

Review

Are there sex differences associated with the effects of ecstasy/3,4-methylenedioxymethamphetamine (MDMA)?

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Abstract

Sex has been identified as an important factor in moderating the effects of several drugs of abuse. Given the increasing popularity of ecstasy (3,4-methylenedioxymethamphetamine [MDMA]) use, it is important for researchers and clinicians to understand the factors that may influence its pharmacological actions to improve education, harm reduction and treatment efforts. This review focuses on preclinical and clinical research that examines the role of sex as an independent variable in the effects of ecstasy/MDMA. A systematic search of PsycINFO and MEDLINE electronic databases from 1966 to April 2006 was conducted. Both preclinical and clinical studies show a sexually dimorphic pattern in the acute, subacute and possibly long-term effects of ecstasy/MDMA. Specifically, adult females are more sensitive than males to the acute and subacute physical and psychological effects of ecstasy/MDMA and long-term alterations in aspects of 5-HT functioning. Conversely, males are more sensitive to the acute physiological effects of ecstasy/MDMA. These findings are consistent with research outcomes reported for other substances such as amphetamines and cocaine. Potential reasons for these sex differences and directions for future research are discussed.

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1. Introduction

Historically, women have been excluded from clinical psychopharmacology research due to concerns about

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pregnancy or because menstrual cycle hormonal fluctuations have been viewed as a confounding factor (Hamilton and Jensvold, 1995; Merkatz et al., 1993). Consequently, findings from predominantly male samples are often generalised to females. This is problematic given that there are known pharmacokinetic and pharmacodynamic differences between males and females (Gandhi et al., 2004; Harris et al., 1995; Yonkers et al., 1992).

Sex differences have been well characterised in animal and human studies of pharmacokinetic and pharmacodynamic responses to many substances of abuse, including alcohol, nicotine, and psychostimulants such as cocaine and amphetamine (Becker et al., 2001; Brady and Randall, 1999; Carroll et al., 2004; Lynch et al., 2002). Growing evidence suggests that females are more prone than males to a range of effects of substances of abuse. In humans, it is often difficult to distinguish whether drug (side) effects are the result of biological, psychological or a combination of both factors. The term 'sex' generally refers to the biological factors differentiating males and females, whereas 'gender' relates to the sociocultural differences between the sexes (Barsky et al., 2001; Hamilton and Jensvold, 1995). For simplicity, the term 'sex' rather than 'gender' will be used throughout this paper, though it is acknowledged that sociocultural and psychological factors may be important in the sex differences associated with drugs of abuse, including ecstasy/3,4-methylenedioxy-methamphetamine (MDMA).

To date, only modest attention has been paid to the variable of sex in relation to the response to ecstasy/MDMA administration. This is explained by the fact that studies investigating the effects of ecstasy/MDMA recruit predominantly male subjects and of the several studies that have recruited female subjects, it is often unclear whether sex was included as an independent variable in the data analysis. Throughout this paper we refer to the term 'ecstasy' when studies have recruited participants who report ecstasy use. Even though the contents of ecstasy tablets are assumed to include MDMA this is usually not verified in research of ecstasy users (Cole and Sumnall, 2003), and research shows that ecstasy tablets may contain various other substances that may or may not be related to MDMA (Baggott et al., 2000; Wolff et al., 1995). We refer to the term 'MDMA' only when it is known with certainty that MDMA was the actual substance administered.

The paucity of research on sex differences in ecstasy/MDMA research is somewhat surprising given the rising popularity of ecstasy use over the past decade (Australian Institute of Health and Welfare [AIHW], 2005; Landry, 2002; Pedersen and Skrondal, 1999; Schuster et al., 1998; Strote et al., 2002). Using Australia as an example, population-level data indicate that lifetime use of ecstasy by Australians aged 14 years and over has risen from 2.4% in 1995 to 6.1% in 2001 and 7.5% in 2004 (AIHW, 2002, 2005). Similarly, recent use (in the previous 12 months) increased more than twofold from 1.2% in 1993 to 3.4% in 2004 (AIHW, 2005). As is the case for other substances (see

AIHW, 2005; Brady and Randall, 1999), the epidemiological literature shows that males outnumber females in their extent of ecstasy use (i.e., prevalence, dose, frequency, years of use) in various countries, including Germany (Schuster et al., 1998), Norway (Pedersen and Skrondal, 1999), New Zealand (Wilkins et al., 2003), England (Rodham et al., 2005), the United States of America (Maxwell, 2003) and Australia (Degenhardt et al., 2003; Lynskey et al., 1999). Notably however, recent reported use (past 12 months) of ecstasy increased significantly among females but not males in Australia from 1995 to 2001 (AIHW, 2002). These data have increased concerns about the specific issues for females and drug use (Isralowitz and Rawson, 2006; Litt, 2003; Maxwell, 2003; Wallace et al., 2003).

In contrast to other amphetamines that mainly act via dopaminergic and noradrenergic systems, MDMA acts primarily through the serotonergic (5-hydroxy tryptamine; 5-HT) system, which results in subsequent actions on the release of dopamine (DA) and noradrenaline (NA) (de la Torre et al., 2000; White et al., 1996). Therefore, the effects of ecstasy are distinguishable from amphetamines and hallucinogens, earning ecstasy its own classification as 'entactogens' (Martinez-Price et al., 2002; Nichols, 1986). Preclinical studies have provided evidence of 5-HT neurotoxicity following MDMA administration (Green et al., 2003), and neuroimaging studies have presented evidence of altered neurochemical functioning in human ecstasy users (Buchert et al., 2004; McCann et al., 1998; Reneman et al., 2001). These alterations in 5-HT functioning may be associated with psychiatric and cognitive deficits (Green et al., 2003; Montoya et al., 2002).

Determining whether there are sex differences associated with the effects of ecstasy/MDMA is important because it will improve our understanding of the pharmacological actions of MDMA and tailor approaches to intervention in both males and females. To date, only a small body of research has evaluated sex differences in animals and humans in the behavioural, subjective and biological responses to ecstasy/MDMA, although researchers are recognising the need for further research in this area (e.g., Easton and Marsden, 2006; Reneman et al., 2006). The purpose of this review is to provide a thorough overview of the literature pertaining to the variable of sex and its relationship to the effects of ecstasy/MDMA in animals and humans. Potential explanations for the apparent sex differences and directions for future research will also be discussed.

2. Method

The PsycINFO and MEDLINE electronic databases were searched for articles published from 1966 to April 2006 using the following terms: 'MDMA' or 'ecstasy' combined with 'sex', 'sex differences', 'gender' or 'gender differences'. Only English-language articles were included. There were 135 articles identified by the initial search.

These articles were screened for relevance based on title, key words and abstract. For the purpose of this review, articles were required to include sex/gender as an independent variable in data analysis or have a focus on sex/gender as a potential factor in the effects of ecstasy/MDMA. The screening resulted in the elimination of 107 articles, leaving 28 articles. The reasons for 107 articles being eliminated were as follows: 27 articles focused on men who have sex with men, 15 articles focused on aspects of sexuality (i.e., sexual behaviour, risk, identity, functioning or abuse), 11 articles did not include sex as an independent variable, nine articles included sex-matched controls, but did not include sex as an independent variable, 12 articles were excluded for miscellaneous reasons (e.g., they referred to the emotion of ecstasy not the drug, herbal ecstasy, history of sex, ecstasy was not analysed in isolation from other drugs, etc.), 5 articles were reviews, four articles were single case reports, and two articles were comments. Furthermore, 21 articles focused on epidemiological data and sex differences in human patterns of ecstasy use across various samples, and therefore were not deemed relevant to the focus of the current review. The reference lists of the included articles were also perused for relevant articles not detected by the database search and the authors' own database was also searched. This resulted in identification of an additional 10 relevant articles. Therefore, a total of 38 articles were included in this review (15 animal studies, 23 human studies).

3. Animal studies

The majority of animal studies that have examined the effects of MDMA have used only males. However, there is a small body of research that has used males and females (primarily rat studies), which shows a dissociation between the sexes in the acute behavioural effects of MDMA (see Table 1). The earliest study to examine sex differences in the effects of MDMA was conducted by Slikker et al. (1989). They measured a range of behaviours in adult Sprague-Dawley rats (SD) following oral administration of 5 or 10 mg/kg MDMA for 4 consecutive days. Acute serotonin syndrome behaviour (i.e., splayed hind limbs, Straub tail, abdominal contact with the floor, etc.) on each of the 4 days 1 h following MDMA administration was measured, in addition to chronic behavioural effects (i.e., 2–4 weeks following MDMA treatment), including auditory startle habituation, emergence from dark chamber, and latency of response to a hot plate. Despite a significant increase in serotonin motor syndrome behaviour in the MDMA-treated groups compared to controls on day 1, no sex differences were observed. This finding is in contrast to studies that have shown female rats to exhibit a greater degree of serotonin syndrome behaviour than males following administration of the monoamine oxidase inhibitor, pargyline, plus the 5-HT precursor, tryptophan (Carlsson et al., 1985; Dickinson and Curzon, 1986; Fischette et al., 1984). The contrasting results might be

explained by differences in route of administration (oral in the Slikker et al. (1989) study versus injection in the other studies), or by the fact that the actions of MDMA are not limited to the serotonergic system, and thus may mask any underlying sex differences in 5-HT functioning. There was neither group (i.e., MDMA versus control) nor sex differences demonstrated on any of the chronic behavioural measures. Brain 5-HT and metabolite (5-hydroxyindoleacetic acid [5-HIAA]) levels were also examined four weeks post MDMA administration. Despite the finding of significant reductions of these neurochemicals in the MDMA-treated rats, unfortunately it was not reported whether there were sex differences.

McNamara and colleagues were the first to provide evidence for qualitative sex differences in the acute effects of MDMA in studies using SD rats (McNamara et al., 1995a, b). Specifically, they found sex differences in body temperature, activity levels, serum corticosterone, and neurotransmitter (5-HT, DA and NA) and metabolite (5-HIAA and 3,4-dihydroxyphenyl-acetic acid [DOPAC]) concentrations following 5, 10 and 20 mg/kg of MDMA. However, the differences were not consistently associated with either sex across any of these measures, making interpretation difficult.

Chu et al. (1996) examined the levels of MDMA and its metabolite—3,4-methylenedioxyamphetamine (MDA)—in male and female SD rats following acute administration of a range of MDMA doses. They found no significant differences between males and females in brain and plasma levels of MDMA and there was equal depletion of 5-HT in the brains of both sexes. However, there were sex differences in the metabolism of MDMA to MDA; females had significantly lower levels of brain MDA than males. This finding is suggestive of sex differences in liver N-demethylation activity. Interestingly, Gollamudi et al. (1989) compared the N-demethylation of MDMA to MDA *in vitro* of the two MDMA enantiomers ((S)-(+)-MDMA and (R)-(-)-MDMA) and found that in the female SD rat significantly more MDA was formed from the (S)-(+)- enantiomer, whereas no stereoselectivity was observed in the male SD rat.

With the exception of the studies discussed above, locomotor activity has been the major dependant variable of interest following acute MDMA administration, as it provides a specific and robust index of stimulant drug sensitivity (Martinez-Price et al., 2002). In one of the earlier studies assessing locomotor activity and sex differences in the neurochemical action of MDMA, Bubar et al. (2001) found that female SD rats exhibited significant increases in peripheral, central and vertical locomotor activity in response to MDMA (4 mg/kg) administration. The locomotor activity of the male rats also increased, but the increase was not significant.

Palenicek et al. (2005) extended this research and examined sex differences in locomotor activity of adult Wistar rats in response to one of three MDMA doses: 2.5, 5 or 10 mg/kg. They examined a wider range of locomotor

Table 1
Animal studies of sex differences in various endpoints following MDMA administration

Reference	Subjects	Total MDMA dose	Dependent variables	Main findings
Slikker et al. (1989)	Adult SD rats	5 or 10 mg/kg orally for 4 consecutive days	Acute serotonin syndrome behaviour 2–4 week auditory startle habituation, emergence, hot plate response	F = M MDMA = Control F = M on all measures
McNamara et al. (1995a)	Adult SD rats	20 mg/kg IP	Serum corticosterone, rectal temperature, brain 5-HT, 5-HIAA, DA, DOPAC & NA	Increase in corticosterone: F = M Increase in temperature: F = M, but M earlier Monoamines/metabolites: F/M variable changes across brain regions
McNamara et al. (1995b)	Adult SD rats	5, 10, 20 mg/kg IP	Rectal temperature, locomotor activity	Temperature: F ↑ at 10 and 20 mg/kg Locomotion: F ↑ = M ↑, but M earlier, F for longer
Chu et al. (1996)	Adult SD rats	5, 10, 20, 40 mg/kg SC	Brain & plasma MDMA, brain MDA, brain 5-HT	MDMA: F = M all doses MDA: M > F all doses 5-HT depletion: F = M
Bubar et al. (2001)	Adult SD rats	4 mg/kg IP	Locomotor activity	F ↑
Palenicek et al. (2005)	Adult Wistar rats	2.5, 5, 10 mg/kg SC	Locomotor activity	F > M
Koenig et al. (2005)	Pubescent Long-Evans rats	Experiment 1: 30 mg/kg IP Experiment 2: 6, 15, 30 mg/kg IP	Locomotor activity, death ^a Rectal temperature, death ^a	Locomotion: M > F Death: M > F Temperature: M > F at 30 mg/kg Death: F = M
Cadet et al. (1994)	Adult CuZnSOD transgenic mice	40, 60, 80, 100, 120 mg/kg IP	Death	M > F
Miller & O'Callaghan (1995)	Adult C57BL6/J mice	80, 120, 160 mg/kg SC	Death ^a	M > F

'SD' = Sprague-Dawley; 'IP' = intraperitoneally; 'M' = male; 'F' = female; 'SC' = subcutaneously; '↑' = significant increase; 'M > F' = MDMA caused a significantly greater effect in males; 'F > M' = MDMA caused a significantly greater effect in females; 'F = M' = there was no significant difference in MDMA's effect in females vs. males.

^aSex difference in lethality was not the primary focus of these studies.

variables. As in the previous study, MDMA-induced locomotor activity (i.e., horizontal activity, vertical activity, open field trajectory) was significantly greater in female compared to male rats. Furthermore, there was a biphasic effect of MDMA on vertical activity in the female rats only, with significant increases after 2.5 and 5 mg/kg doses, but a decrease after the 10 mg/kg dose (Palenicek et al., 2005). This finding is somewhat consistent with previous research, which shows that higher doses of MDMA are associated with low body posture and decreased rearing in rats, although only male rats were studied (O'Loinsigh et al., 2001; Spanos and Yamamoto, 1989). Finally, thigmotaxis (spatial characteristics of open field trajectory) differed between males and females, whereby female rats showed a greater preference for peripheral zones in the open arms following MDMA at all doses examined, a difference that was statistically significant at a dose of 10 mg/kg. Males did not show this effect (Palenicek et al., 2005). The authors concluded that this finding is most likely due to the stereotypy-inducing effects of MDMA, rather than to anxiogenic activity of MDMA (see

Martinez-Price et al., 2002). This was based on the fact that there was a significant increase in time spent by both sexes in the open arms of the elevated plus-maze following 10 mg/kg MDMA, indicating low anxiety levels (Palenicek et al., 2005).

In contrast to these studies, Koenig et al. (2005) demonstrated that in pubescent Long-Evans rats, males are more sensitive to the stimulatory locomotor effects (measured as number of cage crossings) of MDMA than females. In this study, three successive 10 mg/kg doses of MDMA were administered, resulting in a much higher total dose than was used in the abovementioned studies. The sex difference emerged after the second MDMA injection was given. Following the third injection, three female and all ten male rats died. The sex difference in lethality was statistically significant. Although lethality was not the focus of this study, the results are consistent with two studies showing that male mice are more sensitive to the toxic lethal effects of high doses of MDMA (40 mg/kg or greater) than are female mice (Cadet et al., 1994; Miller and O'Callaghan, 1995). This finding may be associated

with sex differences in metabolic activity. However, caution is advised regarding a hypothesis of greater sensitivity to MDMA-toxicity in males, as Koenig et al. (2005) used pubescent rats in their study (discussed below) and the pharmacology of MDMA in mice is known to be different to that of other animal species (i.e., rats, guinea pigs, primates) (Easton and Marsden, 2006).

A second experiment was conducted by Koenig et al. (2005) in order to examine the effect of MDMA on body temperature across sexes, given the robust finding of MDMA-induced hyperthermia (Dafters, 1995; O'Loinsigh et al., 2001). Due to the fatalities in the first experiment, the effect of successive administration of lower MDMA doses (2 or 5 mg/kg) was examined as well as 10 mg/kg in pubescent male and female rats. At the 2 and 5 mg/kg doses no sex differences emerged, whereas at the 10 mg/kg dose males showed a greater hyperthermic effect than females after the second injection.

There are several possible explanations for the disparate results in MDMA-induced rat locomotor activity between the Koenig et al. (2005) and other studies. The first is that Koenig et al. (2005) used pubescent as opposed to adult rats, therefore gonad and brain development was incomplete in their subjects. Interestingly, the density of striatal DA receptors is much greater in male pubescent rats compared to females, a difference which disappears in adulthood and is independent of pubertal gonadal hormones (Anderson et al., 1997, 2002). Hence, males may be more sensitive than females to the locomotor stimulating effects of MDMA only during pubescence. Secondly, Koenig et al. (2005) administered much higher doses of MDMA than the previously described studies. As described in the Palenicek et al. (2005) study, aspects of locomotor behaviour (i.e., vertical activity) were shown to be reversed in females at higher doses. Thirdly, rat strain differences may account for the contrasting results. For example, Long-Evans rats are more sensitive to the stimulatory locomotor effects of nicotine than are SD rats (Faraday et al., 2003) and female Fischer rats are more sensitive to acute cocaine-induced hyperactivity than female SD rats (Sircar and Kim, 1999). Strain differences may also be indicative of individual differences that may be expected in humans (e.g., Fernandez et al., 2003; Lopez-Rubalcava and Lucki, 2000).

Despite some inconsistent results, preclinical studies demonstrate sex to be an important moderator in the acute stimulatory effects of MDMA. This may be a reflection of the important role of gonadal hormones in regulating the sensitivity and reactivity of the 5-HT and DA neurotransmitter systems (Attali et al., 1997; Di Paolo, 1994; Fischette et al., 1983; Sumner and Fink, 1995; Zhou et al., 2002). There is evidence in preclinical research that ovarian hormones modulate the acute biochemical and behavioural response to cocaine and amphetamine (Becker et al., 2001; Becker and Rudnick, 1999; Festa and Quinones-Jenab, 2004; Peris et al., 1991; Sell et al., 2000). Specifically, the presence of oestrogen (possibly in addition

to low levels of progesterone) is associated with increased stimulatory effects of cocaine and amphetamine (Camp et al., 1986; Quinones-Jenab et al., 1999; Savageau and Beatty, 1981; Sell et al., 2000)—a finding which seems to occur only following the onset of adulthood (Bowman and Kuhn, 1996). Testicular hormones on the other hand are shown to have minimal to no effect on amphetamine-stimulated DA release and behaviour in rats (Camp et al., 1986; Forgie and Stewart, 1994; Myers et al., 2003; Savageau and Beatty, 1981). Furthermore, in rats, the acute effects of drugs that act on the serotonergic system have also been shown to vary by female hormonal status, including the hypothermic (Matsuda et al., 1991) and hyperphagic (Currie et al., 2004; Uphouse et al., 1991) effects of the selective 5-HT_{1A} agonist, 8-OH-DAT, the anxiolytic/anxiogenic effects of the selective 5-HT₂ antagonist, ketanserin (Diaz-Veliz et al., 1997), and the anorectic effect of the selective serotonin reuptake inhibitor (SSRI), fenfluramine (Eckel et al., 2005).

To test the hypothesis of ovarian hormones moderating the acute effects of MDMA, a recent study assessed the role of oestrogen in the locomotor-inducing effects of MDMA in ovariectomized (OVX) and ovariectomized plus estradiol implanted (OVX + E) adult SD rats (Zhou et al., 2003). A differential dose–response relationship for MDMA-induced locomotor hyperactivity was established in OVX and OVX + E female rats. The oestrogen-treated rats demonstrated significantly greater locomotor activity after MDMA (4 mg/kg) administration compared to non-treated rats, providing evidence of a role for oestrogen in modulating the locomotor stimulant effects of MDMA.

In an examination of endogenous gonadal hormones, Bubenikova et al. (2005) assessed the impact of sex and oestrous phase on prepulse inhibition (PPI) and acoustic startle reflex (ASR) in response to MDMA (2.5, 5 or 10 mg/kg) in adult Wistar rats. PPI and ASR are aspects of sensorimotor gating—the inhibition of a motor response to intense stimuli, governed by various neurotransmitter systems, including 5-HT (Koch, 1999; Swerdlow et al., 2001). In this study, males and female rats in diestrous and metestrous phases were shown to exert similar deficits in PPI following 5 and 10 mg/kg of MDMA. These responses were similar to those reported in other studies that used male rats as subjects (Martinez-Price et al., 2002; Vollenweider et al., 1999). However, female rats in proestrous and oestrous phases showed a significantly higher PPI than metestrous and diestrous females following 5 mg/kg MDMA, and significantly higher PPI than males and metestrous and diestrous females following 10 mg/kg MDMA. ASR did not differ between groups. These results also suggest a role of gonadal hormones in modulating the pharmacodynamic effects of MDMA. Interestingly however, oestrogen and progesterone (which are both highest in the proestrous phase) prevented the MDMA-induced disruption of PPI in females. This suggests that the presence (or not) of progesterone may be as important, if not more important, than oestrogen in moderating the

acute effects of MDMA. Indeed, recent studies of cocaine suggest that its stimulatory effects are enhanced when progesterone levels are low (Festa and Quinones-Jenab, 2004; Turner and de Wit, 2006). It is important to note a species difference here. Vollenweider et al. (1999) found MDMA to have opposite modulatory effects on PPI in humans compared to rats; MDMA actually increased PPI in humans, whereas it decreased PPI in male SD rats. Replication of this study with human males and females at different menstrual cycle phases would advance our understanding of the role of oestrogen and progesterone in modulating the effects of MDMA on sensorimotor gating parameters.

While these studies do indeed demonstrate roles for oestrogen and progesterone in modulating the effects of MDMA, the precise relationship between these ovarian hormones and neurochemical and behavioural responses to MDMA remains unclear. This relationship is likely to be different to other stimulant drugs due to the complex and unique neurochemical actions of MDMA (Nichols, 1986). Furthermore, the aforementioned studies examined different pharmacodynamic responses (i.e., locomotor activity, PPI) that are driven by different and complex underlying neurobiological mechanisms, which are yet to be fully understood (Martinez-Price et al., 2002). Nevertheless, ovarian hormones have been associated with alterations in the expression of 5-HT receptors, transporters and metabolism, affecting the availability of 5-HT for release (Fischette et al., 1983; Gundlach et al., 1998; McQueen et al., 1997; Sumner and Fink, 1995). Moreover, ovarian hormones have also been shown to alter the expression and activity of DA (Bazzett and Becker, 1994; Bosse et al., 1997; Di Paolo et al., 1985). Further preclinical research is needed to elucidate the role of endogenous hormones on the pharmacological actions of MDMA.

In addition to the effects of ovarian hormones on both the expression of 5-HT and DA and in moderating their response to MDMA, there is also evidence of baseline sex differences in these neurotransmitter systems that are independent of hormonal influences, which may also account for sexually dimorphic responses to MDMA. For example, in untreated adult rats, compared to males, females have shown greater central serotonergic expression in the form of 5-HT, 5-HIAA, and tryptophan levels and 5-HIAA/5-HT ratio in several brain regions (Carlsson and Carlsson, 1988; Carlsson et al., 1985; Dominguez et al., 2003; Festa et al., 2004; Haleem et al., 1990). This suggests that the 5-HT neurones of females may have greater storage capacity, a higher enzymatic activity and higher rate of 5-HT synthesis than males. With regards the DA system, findings of a basal sex difference are more mixed, with some preclinical studies showing no sex difference in DA expression (Carlsson and Carlsson, 1988; Carlsson et al., 1985), others reporting males to have greater extracellular levels of striatal DA than females (Castner et al., 1993), and some reporting a greater density of DA transporters (Rivest et al., 1995) and functional DA release

and uptake (Walker et al., 2000) in female than male rats. Basal sex differences in neurotransmitter expression could mediate sex differences in physiological and behavioural responses to ecstasy/MDMA. This hypothesis has not yet received attention in the ecstasy/MDMA literature, but is worthy of further investigation.

Given the evidence for sex differences in the acute stimulating effects of MDMA, another important direction for future animal research would be to examine the potential sex differences in the long-term neurotoxicity of MDMA, given that MDMA is known to be neurotoxic in animals (Green et al., 2003). Ethical and practical constraints often preclude such prospective investigation in humans. It is also important to mention that there are several issues that limit our ability to extrapolate results of animal studies to humans, including dosing regimen, route of administration, experimental conditions and interspecies variations (see de la Torre and Farre, 2004; Easton and Marsden, 2006; Grob, 2000), as seen in the study by Vollenweider et al. (1999) showing opposite effects of MDMA on sensorimotor gating in rats and humans. As the studies reviewed here have only evaluated rodent responses, it would be informative to examine sex differences in non-human primates given that as a species they are much more closely related to humans than rodents and are known to be even more sensitive to the neurotoxic effects of MDMA (Green et al., 2003). Even though caution is recommended in directly extrapolating results of animal studies to humans, the results of these animal studies illustrate that sex differences in MDMA effects can occur and provide impetus for sex-based research in humans and non-human primates.

4. Human studies

Table 2 summarises the human studies that have examined the role of sex as a variable in the effects of ecstasy/MDMA. The findings are discussed according to acute/subacute administration, long-term neurological effects (neurotoxicity) and long-term cognitive/psychological sequelae. It is important to note that differentiating acute and subacute effects from long-term (potentially neurotoxic) effects is often difficult. This is because MDMA can only be biochemically detected 24–48 h after use, even though the psychological and somatic effects may persist for several more days (Curran, 2000). Human data show that the elimination half-life of MDMA is approximately 8–9 h; however, the elimination of its metabolites (MDA, 3,4-dihydroxymethamphetamine [HHMA], 3,4-dihydroxyamphetamine [HAA]) is even longer (de la Torre et al., 2000; Mas et al., 1999) and each may be pharmacologically active (Kalant, 2001). It takes about five half-lives (approximately 40 h) for greater than 95% of MDMA to be eliminated from the body (Kalant, 2001) and rebound low mood and aggression effects of ecstasy return to baseline levels by 7 days following use (Curran et al., 2004; Parrott and Lasky, 1998). Therefore, for long-term

Table 2
Human studies of sex differences associated with ecstasy/MDMA administration

Reference	Participants	Ecstasy/MDMA dose/use	Dependent variables	Main Findings: female versus male ecstasy users
Acute/subacute effects				
Cregg & Tracey (1993)	Review of 37 cases	Not reported	Reports to Poisons Information Centre	M > F
Budisavljevic et al. (2003)	Review of 19 cases	1–3 pills on that occasion	Hyponatraemia	F > M
Schifano et al. (2003b)	Review of 182 cases	Not reported	Ecstasy-related deaths	M > F
Schifano et al. (2003a)	Review of 81 cases	Not reported	Ecstasy-related deaths	M > F
Liechti et al. (2001)	Healthy volunteers (54M, 20F)	1.35–1.8 mg/kg (totalling 70–150 mg)	AM Scale, OAV Scale, LC Scale, BP, HR & body temperature	AM: F > M OAV: F > M LC: F > M B P: M > F HR: M > F Temperature: M > F
Ter Bogt and Engels (2005)	372 ecstasy-using rave attendees (372M, 103F)	Not clearly defined	Perceived positive & negative effects	Positive effects: F = M Negative effects: F > M
Topp et al. (1999)	329 ecstasy users (51%F)	Median use: 10 days in past 6 months (range 1–100)	6-month history of acute/subacute physical & psychological side effects	Physical side effects: F > M Psychological side effects: F > M
Verheyden et al. (2003)	430 ecstasy users (238M, 192F)	Mean years of use: M = 5.35, F = 4.93	Acute & subacute effects	F = M
Verheyden et al. (2002)	80 club attendees: 40 ecstasy users (21M, 19F); 40 polydrug controls (19M, 21F)	Minimum 20 past occasions of use Mean pills on day 0: M = 2.1, F = 1.8	Day 0 and 4: BDI, mood scale, aggression scale, impulsivity, bodily symptoms, HR	BDI and mood: F > M day 4 Aggression: F ↑ = M ↑ day 4 Impulsivity: F = M Bodily symptoms: F = M HR: F = M
Hoshi et al. (2006)	107 club attendees: 48 ecstasy users (31M, 17F); 59 controls (35M, 24F)	Mean years of use: M = 2.92, F = 2.09 Mean pills per occasion: M = 3.15, F = 2.29 Dose on day 0 not reported	Day 0 and 4: aggression, mood, subjective effects, BDI, HR Day 4: interpretative bias computer task	Aggression: F ↑ = M ↑ day 4 BDI: F ↑ = M ↑ day 4 HR: F ↑ = M ↑ day 0 Computer task: F = M both showing bias toward aggressive sentences
Long-term neurological effects				
McCann et al. (1994)	30 ecstasy users (18M, 12F); 28 polydrug controls (11M, 12F)	Mean exposures: 94 (range 25–300)	CSF 5-HIAA and HVA	5-HIAA: M > F HVA: F < controls
Croft et al. (2001)	22 ecstasy users (13M, 9F); 19 cannabis users (13M, 6F); 20 drug-naïve healthy controls (10M, 10F)	Mean years of use: 4.5 Mean total pills consumed: 225.9	Intensity dependence of auditory-evoked potentials (N1/P2 slope)	N1/P2 slope: F > M
McCann et al. (1998)	14 ecstasy users (9M, 5F); 15 controls (9M, 6F)	Mean exposures: 228 (range 70–400)	SERT binding of radioligand [¹¹ C]McN5652 using PET	F = M
Reneman et al. (2001)	15 moderate ecstasy users (9M, 6F); 23 heavy ecstasy users (12M, 11F); 16 1-year abstinent heavy ecstasy users (8M, 8F); 15 polydrug controls (7M, 8F)	Moderate users: 1–50 occasions Heavy & abstinent users: > 50 occasions	SERT binding of radioligand [¹²⁵ I]β-CIT using SPECT	Heavy users: F < controls
De Win et al. (2004)	15 moderate ecstasy users (9M, 6F); 23 heavy ecstasy users (12M, 11F); 16 1-year abstinent heavy ecstasy users (8M, 8F); 15 polydrug controls (7M, 8F)	Moderate users: 1–50 occasions Heavy and abstinent users: > 50 occasions	SERT binding of radioligand [¹²⁵ I]β-CIT using SPECT, CIDI mood disorder diagnosis and BDI	SERT binding: Heavy users: F < controls CIDI: F = M BDI: F = M
Buchert et al. (2004)	30 current ecstasy users (15M, 15F); 29 20-week abstinent ecstasy users (15M, 14F); 29 non-ecstasy polydrug users (15M, 14F); 29 drug-naïve controls (15M, 14F)	Mean cumulative total pills: Current users = 831 (range 10–6873); Abstinent users = 793 (range 78–3111)	SERT binding of isotope [¹¹ C](+)McN5652 using PET	Current users: M > F

Table 2 (continued)

Reference	Participants	Ecstasy/MDMA dose/use	Dependent variables	Main Findings: female versus male ecstasy users
Long-term psychological/cognitive effects				
Topp et al. (1999)	329 ecstasy users (51%F)	Median use: 10 days in past 6 months (range 1–100)	Ecstasy-related problems	Work/study problems: F > M
Verheyden et al. (2003)	430 ecstasy users (238M, 192F)	Mean years of use: M = 5.35, F = 4.93	Lon-term subjective effects	F = M
Rokach (2002)	106 ecstasy users (56M, 50F); 88 non-ecstasy drug users (33M, 55F); 624 non-drug users (186M; 438F)	Not stated	Loneliness	F = M
Fingeret et al. (2005)	83 ecstasy users (52M, 31F); 91 cannabis controls (42M, 49F)	34% 1–50 times used 66% > 50 times used	BIS, HAM-D, HAM-A	BIS: F = M ↑ controls HAM-D: F = M ↑ controls HAM-A: F = M ↑ controls
Milani et al. (2004)	Non-drug users (60M, 89F); alcohol/tobacco users (100M, 84F); cannabis/alcohol/tobacco users (57M, 39F); non-ecstasy polydrug users (72M, 28F); light (1–20 times) polydrug ecstasy users (68M, 45F); heavy (>20 times) polydrug ecstasy users (94M, 21F)	Mean occasions of use: Light users M = 7.3, F = 7.2 Heavy users M = 232, F = 168 Mean pills per occasion: Light users M = 1.4, F = 1.2 Heavy users M = 2.5, F = 1.7	SCL-90: Somatization, Depression and Anxiety Scales	Somatization: F = M Depression: F > M, in light ecstasy users only Anxiety: F = M
Bolla et al. (1998)	24 ecstasy users (14M, 10F); 24 polydrug controls (18M, 6F)	Median occasions of use: 60 (range 25–300)	Four memory factors: immediate verbal memory, immediate visual memory, delayed verbal memory, delayed visual memory)	Delayed verbal memory: F > M Delayed visual memory: F > M
Rodgers et al. (2003)	199 ecstasy users (98M, 101F); other groups not clearly defined	Not clearly defined	EMQ, PMQ, Memory techniques	EMQ: F = M PMQ: F = M Techniques: F = M
von Geusau et al. (2004)	26 ecstasy users (17M, 9F); 33 controls (12M, 21F)	Mean cumulative total pills used: M = 58.8 (range 10–120), F = 38.8 (range 14–60)	Four domains of EF: flexibility, working memory, response inhibition, complex EF, SCL-90	Flexibility: M < controls Complex EF: M < controls SCL-90: M < controls
Medina et al. (2005)	48 ecstasy users (26M, 22F); 17 cannabis users (8M, 9F)	Mean pills used in past year: 15 (range 1–116) Mean pills used in lifetime: 267 (range 1–2310)	Test battery that assessed attention, working memory, aspects of EF, visual and verbal memory	Verbal memory: F = M Design fluency: M > F

'M' = male; 'F' = female; 'AM' = Adjective Mood Scale; 'OAV' = Altered States of Consciousness Scale; 'LC' = List of Complaints Scale; 'BP' = blood pressure; 'HR' = heart rate; 'BDI' = Beck Depression Inventory; 'CSF' = cerebrospinal fluid; '5-HIAA' = 5-hydroxyindoleacetic acid; 'HVA' = homovanillic acid; 'SERT' = serotonin transporter; 'SPECT' = single-photon-emission computed tomography; 'CID-I' = Composite International Diagnostic Interview; 'PET' = Positron Emission Tomography; 'BIS' = Barratt Impulsiveness Scale; 'HAM-D' = Hamilton Depression Rating Scale; 'HAM-A' = Hamilton Anxiety Rating Scale; 'SCL-90' = Symptom Checklist-90; 'EMQ' = Everyday Memory questionnaire; 'PMQ' = Prospective Memory Questionnaire; 'EF' = Executive Functioning; '↑' = significant increase; '>' = significantly greater than; '<' = significantly less than; 'F = M' = no significant difference in effect of ecstasy/MDMA in females vs. males.

effects to be detected in humans testing must occur at least 1 week following the last dose and some researchers have suggested that even longer abstinence periods are necessary (Curran, 2000; Parrott, 2001; Reneman et al., 2006).

4.1. Acute and subacute effects

Serious and life-threatening medical complications (i.e., toxicity) have been associated with ecstasy use (Kalant, 2001). One of the less well known of these is hyponatraemia—low sodium levels in the blood caused by excessive ingestion of water, which is often used as a harm

reduction strategy to counteract the hyperthermic effects associated with ecstasy use (Allott and Redman, 2006; Budisavljevic et al., 2003; Cole et al., 2002a). Reviews of case reports show that females who use ecstasy are more likely to experience hyponatremia (Budisavljevic et al., 2003). This finding concurs with epidemiological evidence in the medical literature showing that premenopausal women are more susceptible to acute hyponatremia and encephalopathy than males (Arieff, 1986, 1993; Fraser and Arieff, 1997). Conversely, reviews of ecstasy-related deaths have found a male/female ratio of approximately 4:1 (Schifano et al., 2003a, b). The mechanism for

ecstasy-related death is not well understood; although the cause of many ecstasy-related deaths is determined to be accompanied by polysubstance poisoning (Schifano et al., 2003a,b; White et al., 1997). In an early retrospective review of 37 ecstasy-related calls made to the Poisons Information Centre in Ireland, Cregg and Tracey (1993) found that 80% of calls were made by males, two of whom later died. The unequal sex ratio found in these studies may be accounted for by the fact that males use more ecstasy (and other drugs) than females.

Three studies have prospectively examined the influence of sex on the acute and subacute effects of ecstasy (MDMA) in humans. The first of these was a well-designed study that administered MDMA under controlled laboratory conditions and examined its acute physiological and subjective effects in males and females (Liechti et al., 2001). MDMA (1.35–1.8 mg/kg; ranging a total of 70–150 mg) or placebo was administered to normal healthy volunteers who had never or rarely used MDMA. The measures administered included the Adjective Mood Rating Scale (AM) and the Altered States of Consciousness Scale (OAV) that comprised three subscales: Oceanic Boundlessness (OB), Anxious Ego Dissolution (AED) and Visionary Reconstruction (VR). The physiological measures included heart rate, blood pressure and body temperature. Adverse effects reported by participants were also documented via a List of Complaints (LC). In this study, a number of sex differences emerged in response to MDMA consumption. Overall, females reported more intense subjective effects than males. This was significant for all three scales on the OAV. For example, on the OB scale women reported increased feelings of being carefree, feeling boundless joy, being at one with their surroundings and experiencing physical sensations as more pleasurable compared with males. On the AED scale, among other items, females experienced higher thought disturbance and fear of loss of body control than did males. Sex differences were most marked on the VR subscale, whereby females experienced greater perceptual changes than males, including (pseudo) visual hallucinations, vivid imagination, and seeing flashes of light, colour or simple patterns. Furthermore, a significant correlation existed between dose of MDMA and VR scores for females only. On the AM scale, females also scored significantly higher on anxiety and depression subscales and the dose of MDMA in females was significantly correlated with anxiety scores. By contrast, males' scores did not increase on these measures compared with placebo. However, males showed greater responses on physiological parameters following MDMA ingestion. They had significantly greater enhancement of systolic blood pressure, heart rate and body temperature compared with females. This is in line with preclinical studies showing male rats to be more sensitive to the hyperthermic effects of MDMA (Koenig et al., 2005) and human case reports of acute ecstasy-induced hyperthermia (body temperature >38 °C) being dominated by males (Gowing et al., 2002). On the AM, men reported feeling significantly

more active and energetic than did women, which may have been associated with their increased physiological activation.

With regard to physical adverse effects, females reported these much more frequently than did males, and this difference was sustained for 24-h post MDMA ingestion, during the subacute period. Adverse effects included jaw clenching, dry mouth, decreased appetite, fatigue, muscle ache and headache. These results accord with two epidemiological studies in which it was found that females retrospectively reported a significantly greater incidence of perceived acute negative side effects from ecstasy, such as depression, nausea, dizziness and headache (Ter Bogt and Engels, 2005), and a greater incidence of ecstasy-related acute/subacute physical and psychological side effects in the previous 6 months compared with male users (Topp et al., 1999). Studies of other substances have reported similar findings. For example, intranasal cocaine has been shown to induce greater nervousness in females compared to males (Kosten et al., 1996), and research of licit psychotropics has shown a greater susceptibility in females for experiencing side effects from antipsychotic medications (Gandhi et al., 2004; Halbreich et al., 1984; Yonkers et al., 1992). One recent study however, found no association between sex and retrospective subjective reports of acute and subacute effects of ecstasy (Verheyden et al., 2003). It is important to be mindful of the fact that the reliability of the participants' recall may be reduced in studies such as these that have used retrospective methodology.

In the second of the three prospective studies, Verheyden et al. (2002) investigated the influence of sex on the acute and subacute effects of ecstasy use on levels of depression and aggression. Eighty participants were recruited from various party settings: 40 participants had consumed relatively similar amounts ecstasy at the time of recruitment and 40 participants were allocated to the polydrug control group with minimal previous history of ecstasy use. Participants were assessed during the evening of a party (day 0) and re-assessed 4 days later (day 4). Assessment at both time-points included a modified version of the Beck Depression Inventory (BDI) and 4 visual analogue scales assessing mood, aggression, impulsivity and bodily symptoms. Additional trait measures were taken on day 4, including the Hospital Anxiety and Depression Scale (HADS) and the Aggression Questionnaire (AQ). With regards to history of ecstasy use, males and females within the ecstasy group did not differ in frequency of ecstasy use; however, males reported significantly greater doses of ecstasy ingestion than females, as well as a significantly longer history of use and a higher cumulative total dose of ecstasy tablets. There were no significant sex differences for history of other substance use.

The most striking finding of this study was that female ecstasy users showed a significantly larger increase in BDI scores than male ecstasy users and control participants 4 days after ecstasy ingestion. In fact, greater than one third

of female ecstasy users scored in the mild to moderate depression range on the BDI at day 4. Furthermore, the increase in BDI scores over the 4 days was positively related to the amount of ecstasy ingested on day 0. This correlation was seen in females only. The finding of a correlation between dose of MDMA and depressive symptoms in females was also reported by Liechti et al. (2001) who found that the amount of ecstasy ingested was correlated with psychological scores for females only. It could be argued that the results of the Verheyden et al. (2002) study reflect pre-existing high depression scores in the female ecstasy users as pre-drug baseline measures were not recorded; however, the authors argue that this seems unlikely as there were no group differences on the HADS, the measure used to assess trait depression. To clarify this further, future research should measure mood prior to ecstasy consumption and then during the acute and subacute periods (as in the study by Liechti et al., 2001). Finally, relative to controls, ecstasy users showed an increase in aggression scores on day 4. However, there were no sex differences in ratings of aggression, although a positive relationship between the number of ecstasy tablets consumed on day 0 and change in aggression score was found for male ecstasy users.

Using the same study design as Verheyden et al. (2002), Hoshi et al. (2006) further explored the potential effects of sex on state aggression during the acute (day 0) and subacute (day 4) periods of ecstasy use. They assessed aggressive mood using visual analogue scales on day 0 and 4 and aggressive interpretative bias via a sentence interpretation computer task on day 4 in ecstasy users and controls. They also assessed mood using the BDI. As in the previous study, the ecstasy users rated themselves as less aggressive on day 0 and more aggressive on day 4 relative to controls, and on the computer task they recognised aggressive sentences more quickly than controls, suggesting a bias toward aggressive stimuli. However, again there were no sex differences in these subjective and objective measures of aggression. Depressed mood also increased on day 4 relative to controls; however, in contrast to Verheyden et al. (2002) there were no sex differences.

A limitation of these two studies is that it was not confirmed whether MDMA was the actual substance consumed—the ecstasy pills used by the participants were not tested for MDMA or other substances, and/or blood/urine samples were not taken to test for the presence of MDMA. Despite these limitations, the findings of the Verheyden et al. (2002) study suggest that female ecstasy users may be more susceptible to the mid-week low or 'comedown' mood effects of ecstasy withdrawal, which is likely associated with 5-HT depletion, as shown in animal studies (Green et al., 2003). However, this finding would need to be replicated as the study by Hoshi et al. (2006) found no sex differences in subacute BDI scores.

One possible explanation for the findings of a female tendency for increased sensitivity to some of the effects of

MDMA is simply that females differ from males in their recognition and reporting of current mood states as reflected by the higher scores in their self-ratings, but may actually experience MDMA the same as males. There is evidence showing that in general, women are inclined to report a greater number and intensity of bodily symptoms than men (Barsky et al., 2001). In the depression literature, there is also a hypothesis suggesting that females tend to report symptoms of depression more readily than males, known as the reporting hypothesis (Hankin and Abramson, 1999). However, these explanations seem unlikely or at least insufficient in this instance because the placebo/initial scores of males and females were not significantly different in these studies, and among the ecstasy users, there were no sex differences in aggression scores at day 4 (Hoshi et al., 2006; Verheyden et al., 2002), despite evidence of sex differences in depressed mood at that time (Verheyden et al., 2002).

Some of the findings of these studies point to the possibility that females have an increased susceptibility to the 5-HT releasing effects of MDMA. This may be associated with underlying sex differences in the 5-HT neurotransmitter system as discussed in the section on animal studies. In line with this, some human studies have found healthy females to have higher 5-HT activity and transporter availability *in vivo* than males (Biver et al., 1996; Chugani et al., 1998; Staley et al., 2001), although one study found rates of serotonin synthesis to be higher in males (Nishizawa et al., 1997). Similarly, healthy females have also been shown to have significantly greater DA transporter availability (Lavalaye et al., 2000; Mozley et al., 2001), D₂ receptor binding potential (Kaasinen et al., 2001) and presynaptic DA synthesis capacity (Laakso et al., 2002) than males. These baseline differences in neurotransmitter systems could mediate sex differences in physiological and behavioural responses to ecstasy/MDMA.

Pharmacokinetic factors may be another explanation for sex differences in the acute/subacute effects of MDMA. Participants were administered equal doses of MDMA per kilogram of body weight in the first study (Liechti et al., 2001) and there were no significant dose differences by sex in the second study (Verheyden et al., 2002). An equal amount of MDMA per kilogram of body weight suggests that sex differences may lie in the pharmacodynamic actions of MDMA (Liechti et al., 2001). However, pharmacokinetic differences may still be important because even in the case of equal body weight, females normally have a higher proportion of body fat than males, and this may alter the distribution of lipophilic drugs such as MDMA (Gandhi et al., 2004; Harris et al., 1995). Furthermore, there may be sex differences in metabolism of MDMA. As described earlier, female SD rats show significantly lower brain concentrations of MDA than males following various doses of MDMA, which is suggestive of slower metabolism or alternative metabolic pathways in the females (Chu et al., 1996).

Conversely, the activity level of the main liver enzyme responsible for catalysing the demethylation of MDMA, coded by gene CYP2D6 (Tucker et al., 1994), has been shown (although not consistently) to be significantly higher in human females compared with males (Hagg et al., 2001; Tamminga et al., 1999). Whether this is associated with clinically significant effects remains to be seen, but may be associated with sex differences in MDMA metabolism. It has been argued that people deficient in the CYP2D6 enzyme (poor metabolizers [PM]), representing approximately 7% of Caucasians, may be more susceptible to MDMA-induced toxicity (Colado et al., 1995; Tucker et al., 1994), although there is little evidence for this as yet. In fact, case reports of patients suffering hepatotoxicity and adverse reactions following MDMA intoxication have shown those patients to be CYP2D6 extensive metabolizers (EM), suggesting that being a PM is not necessarily sufficient for toxicity (Gilhooly and Daly, 2002; O'Donoghoe et al., 1998; Schwab et al., 1999). In addition, the female Dark Agouti rat (a model for the PM of CYP2D6) shows greater MDMA-induced hyperthermia, although lower 5-HT depleting effects than male and female EM rat strains (Chu et al., 1996; Colado et al., 1995).

The best way to test the hypothesis of a pharmacokinetic (metabolic) sex difference would be to measure the blood plasma concentration levels of MDMA and its metabolites (e.g., see Farre et al., 2004; Ortuno et al., 1999) following administration in human males and females. We are not aware of research that has examined this. Pharmacokinetic factors, such as metabolism, have been associated with sex differences in response to psychotropic medications including benzodiazepines and antipsychotics, as well as alcohol (Lex, 1991; Mumenthaler et al., 1999; Niaura et al., 1987; Pollock, 1997; Yonkers et al., 1992).

Another explanation, as discussed above in the review of the animal literature, suggests that sex differences found in human studies may be attributed to fluctuating hormonal levels, particularly the endogenous oestrogen or progesterone associated with stage of menstrual cycle and/or exogenous hormone (e.g., oral contraceptive [OC]) intake in the female participants (Carroll et al., 2004; Terner and de Wit, 2006). As animal studies have shown, levels of oestrogen and progesterone may alter the sensitivity of 5-HT and DA neurotransmitter systems to psychostimulants such as MDMA (Zhou et al., 2003). Moreover, human studies that have examined the acute effects of d-amphetamine and cocaine across different stages of the menstrual cycle have shown increased sensitivity in females during the (late) follicular phase when there are high oestrogen and low progesterone levels (Evans et al., 2002; Justice and de Wit, 2000; Lukas et al., 1996; Sofuoglu et al., 1999; White et al., 2002). Interestingly, menstrual cycle phase alters the response to drugs of abuse that act directly on DA, such as amphetamines and cocaine (as opposed to other drugs such as alcohol, benzodiazepines, marijuana and opioids), suggesting an interaction between female gonadal hormones and DA neurotransmission (Terner and

de Wit, 2006). In addition, some research has shown that the efficacy of SSRI antidepressants is higher in premenopausal versus postmenopausal women, suggesting a role for endogenous gonadal hormones in therapeutic response to drugs that affect 5-HT neurotransmission (Kornstein et al., 2000; Martenyi et al., 2001; Pinto-Meza et al., 2006). The effects of menstrual cycle phase on the response to MDMA have not yet been studied in humans. Menstrual cycle phase and OC intake were not controlled for in earlier studies (Hoshi et al., 2006; Liechti et al., 2001; Verheyden et al., 2002). Replication of these studies with women in different menstrual cycle phases would help delineate the effects of oestrogen and progesterone in the acute responses to MDMA in humans.

4.2. Long-term effects

4.2.1. Neurological functioning

There is increasing evidence that human ecstasy users may be placing themselves at risk of permanent or semi-permanent (reversible) brain changes in the form of neurotoxicity of the 5-HT neurotransmitter system (Green et al., 2003). Given that there are sex differences in the acute physiological and subjective effects of MDMA, it is reasonable to surmise that there may be sex differences in MDMA-induced changes in neurochemical brain functioning, particularly to the 5-HT and DA systems. A small number of studies have provided evidence that compared to male users, female ecstasy users may be more vulnerable to changes in neurochemical functioning, possibly indicative of neurotoxicity.

Among other variables McCann et al. (1994) measured the cerebrospinal fluid (CSF) levels of monoamine metabolites in male and female ecstasy users. They not only found that the ecstasy users had significantly lower 5-HIAA concentrations compared to control participants, but they also found evidence for significant sex differences within the ecstasy user group. CSF levels of 5-HIAA (a metabolite of 5-HT) were significantly lower in female ecstasy users, with a 46% reduction compared to controls, as opposed to a 20% reduction in male users. Moreover, the DA metabolite homovanillic acid (HVA) was also significantly reduced in the female users, but unchanged in male ecstasy users. It is important to note however, that there was no significant correlation between the extent of ecstasy use (e.g., total exposures, length and frequency of use, time since last use) and monoamine metabolite levels. Nevertheless, these results provide possible indirect evidence of sex differences in 5-HT and DA alterations in ecstasy users, which may reflect neurotoxicity. However, as the past exposure to ecstasy was greater in the female group, the results of this study support the hypothesis of a pharmacokinetic rather than pharmacodynamic difference in MDMA between males and females as discussed above (McCann et al., 1994).

An electrophysiological study that aimed to test 5-HT functioning in long-term ecstasy users examined the

intensity dependence of auditory-evoked potentials (an index of 5-HT function, whereby a strong dependence indicates low serotonergic innervation) (Croft et al., 2001). Three groups were compared: long-term (at least 20 occasions of use) ecstasy users, long-term cannabis users, and drug-naïve healthy controls. Results showed that the ecstasy group had a significantly larger intensity dependence slope than the cannabis or drug-naïve groups, implying that ecstasy users have impaired 5-HT functioning compared with non-ecstasy users. Furthermore, regression analysis found that lifetime total ecstasy consumption, controlling for frequency of use, significantly predicted the slope. The authors argue that this finding strengthens the link between ecstasy use and 5-HT neuronal injury (Croft et al., 2001). Sex also significantly predicted the slope, whereby female ecstasy users were found to have a significantly greater slope than male users, indicating that females' response to auditory stimuli is less attenuated than males', demonstrating poorer 5-HT functioning. This again suggests that females may be more susceptible to 5-HT dysfunction than males following ecstasy consumption. A particular strength of this study was that two control groups were used, one drug-naïve and one non-ecstasy polydrug group, thus controlling for concomitant polydrug use.

In a frequently cited study, Reneman et al. (2001) investigated whether the functioning of brain 5-HT neurons in ecstasy users varied by ecstasy dose, sex and abstinence from ecstasy use. This was measured using the density of binding of the radioligand [^{123}I] β -CIT that binds with high affinity to serotonin transporters (SERT) as well as to DA transporters (DAT), as calculated by single-photon-emission computed tomography (SPECT). This study compared three groups of ecstasy users: moderate users, heavy users and 1-year abstinent heavy users. A control group of drug users who had never used ecstasy was also included. Results showed that there was an effect of ecstasy use on binding ratios, which were found to differ significantly for males and females. Despite males reporting higher doses of ecstasy use, binding ratios were significantly lower in female heavy ecstasy users compared with female controls, an effect that was not evident in males. A lower binding ratio suggests a reduction in the density of brain SERT and hence axonal damage. Furthermore, the lower binding ratios observed in females were found in all brain regions that were studied. Male and female moderate ecstasy users did not differ significantly from controls in their binding ratios. Female abstinent heavy ecstasy users showed significantly higher binding ratios than non-abstinent female heavy ecstasy users, but were not different from controls, implying that this effect may be reversible. A significant correlation existed between previous extent of ecstasy use and binding ratios for women but not for men. This coincides with the results of other studies (e.g., Liechti et al., 2001; Verheyden et al., 2002) to suggest that the effect of MDMA in females appears dose-related. The findings of this study again imply that (current) female

heavy ecstasy users may be more susceptible to the neurotoxic effects of MDMA than male heavy ecstasy users.

Interpretation of the Reneman et al. (2001) study is, however, complicated by the fact that a small proportion of the female and male participants were experiencing a current depressive episode, therefore concluding a strong link between 5-HT functioning and ecstasy use may be premature (Ricaurte and McCann, 2001). In a later article, the same research group reported on additional analyses conducted on the same sample and showed that current and lifetime mood disorder diagnosis and BDI scores did not differ between groups or sexes, nor were they significantly associated with SERT binding density (de Win et al., 2004). Nevertheless, since 5-HT dysfunction is known to be associated with depression (Naughton et al., 2000), any exploration of sex differences in 5-HT function of ecstasy users must exclude participants suffering current psychiatric illnesses known to be associated with serotonergic dysfunction.

Indeed, Buchert et al. (2004) improved on the previous study by recruiting a larger sample and excluding participants if a major DSM-IV (APA, 1994) psychiatric disorder was detected. They conducted a PET study using a more highly selective SERT ligand than the previous study—[^{11}C](+)McN5652—and compared the density of SERT binding in several brain regions of four groups, each containing relatively equal numbers of males and females. The four groups were current regular ecstasy users, 20-week abstinent ecstasy users, non-ecstasy polydrug users and drug-naïve controls. Similar to the study by Reneman et al. (2001), relative to the other three groups current ecstasy users showed reduced SERT binding in most of the cortical regions that were studied. A significant negative relationship was found between the typical ecstasy dose and the distribution volume ratio in the occipital cortex and left precentral sulcus. Again, female current ecstasy users showed a significantly greater reduction in SERT availability than did males. One limitation of this study is that participants were only required to be drug free for three days prior to the PET study, with the implication that results may pertain to subacute rather than long-term effects, as MDMA also binds to SERT. However, reduced binding in current ecstasy users versus polydrug controls was still present when the researchers repeated the analysis after removing the participants who had abstained for less than 2 weeks ($n = 6$). Unfortunately, they did not report on whether the sex difference also remained (perhaps due to a reduction in statistical power). In an earlier [^{11}C]McN5652 PET study, McCann and colleagues (1998) examined SERT binding in at least 3-week abstinent ecstasy users and found significantly reduced binding compared to matched controls. There was no difference between males and females in SERT binding, although the sex comparison was based on a small sample (9 male, 6 female).

In combination, the findings of these biological studies suggest that females may be more susceptible than males to

altered 5-HT functioning after regular ecstasy use, as measured by the concentration of monoamine metabolites, electrophysiological functioning and SERT binding density. Furthermore, in females particularly, there is some evidence for a significant negative relationship between the extent of ecstasy use and parameters of 5-HT functioning.

4.2.2. Psychological and cognitive functioning

Given the preliminary evidence for the existence of sex differences in the degree of altered neurochemical functioning following recreational ecstasy use, an important question is whether such changes are associated with sex differences in functional difficulties. Specifically, recreational ecstasy use has been associated with a number of persistent psychological and cognitive deficits, including depressive symptoms, anxiety and compromised functioning in memory and attention (Montoya et al., 2002; Morgan, 2000; Parrott, 2001). In a sample of 430 regular ecstasy users Verheyden et al. (2003) found tolerance to the effects of ecstasy, poor concentration and depressive mood to be the three most common long-term subjective effects of ecstasy use. However, analysis by sex revealed that males and females did not differ in their self-report of these effects. In a large sample of ecstasy users, Topp et al. (1999) found that significantly more women than men (50% vs. 34%) experienced subjective ecstasy-associated work or study problems, such as poor concentration, decreased performance and amotivation. However, polydrug and/or intravenous drug use was common among the sample and these may be confounding factors in interpreting the results. To factor out the effects of concomitant polydrug use it is important to include a polydrug control group to account for the use of substances other than ecstasy.

One study that did include a polydrug control group, administered the Barratt Impulsiveness Scale (BIS-11), Hamilton Depression Rating Scale (HAM-D) and Hamilton Anxiety Rating Scale (HAM-A) to ecstasy polydrug users and cannabis user controls (Fingeret et al., 2005). The ecstasy group scored significantly higher than controls on all three scales. However, there were no significant differences based on sex or sex by group interactions. Since it is uncertain how long participants were drug-free prior to completing the questionnaires, it is unclear whether the higher psychological scores in the ecstasy group were due to subacute or long-term effects of substance use. Moreover, participants with a current or past axis I disorder were excluded, which limits the ability to generalise these findings to clinical populations with the possibility of revealing clinical sex differences (although it is important to acknowledge that in the general population females outnumber males in their prevalence of clinical mood disorders) (Fingeret et al., 2005).

In a study examining self-reported levels of loneliness (i.e., emotional distress, social inadequacy and alienation, growth and discovery, interpersonal isolation and self-alienation) amongst young adults, it was found that ecstasy users scored higher than non-ecstasy drug users and

individuals from the general population on all dimensions of loneliness except growth and discovery (Rokach, 2002). However, male and female ecstasy users did not differ on any of the loneliness subscales. The cross-sectional nature of the data and the fact that there was no analysis of whether loneliness scores were associated with ecstasy use variables (which were not reported), makes it difficult to interpret the findings of this study. Furthermore, drug-free status of participants was not tested, therefore subacute effects cannot be ruled out.

Milani et al. (2004) administered the Symptom Checklist-90 (SCL-90) to 768 young people from multiple locations across Italy and the UK who were divided into six *post hoc* comparison groups: non-drug users, alcohol and/or tobacco users, cannabis and/or alcohol and/or tobacco users, non-ecstasy polydrug users, light (<20 occasions) polydrug ecstasy users, and heavy (>20 occasions) polydrug ecstasy users. Sex and group differences were analysed on three subscales: somatization, depression and anxiety. Females tended to score higher than males on all three scales regardless of group. However, significant sex differences (with females scoring higher) were found only in the alcohol/tobacco group for all three subscales, and in the cannabis, alcohol and tobacco group and light ecstasy polydrug group for the depression scale. In terms of group differences, in the male sample, ecstasy and non-ecstasy polydrug users scored significantly higher than the other groups on the somatization and anxiety subscales. There were no significant group effects in the female sample, whose scores remained relatively similar across groups.

Unfortunately, clear conclusions cannot be made about sex differences in the specific effects of ecstasy use on psychopathology found in this study. This is because there were several methodological limitations, including groups not being well matched, the use of a modified (and therefore not well validated) version of the SCL-90, uncertainty regarding whether participants were drug free at the time of assessment, and knowing whether the mean SCL-90 scores in this study reached a clinical threshold (see Cole et al., 2002c). Tentatively, these findings may indicate that females are more vulnerable to the psychological effects of drugs regardless of drug type. Alternatively, males may be more likely than females to develop psychopathological symptoms following drug use, whereas such symptoms may already be present in females prior to the onset of drug use (Milani et al., 2004). There is some evidence for this latter suggestion as shown in studies of psychiatric comorbidity with other substances of abuse (see Brady and Randall, 1999). These questions would be best addressed via longitudinal prospective designs that utilise more thorough and valid structured clinical assessment in addition to symptom checklists (e.g., Lieb et al., 2002).

In the first study to assess cognitive functioning of ecstasy users across sexes, Bolla et al. (1998) tested the immediate and delayed verbal and visual memory

functioning of at least 2-week abstinent ecstasy users versus control participants. Regression analysis found that the estimated monthly dose (milligrams) of MDMA was significantly associated with reduced immediate verbal memory and delayed visual memory scores. Sex was also found to be predictive of performance, whereby males showed greater decrements in delayed verbal and visual memory with increasing monthly dose of MDMA relative to females. Sex differences were also seen in control participants, where women performed better than men. It may be that females possess a degree of ‘cognitive reserve’ in terms of memory abilities, which may result in an increased threshold for ecstasy-related memory deficits. In terms of cognitive functioning, it is important for studies assessing sex as an independent variable to account for the fact that there are known baseline differences between males and females in aspects of cognition, particularly memory (e.g., see Kimura and Clarke, 2002; Lezak et al., 2004; Springer and Deutsch, 1998).

Using a web-based self-report questionnaire, Rodgers et al. (2003) asked ecstasy-using participants about subjective everyday memory, aspects of prospective memory and memory techniques. The number of errors made while completing the questionnaire was also recorded. There was no difference between males and females in the extent of their ecstasy use (i.e., frequency, lifetime total, and dose). Compared to non-drug and other drug users, ecstasy users reported significantly more difficulties in long-term prospective memory (e.g., ‘I forgot to pass on a message to someone’) and made significantly more questionnaire completion errors, which were both predicted by the extent of ecstasy use. However, there were no sex differences in self-reports of memory functioning.

A study assessing the performance of psychology undergraduate male and female moderate (10–120 occasions) ecstasy users on objective tasks of executive functioning, found that males performed significantly worse than non-drug using controls on tasks of cognitive flexibility and higher level executive functioning (von Geusau et al., 2004). There was virtually no difference in performance between female ecstasy users and controls. Although not significant (possibly due to small sample size), the males had used on average, a greater cumulative number of ecstasy tablets than the females (53.82 vs. 38.78), which may have contributed to the observed findings. Furthermore, although participants were asked to abstain from psychoactive substances for a minimum of 2 weeks, this was not biochemically confirmed; therefore, subacute effects may factor into the findings.

To date, the most rigorous study to examine the role of sex in the long-term cognitive effects of ecstasy use assessed various domains of cognitive functioning among abstinent (mean = 161 days) male and female ecstasy users and cannabis users while statistically controlling for age, sex, ethnicity, education level, estimated premorbid intelligence and frequency of other drug use (Medina et al., 2005). Regression analysis showed that ecstasy exposure was

significantly related to poorer verbal memory and better design fluency in a dose-dependant fashion. The only influence of sex was that it moderated the relationship between ecstasy use and design fluency, whereby men tended to perform better with increasing use of ecstasy while women performed worse. The finding of better design fluency among male higher ecstasy users is surprising and warrants further investigation, but may be due to sacrificed accuracy relative to number of designs (Medina et al., 2005) or ‘cortical disinhibition’ (see Yip and Lee, 2005).

Although clear sex differences have emerged in terms of the acute and subacute psychoactive effects of ecstasy, with females appearing to be more affected, the current data on long-term psychological and cognitive sequelae provides little evidence for sex differences, with a few minor exceptions (e.g., Medina et al., 2005; von Geusau et al., 2004). However, given the presence of methodological limitations in many of these studies, future research that employs prospective designs, with larger sample sizes, and well-matched control groups, including polydrug control groups, will clarify whether the effect of sex of the ecstasy user influences the drugs’ long-term effects.

In addition, another important area for future ecstasy/MDMA research is the assessment of whether there are sex differences in the acquisition, maintenance and relapse of ecstasy administration. There is a large body of evidence showing that sex differences occur in these phases of addiction for other substances, such as cocaine, nicotine and opiates (for reviews see Carroll et al., 2004; Festa and Quinones-Jenab, 2004; Gritz et al., 1996; Lynch et al., 2002). Regular ecstasy use appears to be associated with a rapid development of tolerance (Parrott, 2005; Solowij et al., 1992) and ecstasy dependence according to DSM-IV (APA, 1994) criteria has been reported (Cottler et al., 2001; Jansen, 1999; von Sydow et al., 2002), therefore the assessment of whether there are differences by sex is important. Although one study found no sex differences in self-reported tolerance (Verheyden et al., 2003), two studies have found that being male is associated with a greater risk of developing ecstasy abuse and dependence (von Sydow et al., 2002; Yacoubian et al., 2004).

To conclude this discussion of human studies of ecstasy use, it is necessary to mention that there are several important limitations inherent to this area of research. Firstly, as is common in most substance use research, a major limitation of human ecstasy research is the cross-sectional experimental designs that are used. Therefore, factors found to be associated with ecstasy use, such as altered 5-HT functioning, can only be interpreted as being associated with rather than directly caused by ecstasy use. Individuals who use ecstasy may have pre-existing altered 5-HT functioning, which may make them more likely to use in the first place. Thus, there is a need for prospective research designs to assess sex differences in the effects (particularly long-term) of MDMA. Some research studies have successfully utilised this design, albeit without assessment of sex differences (e.g., see de Win et al.,

2005; Gerra et al., 2000; Lieb et al., 2002; Zakzanis and Young, 2001). Unfortunately, as with any illicit drug research, the illegal status of ecstasy use makes prospective research with participants who are identified, very difficult for ethical and practical reasons. Studies that rely on retrospective self-reporting of ecstasy use may be highly unreliable, both in terms of reporting the amount of use and the fact that the drug(s) actually present in ecstasy tablets varies and may not always be MDMA (Bedi and Redman, 2006; Cole et al., 2002b; Parrott, 2004). Finally, polydrug use is the norm among ecstasy users (Allott and Redman, 2006; Topp et al., 1999), which confounds the interpretation of results; therefore it is important for studies with humans to at least recruit well-matched control groups in an attempt to control for the confounding effects of substance use other than ecstasy.

5. Discussion and conclusions

Based on a review of a small body of literature, the combined findings of preclinical and clinical studies that have included sex as an independent variable suggest that adult females are more susceptible than males to the acute and subacute psychological and physical adverse effects of ecstasy/MDMA. However, males appear more sensitive to the acute physiological effects of ecstasy/MDMA. In addition, alterations in various measures of 5-HT functioning are more pronounced in female current ecstasy users. Moreover, there appears to be a significant relationship between the amount of ecstasy/MDMA use and its effects, at least in females. As these conclusions are based on a relatively small body of research, they are tentative and further studies are needed. Only sex differences in the pharmacodynamic effects of MDMA have been studied to date (with the exception of Chu et al., 1996). There is a paucity of research examining whether there are acute pharmacokinetic sex differences following the administration of MDMA in both animals and humans. This is an important direction for future research as it is suggested that this may be one explanation for sex differences in pharmacodynamic effects.

To date, there is no clear evidence that there are sex differences in long-term psychological and cognitive functioning following regular ecstasy use. However, it is now well recognised that MDMA use and clinical depression are independently associated with 5-HT malfunctioning (Brown et al., 1991; Green et al., 2003; Naughton et al., 2000). The sex differences reported regarding the acute and subacute psychological responses to MDMA are particularly salient with regard to the well-documented finding in the epidemiological literature of a female preponderance for mood disorders, particularly depression (Bebbington et al., 1998; Gater et al., 1998). Interestingly, one study found that healthy euthymic women were more susceptible to a significant lowering of mood in response to acute tryptophan depletion relative to a comparable sample of males (Ellenbogen et al., 1996).

Furthermore, research has shown that the rapid depletion of tryptophan in females who are in remission from clinical depression results in an acute relapse of depressive symptoms (Smith et al., 1997). Therefore, females who use ecstasy, particularly those with a history of depression, may be at a greater risk for future psychological difficulties, such as a relapse of their depression. There is also evidence to suggest that for females, the stage of their menstrual cycle and/or OC intake may influence the subjective effects of ecstasy/MDMA, which may in turn alter consumption levels. This is also an important avenue for future research.

Ecstasy users who attend dance parties have reported engaging in unprotected sex (McElrath, 2005; Riley et al., 2001). Therefore, another important issue specific to female ecstasy users is the concern that there is a risk of (accidental) gestational exposure in women of childbearing age, particularly in women with unplanned pregnancies (Ho et al., 2001). Gestational exposure to ecstasy may lead to congenital defects and/or increased risk for abnormal neurodevelopment (Broening et al., 2001; McElhatton et al., 1999; Meyer et al., 2004; Williams et al., 2003, 2005). Indeed, prenatal (equivalent to human first trimester) MDMA exposure has been associated with persistent neurochemical alterations in rat pups, including lowered monoamine metabolite concentrations (HVA, 5-HIAA), reduced DA and 5-HT turnover, and increased immunoreactive tyrosine hydroxylase fibre density in various brain regions (Koprach et al., 2003). Behavioural alterations, including atypical levels of locomotor activity and absence of habituation to a novel environment, have also been associated with prenatal MDMA exposure in juvenile rats (Koprach et al., 2003).

It is still unclear why sex differences might exist in response to MDMA consumption; however, based on the MDMA (and other psychoactive substance) research presented to date, three possible reasons for such differences are suggested:

- (1) The influence of gonadal hormones, particularly oestrogen and progesterone, in regulating MDMA response in females, either by moderating 5-HT and DA neurotransmission or by regulating gene expression of 5-HT and DA receptors/reuptake transporters that are targeted by MDMA;
- (2) Sex differences in pharmacokinetic variables, such as distribution and metabolism, which may influence the distribution and bioavailability of MDMA; and/or
- (3) The possibility of the presence of already existing sex differences in brain structure (i.e., volume and morphology) (e.g., de Courten-Myers, 1999) and/or neurotransmitter system function, which may provide a different profile of vulnerability for females compared to males. This hypothesis is one which has received attention in the depression and schizophrenia literature as a possibility in explaining the known sex differences in prevalence and phenomenology of these disorders

(DeLisi et al., 1989; Frackiewicz et al., 2000; Goldstein et al., 2002; Kornstein, 1997).

Further examination and explanation of the apparent sex differences in subjective and neurological responses following the use of ecstasy/MDMA should be a major focus of future studies. This would require the routine inclusion of females in studies of ecstasy/MDMA, while controlling for menstrual cycle phase and OC intake (e.g., Becker et al., 2005; Kelly et al., 1999) and the addition of sex as an independent variable in data analyses. Studies such as these will serve to better guide current drug education, harm reduction and treatment approaches. While it is acknowledged that sex may confound the interpretation of results due to the differences in biology of males and females, it is argued that this is the reason to include rather than exclude sex as a variable of interest in studies of substance use.

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