16**: 557–577.

Parrott AC. 2002. Recreational Ecstasy/MDMA, the serotonin syndrome, and serotonergic neurotoxicity. *Pharmacol Biochem Behav* **71**: 837–844

Parrott AC. 2004a. Is Ecstasy MDMA? A review of the proportion of ecstasy tablets containing MDMA, dosage levels, and the changing perceptions of purity. *Psychopharmacology* **173**: 234–241.

Parrott AC. 2004b. MDMA (3,4-methylenedioxymethamphetamine) or Ecstasy: the neuropsychobiological implications of taking it at dances and raves. *Neuropsychobiology* **50**: 329–335.

Parrott AC. 2005. Chronic tolerance to recreational MDMA (3,4-methylenedioxymethamphetamine) or Ecstasy. *Jour Psychopharmacol* **19**: 71–83.

Parrott AC. 2006. MDMA in humans: factors which affect the neuropsychobiological profiles of recreational Ecstasy users, the integrative role of bio-energetic stress. *Jour Psychopharmacol* **20**: 147–163.

Parrott AC. 2007a. The psychotherapeutic potential of MDMA (3,4-methylenedioxymethamphetamine): an evidence-based review. *Psychopharmacology* **191**: 181–193.

Parrott AC. 2007b. How harmful is Ecstasy/MDMA: a empirical evaluation using the 'Lancet' scale for drug-related harm. *Jour Psychopharmacol* **23**: a41.

Parrott AC. 2008. *Drug taking—for better or for worse? Psychologist* **21**: 924–927.

Parrott AC. 2009. Cortisol and MDMA (3,4-methylenedioxymethamphetamine): neurohormonal aspects of bioenergetic-stress in Ecstasy users. *Neuropsychobiology* **60**: 148–158.

Parrott AC. 2010. Conscious awareness versus optimistic beliefs in recreational Ecstasy/MDMA users. In New Horizons in the Neuroscience of Consciousness, Perry E, Collerton D, LeBeau F, Ashton HE (eds). John Benjamins Publishers: Amsterdam.

Parrott AC. 2011. Residual neurocognitive features of Ecstasy use: a reinterpretation of Halpern *et al*. (2011) consistent with serotonergic neurotoxicity. *Addiction* **106**: 1365–1368.

Parrott AC. 2012a. MDMA and temperature: a review of the thermal effects of 'Ecstasy' in humans. *Drug Alcohol Depend* **121**: 1–9.

Parrott AC. 2012b. MDMA and 5-HT neurotoxicity: the empirical evidence for its adverse effects in humans—no need for translation. *Brit Jour Pharmacol* **166**: 1518–1520.

Parrott AC. 2013. MDMA, serotonergic neurotoxicity, and the diverse functional deficits of recreational Ecstasy users. *Neurosci Biobehav Revs* (in press).

Parrott AC, Lasky J. 1998. Ecstasy (MDMA) effects upon mood and cognition; before, during, and after a Saturday night dance. *Psychopharmacology* **139**: 261–268.

Parrott AC, Lees A, Garnham NJ, Jones M, Wesnes K. 1998. Cognitive performance in recreational users of MDMA or "ecstasy": evidence for memory deficits. *Jour Psychopharmacol* **12**: 79–83.

Parrott AC, Sisk E, Turner J. 2000. Psychobiological problems in heavy 'ecstasy' (MDMA) polydrug users. *Drug Alc Depend* **60**: 105–110.

Parrott AC, Milani RM, Gouzoulis-Mayfrank E, Daumann J. 2007. Cannabis and Ecstasy/MDMA (3,4-methylenedioxymethamphetamine): an analysis of their neuropsychobiological interactions in recreational users. *J Neural Transm* **114**: 959–968.

Parrott AC, Milani RM, Parmar R, Turner JJD. 2001. Recreational Ecstasy/MDMA and other drug users form the UK and Italy: psychiatric symptoms and psychobiological problems. *Psychopharmacology* **159**: 77–82.

Parrott A, Morinan A, Moss M, Scholey A. 2004. Understanding Drugs and Behaviour. Wiley: Chichester.

Parrott AC, Rodgers J, Buchanan T, Ling J, Heffernan T, Scholey AB. 2006. Dancing hot on ecstasy: physical activity and thermal comfort ratings are associated with the memory and other psychobiological problems of recreational MDMA users. *Hum Psychopharmacol* **21**: 285–298.

Parrott AC, Lock J, Conner AC, Kissling C, Thome J. 2008. Dance clubbing on MDMA and during abstinence from Ecstasy/MDMA: prospective neuroendocrine and psychobiological changes. *Neuropsychobiology* **57**: 165–180.

Parrott AC, Gibbs A, Scholey AB, *et al*. 2011a. MDMA and methamphetamine: some paradoxical negative and positive mood changes in an acute dose laboratory study. *Psychopharmacology* **215**: 527–536.

Parrott AC, Evans LJ, Howells J, Robart R. 2011b. Cocaine versus Ecstasy/MDMA: comparative effects on mood and cognition in recreational users. *Open Addiction Journal* **4**: 36–37.

Parrott AC, Jones L, Sands HR, *et al*. 2012. High cortisol levels in recent Ecstasy/MDMA users: preliminary findings from the Swansea, Westminster and Dresden collaborative study. Psychobiology Section of the British Psychological Society Annual Scientific Meeting, Conference Abstract, p. 14.

Peroutka SJ. 1989. 'Ecstasy': a human neurotoxin? *Arch Gen Psychiat* **46**: 191.

Peroutka SJ, Newman H, Harris H. 1988. Subjective effects of 3,4-methylenedioxymethamphetamine in recreational users. *Neuropsychopharmacology* **1**, 273–277.

Puerta E, Hervias I, Aguirre N. 2009. On the mechanisms underlying 3,4-methylenedioxymethamphetamine toxicity: the dilemma of the chicken and the egg. *Neuropsychobiology* **60**: 119–129.

Quednow BB, Kuhn KU, Hoenig K, Maier W, Wagner M. 2004. Prepulse inhibition and habituation of acoustic startle response in male MDMA ('Ecstasy') users, cannabis users, and healthy controls. *Neuropsychopharmacology* **29**: 982–990.

Reay JL, Hamilton C, Kennedy DO, Scholey AB. 2006. MDMA polydrug users show process-specific central executive impairments coupled with impaired social and emotional judgement processes. *Jour Psychopharmacol* **20**: 385–388.

Rendell PG, Gray TJ, Henry JD, Tolan A. 2007. Prospective memory impairment in "ecstasy" (MDMA) users. *Psychopharmacology* **194**: 497–504.

Reneman L, de Win MM, van den Brink W, Booij J, den Heeten GJ. 2006. Neuroimaging findings with MDMA/ecstasy: technical aspects, conceptual issues and future prospects. *Jour Psychopharmacol* **20**: 164–175.

Renfroe CL. 1986. MDMA on the street: analysis anonymous. *Jour Psychoact Drugs* **18**: 363–369.

Riahi S, Eynollahi S, Ganjali MR. 2010. Computational studies on effects of MDMA as an anticancer drug on DNA. *Chem Biol Drug Des* **76**: 425–432.

Ricaurte GA, Yuan J, McCann UD. 2000. (+/−)3,4-methylenedioxymethamphetamine (MDMA, "ecstasy")-induced serotonin neurotoxicity: studies in animals. *Neuropsychobiology* **42**: 5–10

Rizzo M, Lamers CTJ, Sauer CG, Ramaekers JG, Bechara A, Anderson GJ. 2005. Impaired perception of self-motion (heading) in abstinent ecstasy and marijuana users. *Psychopharmacology* **179**: 559–566.

Roberts GM, Nestor L, Garavan H. 2009. Learning and memory deficits in ecstasy users and their neural correlates during a face-learning task. *Brain Res* **1292**: 71–81.

Rodgers J. 2000. Cognitive performance amongst recreational users of "ecstasy". *Psychopharmacology* **151**: 19–24.

Rodgers J, Buchanan T, Scholey AB, Heffernan TM, Ling J, Parrott AC. 2003. Patterns of drug use and the influence of gender on self reports of memory ability in ecstasy users: a Web based study. *Jour Psychopharmacol* **17**: 379–386.

Rogers G, Elston J, Garside R, *et al*. 2009. The harmful health effects of recreational ecstasy: a systematic review of observational evidence. *Health Technol Assess* **13**: 1–315.

Roiser JP, Sahakian BJ. 2004. Relationship between ecstasy use and depression: a study controlling for poly-drug use. *Psychopharmacology* **173**: 411–417.

Rosenson J, Smollin C, Sporer KA, Blanc P, Olson KR. 2007. Patterns of ecstasy-associated hyponatremia in California. *Ann Emerg Med* **49**: 164–171.

Saunders N. 1997. Ecstasy Reconsidered. Turnaround: London.

Schifano F. 2000. Potential human neurotoxicity of MDMA ('ecstasy'): subjective self-reports, evidence from an Italian drug addiction centre and clinical case studies. *Neuropsychobiology* **42**: 25–33.

Schifano F, Magni G. 1994. MDMA ('ecstasy') abuse: psychopathological features and craving for chocolate: a case series. *Biol Psychiat* **36**: 763–767.

Schifano F, Di Furia L, Forza G, Minicuci N, Bricolo R. 1998. MDMA ('ecstasy') consumption in the context of polydrug abuse: a report on 150 patients. *Drug Alcohol Depend* **52**: 85–90.

Schifano F, Oyefeso A, Webb L, Pollard M, Corkery J, Ghodse AH. 2003. Review of deaths related to taking ecstasy, England and Wales, 1997–2000. *Brit Med Jour* **326**: 8–81.

Schifano F, Corkery J, Naidoo V, Oyefeso A, Ghodse AH. 2010. Overview of amphetamine-type stimulant mortality data UK, 1997–2007. *Neuropsychobiology* **61**: 122–130.

Scholey AB, Parrott AC, Buchanan T, Heffernan T, Ling J, Rodgers J. 2004. Increased intensity of Ecstasy and polydrug usage in the more experienced recreational Ecstasy/MDMA users: a www study. *Addictive Behav* **29**: 743–752.

Scholey AB, Owen L, Gates J, *et al*. 2011. Hair MDMA samples are consistent with reported Ecstasy use: findings from an Internet study investigating effects of Ecstasy on mood and memory. *Neuropsychobiology* **63**: 15–21.

Shulgin AT. 1986. The background and chemistry of MDMA. *Jour Psychoact Drugs* **18**: 291–304.

Simantov R. 2004. Multiple molecular and neuropharmacological effects of MDMA (Ecstasy). *Life Sci* **74**: 803–814.

Singer LT, Linares TJ, Ntiri S, Henry R, Minnes S. 2004. Psychosocial profiles of older adolescent MDMA users. *Drug Alcohol Depend* **74**: 245–252.

Singer LT, Moore DG, Fulton S, *et al*. 2012a. Neurobehavioral outcomes of infants exposed to MDMA (Ecstasy) and other recreational drugs during pregnancy. *Neurotoxicol Teratol* **34**: 303–310.

Singer LT, Moore DG, Min MO, *et al*. 2012b. One-year outcomes of prenatal exposure to MDMA and other recreational drugs. *Pediatrics* **130**: 407–413.

Smith ID, Simpson KJ, Garden OJ, Wigmore SJ. 2005. Non-paracetamol drug-induced fulminant hepatic failure among adults in Scotland. *Eur Jour Gastroenterol Hepatol* **17**: 161–167.

Soar K, Turner JJD, Parrott AC. 2001. Psychiatric disorders in Ecstasy (MDMA) users: a literature review focusing upon personal predispositions and drug histories. *Hum Psychopharmacol* **16**: 641–645.

Soar K, Mason C, Potton A, Dawkins L. 2012. Neuropsychological effects associated with recreational cocaine use. *Psychopharmacology* **222**: 633–643.

Solowij N, Hall W, Lee N. 1992. Recreational MDMA use in Sydney: a profile of ecstasy users and their experiences with the drug. *Brit Jour Addict* **87**: 1161–1172.

Spruit IP. 2001. Monitoring synthetic drug markets, trends and public health. *Subst Use Misuse* **36**: 23–47.

Steele TD, McCann UD, Ricaurte GA. 1994. 3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy"): pharmacology and toxicology in animals and humans. *Addiction* **89**: 539–551.

Stough C, Downey LA, King R, Papafotiou K, Swann P, Ogden E. 2012. The acute effects of 3,4-methylenedioxymethamphetamine and methamphetamine on driving: a simulator study. *Accid Anal Prev* **45**: 493–497.

Suy K, Gijsenbergh F, Baute L. 1999. Emergency medical assistance during a mass gathering. *Eur Jour Emerg Med* **6**: 249–254.

Tancer M, Johanson CE. 2007. The effects of fluoxetine on the subjective and physiological effects of 3,4-methylenedioxymethamphetamine (MDMA) in humans. *Psychopharmacology* **189**: 565–573.

Topp L, Hando J, Dillon P, Roche A, Solowij N. 1999. Ecstasy use in Australia: patterns of use and associated harm. *Drug Alcohol Depend* **55**: 105–115.

Van Dijken GD, Blom RE, Hene RJ, Boer WH. 2013. High incidence of mild hyponatraemia in females using ecstasy at a rave party. Nephrol Dial Transplant [March 8 epub].

Verheyden SL, Maidment R, Curran HV. 2003. Quitting ecstasy: an investigation of why people stop taking the drug and their subsequent mental health. *Jour Psychopharmacol* **17**: 371–378.

Verkes RJ, Gigsman HJ, Pieters MSM, Schoemaker RC, de Visser S, Kuijpers M. 2001. Cognitive performance and serotonergic function in users of Ecstasy. *Psychopharmacology* **53**: 196–202.

Vogels N, Brunt TM, Rigter S, van Dijk P, Vervaeke H, Niesink RJ. 2009. Contents of ecstasy in the Netherlands: 1993–2008. *Addiction* **104**: 2057–2066.

Vollenweider FX, Gamma A, Liechti M, Huber T. 1998. Psychological and cardiovascular effects and short-term sequelae of MDMA ("Ecstasy") in MDMA-naive healthy humans. *Neuropsychopharmacology* **19**: 241–251.

Wasik AM, Gandy MN, Mclldowie M, *et al*. 2011. Enhancing the antilymphoma potential of 3,4-methylenedioxymethamphetamine ('ecstasy')

through iterative chemical redesign: mechanisms and pathways to cell death. *Invest New Drugs* **30**: 1471–1483.
Webb E, Ashton CH, Kelly P, Kamali F. 1996. Alcohol and drug use in UK university students. *Lancet* **348**: 922–925.
Williamson S, Gossop M, Powis B, Griffiths P, Fountain J, Strang J. 1997. Adverse effects of stimulant drugs in a community sample of drug users. *Drug Alc Depend* **44**: 87–94.
Winstock AR. 1991. Chronic paranoid psychosis after misuse of MDMA. *Brit Med Jour* **302**:1150–1151.
Winstock AR, Griffiths P, Stewart D. 2001. Drugs and the dance music scene: a survey of current drug use patterns among a sample of dance music enthusiasts in the UK. *Drug Alcohol Depend* **64**: 9–17.
Zakzanis KK, Campbell Z. 2006. Memory impairment in now abstinent MDMA users and continued users: a longitudinal follow-up. *Neurology* **66**: 740–741.
Zakzanis KK, Young DA. 2001. Memory impairment in abstinent MDMA ("ecstasy") users: a longitudinal investigation. *Neurology* **56**: 966–969.
Zhou JF, Chen P, Zhou YH, Zhang L, Chen HH. 2003. 3,4-Methylenedioxymethamphetamine abuse may cause oxidative stress and potential free radical damage. *Free Radical Res* **37**: 491–497.

DOI: 10.1002/hup