Oxytocin, cortisol and 3,4-methylenedioxymethamphetamine: neurohormonal aspects of recreational 'ecstasy'

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Most research into 3,4-methylenedioxymethamphetamine (MDMA) has debated its psychobiological effects in relation to neurotransmission. This article debates the contributory roles of the neurohormones oxytocin and cortisol for their psychobiological effects in humans. The empirical literature on these neurohormones is reviewed and suggestions for future research outlined. Acute MDMA or 'ecstasy' can generate increased levels of oxytocin and cortisol, and these neurohormonal changes may be important for its mood-enhancing and energy-activation effects in humans. However, an initial finding of enhanced sociability correlating with oxytocin levels has not been replicated. Potential reasons are debated. There may be dynamic interactions between the two neurohormones, with greater activation under cortisol, facilitating stronger positive feelings under oxytocin. Chronic regular use of MDMA can adversely affect cortisol in several ways. Regular users show increased cortisol in 3-month hair samples, changes to the cortisol awakening response, and indications of greater daily stress. Furthermore, these cortisol findings suggest changes to the hypothalamic–pituitary–adrenal axis. The effects of chronic MDMA usage on oxytocin still need to be investigated. It is concluded that the neurohormones oxytocin and cortisol contribute in various ways to the psychobiological effects of recreational ecstasy/MDMA. *Behavioural Pharmacology* **27:649–658**

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Introduction

3,4-Methylenedioxymethamphetamine (MDMA) is a ring-substituted methamphetamine derivative and a powerful central nervous system stimulant. Its acute administration leads to pronounced psychophysiological arousal and a range of heightened mood states (Meyer, 2013; Parrott, 2013a; Taurah *et al.*, 2014; McCann and Ricaurte, 2014; White, 2014). Neurochemically, MDMA is an indirect agonist for serotonin, noradrenaline and dopamine, and it also affects several other neurotransmitter systems (McDowell and Kleber, 1994; Ricaurte *et al.*, 2000; Green *et al.*, 2003; Roger-Sanchez *et al.*, 2016). Empirical studies and theoretical reviews have focussed primarily on these neurochemical properties and debated its psychological effects in relation to serotonin and other neurotransmitters (Kish *et al.*, 2010; Benningfield and Cowan, 2013; Meyer, 2013; Parrott, 2013a, 2013b; McCann and Ricaurte, 2014).

MDMA also affects the hypothalamic–pituitary–adrenal (HPA) axis and stimulates the release of several neurohormones. Hence, an acute dose of MDMA leads to significant increases in cortisol levels (Dumont and Verkes, 2006; Morefield *et al.*, 2009), whereas regular drug users show altered cortisol rhythms (Gerra *et al.*, 2003; Parrott *et al.*, 2014a, 2014b; Wetherell and Montgomery, 2014). Given the central role of the HPA axis for homeostasis and everyday well-being, these changes to cortisol may contribute to many of the psychobiological sequelae of MDMA (Parrott, 2009; White, 2014). In the past 10 years, oxytocin has become of increasing interest to MDMA researchers. Acute MDMA administration stimulates the release of oxytocin, and it has been hypothesized that this neurohormone may underlie its mood-enhancing and prosocial properties (McGregor *et al.*, 2008; Dumont *et al.*, 2009; Frokjaer *et al.*, 2014; Kamilar-Britt and Bedi, 2015). The core aim of this review is to analyse and debate the contributory roles of these two neurohormones for the psychobiological effects of MDMA in humans. The secondary aim is to suggest interesting questions for future research.

Psychobiological aspects of recreational ecstasy/MDMA

There are two main reasons for using ecstasy/MDMA as a recreational stimulant drug. First, it boosts physical activation, and second it can intensify positive mood states. An acute dose of MDMA generates a pronounced increase in heart rate, along with other indices of sympathomimetic activation. Hysek *et al.* (2012) reported that 125 mg oral MDMA generated a mean heart rate increase of +26.1 bpm over baseline, together with parallel

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increases in systolic and diastolic blood pressure. This heightened arousal can facilitate prolonged periods of dancing, so that there is a strong association between recreational ecstasy/MDMA and all-night clubbing. In an Internet survey, 94% reported that they danced when they were on ecstasy/MDMA (Parrott *et al.*, 2006), whereas many dance for prolonged periods until they are exhausted (Suy *et al.*, 1999). MDMA is also effective at generating euphoric moods. Cohen (1998) interviewed recreational users about its subjective effects, and one user reported that 'ecstasy is more or less a happy speed' (speed being the street name for amphetamine). Other interviewees described sensory enhancement, feelings of pleasure or elation (Cohen, 1998). In another interview study, it was reported that ecstasy/MDMA led to 'Loads of energy to dance. Buzzing. Loved everyone' (Parrott, 2010). Positive mood profiles also emerged when dance clubbers were assessed using mood questionnaires (Parrott and Lasky, 1998; Morefield *et al.*, 2009). In acute-dose placebo-controlled laboratory studies, significant increases in alertness, elation and euphoria were also reported (Liechti *et al.*, 2001; Bedi *et al.*, 2010; Kirkpatrick *et al.*, 2012).

There are, however, potential dangers from the psychophysiological overactivation induced by stimulant drugs (Laviola *et al.*, 1999; Cruickshank and Dyer, 2009; Parrott, 2015). In relation to acute mood, the heightened stimulation induced by MDMA can generate feelings of panic, anxiety, paranoia or depersonalization – hence the following subjective reports by recreational users: 'Out of control. Too much extra energy'; 'I had a bad experience. I felt like I was surrounded by water and drowning' (Cohen, 1998). In laboratory studies, acute doses of MDMA can generate significant feelings of anxiety, loneliness, feeling jittery and 'bad drug effect' (Liechti *et al.*, 2001: Bedi *et al.*, 2010; Kirkpatrick *et al.*, 2012). Psychophysiological adverse effects can include 'Twitching and shaking of the leg'; 'Chews his mouth and lips all night' (Parrott, 2010). The medical dangers of MDMA include cardiac damage, renal problems, liver damage and hyperthermia (Hall and Henry, 2006; Greene *et al.*, 2009; White, 2014). Neurocognitive and psychobiological abreactions include memory deficits, higher cognitive deficits, reduced social intelligence, disrupted sleep architecture and sleep apnoea, reduced immunocompetence, increased pain sensitivity, and a range of psychiatric issues (Kemmerling *et al.*, 1996; Schifano *et al.*, 1998; McCann *et al.*, 2000; Parrott, 2001, 2013a, 2013b; Fisk *et al.*, 2005; Reay *et al.*, 2006; McCann and Ricaurte, 2007, 2014; Montgomery *et al.*, 2010; Brière *et al.*, 2012; Meyer, 2013; White, 2014). There is a great deal of individual variation in these acute reactions, leading to the question of why some individuals seem quite sensitive, whereas others are more robust. Numerous factors may be important, including premorbid personality, sex, and patterns of drug usage. However, another key factor may be the HPA axis and neurohormonal integrity, as any individual differences in baseline neurohormonal levels and/or reactivity may influence the development of acute and chronic psychobiological responses to psychoactive drugs.

Acute MDMA and oxytocin

Dumont and Verkes (2006) reviewed human acute-dose MDMA studies and noted that, although 12 studies had investigated cortisol, and four had assessed prolactin, none had measured oxytocin. The first human study of oxytocin was undertaken by Wolff *et al.* (2006), who took urine samples before and after clubbing from dance clubbers. The dancers with MDMA in their urine demonstrated an increase in oxytocin after clubbing (from 1.28 at baseline to 1.43 pmol/l), whereas nonusers showed reduced oxytocin (from 1.23 at baseline to 1.16 pmol/l after clubbing). Wolff *et al.* (2006) also found changes in vasopressin and urine osmotality, which were debated in relation to the increased risk for potentially fatal cerebral oedema. Emanuele *et al.* (2006) offered a broader psychosocial–psychosexual interpretation for these oxytocin findings. In a detailed commentary on Wolff *et al.* (2006), they suggested that 'Induction of vasopressin and oxytocin release following MDMA assumption could also account for several sociosexual behavioural effects… including attachment and trust… sexual arousal... and libido'. McGregor *et al.* (2008) reviewed the empirical evidence for oxytocin being involved in the prosocial and prosexual behaviours of laboratory animals. They noted that this social neuropeptide was involved in reinforcement and dependency on other psychoactive drugs (e.g. opiates, alcohol) and recommended further research with MDMA.

In the first laboratory study into oxytocin, Dumont *et al.* (2009) found that 100 mg oral MDMA generated robust increases in oxytocin and subjective prosocial feelings. They further noted that the prosocial feelings were significantly associated with oxytocin levels. Furthermore, these positive correlations with oxytocin were stronger that those found with plasma MDMA (Table 1). These findings supported the predicted role of oxytocin in relation to the prosocial effects of ecstasy/MDMA (McGregor *et al.*, 2008). However, subsequent studies have generally failed to replicate this finding. Hysek *et al.* (2012) found that 'Reading the Mind in the Eyes' test was affected in complex ways by MDMA, with enhanced accuracy for positive social stimuli, reduced accuracy for negative emotional stimuli, and no change for neutral stimuli. Plasma oxytocin levels were significantly increased after MDMA, although the increased oxytocin levels were not associated with any of the prosocial feelings or behaviours (Table 1). Schmid *et al.* (2014) compared the acute effects of 75 mg oral MDMA and 40 mg oral methylphenidate in 30 volunteers. MDMA was found to enhance empathy for positively emotionally charged situations and increase feelings of openness and trust, whereas these effects were not found with methylphenidate. MDMA also increased oxytocin and cortisol levels

Table 1 Overview of 3,4-methylenedioxymethamphetamine acute-dose laboratory studies into oxytocin and psychosocial measures

Reference; drug conditions	Oxytocin changes	Psychosocial measures	Associations between oxytocin and the prosocial measures
Dumont *et al.* (2009); 100 mg oral MDMA and placebo	Oxytocin significantly increased	Increased prosocial feelings	Significant positive association between oxytocin and prosocial measures
Hysek *et al.* (2012); 125 mg oral MDMA and placebo	Oxytocin significantly increased	Overall bias towards positive mood judgements, and away from negative mood judgements	No association between oxytocin and any psychosocial measure
Hysek *et al.* (2014); 125 mg oral MDMA and placebo, with equal males and females	Oxytocin significantly increased	Emotional recognition impaired overall, and emotional empathy improved. Complex sex and emotional valence effects	No correlation between oxytocin and any psychosocial measure
Schmid *et al.* (2014); 75 mg oral MDMA, 40 mg methylphenidate and placebo	Oxytocin significantly increased	Enhanced empathy and increased feelings of openness/trust	No correlation between oxytocin and any emotional or sociocognitive measure
Kuypers *et al.* (2014); 75 mg oral MDMA oxytocin nasal spray and placebo	Borderline trend for increased oxytocin ($P=0.071$, two-tailed)	Increased emotional empathy. No gains in cognitive empathy or trust	No correlation between oxytocin and emotional empathy or other measures
Kirkpatrick *et al.* (2014b); 75 mg and 125 mg oral MDMA, nasal oxytocin and placebo	Oxytocin significantly increased by 125 mg MDMA. Nonsignificant trend with 75 mg dose	Increased euphoria and sociability after the higher dosage	No correlation between oxytocin and mood gains

MDMA, 3,4-methylenedioxymethamphetamine.

significantly, whereas methylphenidate increased cortisol but not oxytocin. However, there were no significant correlations between any of the emotional and psychosocial gains, and the increased levels of oxytocin.

Hysek *et al.* (2014) administered oral doses of 125 mg MDMA to 32 healthy volunteers, which included equal numbers of men and women. Oxytocin, cortisol and prolactin were significantly increased (each at $P<0.001$). Performance levels on the Multifaceted Empathy test, the Social Values Orientation test, and the Facial Affect Recognition test were affected in complex ways. MDMA impaired the accuracy of emotional recognition overall in comparison with placebo, regardless of emotional valence, although this deficit mainly reflected an impairment in the accuracy of perceiving negative valence faces (e.g. fearful, angry, or disgusted). MDMA increased explicit and implicit emotional empathy ratings overall, although these increases were mainly for positive valence stimuli rather than for negative valence stimuli; again, there were sex differences. On the social orientation measure, MDMA increased prosociality overall, although this was primarily due to an increase in male volunteers, with female volunteers showing no change. Overall, this assessment battery showed a surprisingly complex pattern of changes, with increased positive perceptions on some measures, along with neutral or negative findings on other measures. Despite the large number of dependent variables, none were associated with the changes in oxytocin, cortisol or prolactin, Hysek *et al.* (2014) commented that 'No correlations were found between the effects of MDMA on emotional recognition and the endocrine effects of MDMA'.

Kuypers *et al.* (2014) compared four treatment conditions: 75 mg oral MDMA with/without 20 mg oral pindolol (a partial 5-HT_{1A} receptor blocker), nasal oxytocin spray, and placebo. The oxytocin spray led to plasma oxytocin levels 2.5 times higher than placebo ($P=0.033$), 75 mg oral MDMA led to plasma oxytocin levels 2.3 times higher than placebo ($P=0.071$), whereas MDMA + pinidol led to an oxytocin increase 2.0 times higher than placebo ($P=0.071$). Hence, although the increases in oxytocin under the two MDMA conditions were nonsignificant, they were statistically borderline and in the predicted direction (note: both MDMA conditions generated highly significant increases in cortisol). MDMA led to an increase in emotional empathy, but left the measures of cognitive empathy, reciprocity and trust unaffected. Finally, the changes in emotional empathy were not statistically related to plasma oxytocin levels (Table 1).

Kirkpatrick *et al.* (2014a, 2014b) compared the effects of 75 mg and 125 mg oral MDMA, nasal oxytocin and placebo in 14 abstinent recreational ecstasy/MDMA users. The lower dose of MDMA led to a slight (nonsignificant) trend for increased oxytocin, whereas the 125 mg dose of MDMA led to a pronounced oxytocin increase, with values 450% higher than those of placebo. In cardiovascular terms, MDMA led to significant dose-related increases in heart rate and blood pressure. The higher dose of MDMA also led to significant increases in self-rated euphoria, sociability and friendliness. However, these positive mood changes were independent of oxytocin levels, with Kirkpatrick *et al.* (2014b) noting that none of the subjective or cardiovascular responses to MDMA were significantly correlated with plasma oxytocin. To summarize, the early finding of an association between oxytocin and prosocial feelings (Dumont *et al.*, 2009) has not been confirmed in subsequent studies (Hysek *et al.*, 2012, 2014; Kuypers *et al.*, 2014; Schmid *et al.*, 2014; overview in Table 1).

Acute MDMA and cortisol

In their review of acute MDMA research, Dumont and Verkes (2006) noted that the cortisol findings were very consistent, with significant increases in 11 of 12 studies, whereas the only nonsignificant study had utilized a low

dosage. To give some examples of these cortisol findings, Mas *et al.* (1999) reported significant increases following acute doses of both 75 and 125 mg oral MDMA. Pacifici *et al.* (2001) reported significant increases in cortisol following both single and closely repeated doses of MDMA. Harris *et al.* (2002) found that a low dose of 0.5 mg/kg led to a cortisol increase of around 100%, whereas the higher and more typical dose of 1.5 mg/kg led to an increase of 150% compared with baseline. Spaced dosing was empirically investigated by Farre *et al.* (2004), who found that each dose led to significant increases in cortisol. Seibert *et al.* (2014) administered oral doses of 125 mg MDMA to in-bed volunteers resting in a hospital setting. Significant increases in cortisol, corticosterone and 11-dehydroxycorticosterone were found, with peak effects 1–3 h after drug administration.

Neurohormonal changes have also been investigated in real-world studies of dance clubbers. Parrott *et al.* (2008) prospectively monitored recreational ecstasy/MDMA users over successive weekends, when dance clubbing at a city venue with the same group of friends. On one weekend they partied as usual, whereas on the other they abstained from MDMA (with order counterbalanced). Saliva analyses confirmed MDMA in every participant during their 'normal' weekend and its absence during the weekend off MDMA. Dance clubbing while on MDMA led to a peak increase of 800% in salivary cortisol, whereas cortisol was not significantly changed during the off MDMA weekend. This pronounced cortisol enhancement was confirmed in another real-world study, with more experienced drug users at weekend 'house parties' (Parrott *et al.*, 2007). There was a group mean peak increase of 800% in cortisol when partying on MDMA but again no significant change in cortisol when partying off MDMA. Wolff *et al.* (2012) recorded cortisol levels of dance clubbers before and after clubbing. Urine analyses revealed that 21 had used MDMA, whereas 18 were nonusers. Postclubbing cortisol levels were significantly higher in MDMA users compared with those in nonusers, with a comparative increase of 110%. These postclubbing samples were collected between 03:00 and 08:00 in the morning, and covered a time of post-MDMA recovery (note: cortisol was not measured at the club, when peak drug effects would be expected). Wolff *et al.* (2012) also investigated genetic factors and found significant associations between low activity in the COMT genotype and heightened cortisol responses in both groups. There was also an association between the CYP2D2 genotype and heightened cortisol levels but only in the MDMA subgroup. For an extended debate about these real-world cortisol findings, see Parrott *et al.* (2013) and Wolff and Aitchison (2013).

There are some interesting differences in the acute neurohormonal effects of MDMA at dance clubs versus the laboratory. Partying on ecstasy/MDMA led to peak increases in cortisol of around 800%, whereas peak increases in the laboratory studies were around 150–200%. The greater neurohormonal response when dancing and partying may reflect the combined effects of taking a central nervous system stimulant drug in stimulatory conditions. Hence, it has been suggested that prolonged physical exertion, loud music and social crowding may potentiate the stimulatory drug effects (Parrott *et al.*, 2006). It may also be influenced by other factors such as circadian rhythms (Herbert *et al.*, 2007), or differences in dosage levels. However, it should be noted that in the study by Parrott *et al.* (2007) the more experienced users took larger amounts of ecstasy/MDMA than did the less experienced users in the study by Parrott *et al.* (2008); yet both groups achieved similar peak increases in cortisol. This self-titration of different doses may reflect the development of chronic tolerance (review: Parrott, 2005); yet it was interesting that both groups achieved similar peak levels of cortisol. Whatever the reasons for the differences between the laboratory and real-world findings, recreational ecstasy/MDMA users certainly experience very high levels of cortisol while partying.

Chronic MDMA and cortisol

Gerra *et al.* (2003) were the first to empirically investigate the neurohormonal consequences of chronic ecstasy/MDMA usage. They found significant differences between long-term recreational ecstasy users and nonuser controls, both in baseline cortisol and cortisol reactions to a 'psychosocial' stressor. Gerra *et al.* (2003) concluded that 'HPA basal hyperactivation and reduced responsiveness to stress may represent a complex neuroendocrine dysfunction associated with MDMA use'. Cortisol can be measured in hair samples (Kirschbaum *et al.*, 2009; Stalder and Kirschbaum, 2012), with 3-cm lengths providing an index of neurohormonal activity over the previous 3 months. Parrott *et al.* (2014a) analysed hair samples of 101 young participants: light and heavier ecstasy/MDMA users during the previous 3 months, and nonuser controls. The recent heavy ecstasy/MDMA users had mean cortisol levels 400% higher than that of nonuser controls, whereas the recent light users showed a nonsignificant trend for higher cortisol. These cortisol findings indicate that a high level of psychobiological stress is being experienced by regular recreational ecstasy/MDMA users. A high variance of the heavy user group should also be noted, especially in comparison with the low variance of the control group, as it indicates considerable variation in their levels of psychobiological stress.

The secretion of cortisol follows a regular diurnal rhythm (Khoury *et al.*, 2015; Stalder *et al.*, 2016): the act of awakening from sleep is followed by a cortisol peak around 30 min later. This pattern has been termed the cortisol awakening response, where awakening in the morning generated a peak 50–75% rise in plasma cortisol (Stalder *et al.*, 2016). The cortisol awakening response provides neuroendocrinology research with a standard index for the integrity of the HPA axis (Fries *et al.*, 2009; Frokjaer

et al., 2014; Khoury *et al.*, 2015; Stalder *et al.*, 2016). It has been investigated with recreational ecstasy/MDMA users in two recent studies. Wetherell and Montgomery (2014) compared light and heavy ecstasy/MDMA users with nonuser controls on a low-stress day and a high-stress day. The cortisol awakening response was similar for all three groups on the low-stress day but was significantly raised in the heavy ecstasy user group on the high-stress day. Cortisol levels before bedtime were also significantly raised in both ecstasy/MDMA groups on the high-stress day. Frokjaer *et al.* (2014) compared 18 drug-free recreational ecstasy/MDMA users with 32 nonuser controls. The cortisol awakening response was significantly higher in the ecstasy/MDMA users, compared with controls (see figure 2 from Frokjaer *et al.*, 2014). Furthermore, the degree of enhancement of the cortisol awakening response was significantly associated with greater prefrontal binding of the serotonin transporter. To summarize, regular ecstasy/MDMA users can display raised levels of cortisol both after awakening and later in the diurnal cycle (Frokjaer *et al.*, 2014; Wetherell and Montgomery, 2014). They also demonstrate significant increases in 3-month cortisol levels in hair samples and altered cortisol reactivity to stress (Gerra *et al.*, 2003; Parrott *et al.*, 2014a, 2014b). Khoury *et al.* (2015) noted that mainstream cortisol research generated two key measures: total cortisol and cortisol change/reactivity. Both elements have been investigated in MDMA research, and both show significant drug effects. Hence, there are clear hormonal indications of HPA axis impairments in recreational ecstasy/MDMA users.

In terms of functional implications, cortisol is involved in many core areas for well-being, including homeostasis, sleep, waking, appetite, memory, cognition, psychiatric aspects and neuronal integrity. In an overview of the nonpharmacological research, Herbert *et al.* (2007) noted that high levels of corticosteroids were potentially damaging to many of these core functions. Excess levels of corticosteroids could damage the brain directly, or increase its susceptibility to damage by other noxious agents. These neuropsychobiological deficits are summarized in Table 2. In another cortisol review, it was noted that many of these same functions were also affected in drug-free recreational ecstasy/MDMA users (Parrott, 2009). Hence, these changes in cortisol might play a contributory role in many of the adverse psychobiological effects of recreational ecstasy/MDMA (Table 2). Since that review, further studies have generated further empirical evidence for drug-related functional deficits (McCann *et al.*, 2009, 2011; Brière *et al.*, 2012; Singer *et al.*, 2013, 2016; Ogeil *et al.*, 2011; Parrott, 2013a, 2013b, 2014; Taurah *et al.*, 2014; Downey *et al.*, 2015). The relative contributory role of neurohormones such as cortisol and oxytocin, and neurotransmitters such as serotonin, dopamine and noradrenaline, is a complex question. Most reviews have focussed on the role of neurotransmission (Kish *et al.*, 2010; Benningfield and Cowan, 2013; Parrott, 2013b; Meyer, 2013; McCann and Ricaurte, 2014; Taurah *et al.*, 2014). However, cortisol may also have a contributory role. Some of its effects will be indirect, by modulating serotonergic neurotransmission, and hence affecting a wide variety of psychobiological functions (Chaouloff, 2000; Frokjaer *et al.*, 2014). Other effects may be through alterations in the HPA axis, with impaired homeostasis, disturbed sleep, increased stress, fluctuating moods and other indices of increased psychobiological vulnerability (McCann and Ricaurte, 2007; Parrott, 2009, 2013a, 2013b; Scholey *et al.*, 2011; Ogeil *et al.*, 2011, 2013; Wetherell and Montgomery, 2012, 2014). Future studies may illuminate this complex issue.

Broad overview

Recent theoretical interest in the neurohormonal aspects of MDMA has focussed mostly on oxytocin. Here the proposed functional model is very clear: oxytocin is thought to underlie the positive moods and prosocial feelings engendered by recreational MDMA (McGregor *et al.*, 2008; White, 2014; Kamilar-Britt and Bedi, 2015). In empirical support of this model, Dumont *et al.* (2009) found a significant association between oxytocin release and the prosocial feelings induced by MDMA. Subsequent studies have also demonstrated increased levels of oxytocin, and they have often been accompanied by increases in prosocial behaviours. However, against this model, these same studies have consistently failed to demonstrate an association between psychosocial measures and increases in oxytocin levels (Table 1). The absence of the predicted correlations has been noted by every research group in this field. Hysek *et al.* (2014) commented that, although they found increases in oxytocin and emotional cognition, 'We found no correlation between MDMA-induced endocrine and emotional changes'. Kirkpatrick *et al.* (2014a, 2014b) compared the effects of oral MDMA with nasal oxytocin, but they noted that MDMA and oxytocin did not produce similar effects. Kamilar-Britt and Bedi (2015) similarly concluded that in humans the degree to which oxytocin was involved in the prosocial effects of oxytocin remained unclear.

These researchers have also debated potential explanations for the absence of the expected association. The difficulty of estimating central oxytocin levels from peripheral measures has often been noted (Hysek *et al.*, 2014; Kamilar-Britt and Bedi, 2015; others). The practical difficulties of researching nasal oxytocin in humans have been outlined by Churchland and Winkielman (2012). They noted that oxytocin was an unstable hormone, with many diverse effects on body and brain. It was also unclear whether nasal oxytocin reached the brain, because of the intricacies of the blood–brain barrier. Leng and Ludwig (2016) similarly noted that little of intranasally administered oxytocin reached the cerebrospinal fluid, whereas peripheral concentrations could

Table 2 Psychobiological functions affected by cortisol and ecstasy/3,4-methylenedioxymethamphetamine: a broad overview (after Parrott 2009, with some updated references)

Psychobiological functions	Cortisol	MDMA/ecstasy
Memory: task performance deficits	Backhaus *et al.*, 2006	McCann and Ricaurte, 2014
Memory: subjective complaints	Wolf *et al.*, 2005	Rodgers *et al.*, 2003
Higher cognition: performance deficits	McMorris *et al.*, 2006	Fox *et al.*, 2002
Other cognitive task impairments	Oei *et al.*, 2006	Montgomery *et al.*, 2010
Sleep and circadian rhythm	Stalder *et al.*, 2016	Ogeil *et al.*, 2011
Eating and feeding	Nieuwenhuizen and Rutters, 2008	Turner *et al.*, 1998
Depression	Nemeroff and Vale, 2005	Brière *et al.*, 2012
Impulsivity	Fishbein *et al.*, 1989	Taurah *et al.*, 2014
Other clinical disorders	Strohle and Holsboer 2003	Parrott, 2013a,b
Oxidative stress	McEwan 2006	Zhou *et al.*, 2003
Hippocampal changes	Nagaraja *et al.*, 2007	Jacobsen *et al.*, 2004
Neuronal damage	Herbert *et al.*, 2007	Benningfield and Cowan, 2013

MDMA, 3,4-methylenedioxymethamphetamine.

be increased substantially. Another issue is the broadness and diversity of the concept of psychosocial benefits as it can encompass a wide range of emotions and cognitions. Indeed, this may be a crucial factor in explaining the difference between the animal and human findings. Each person can respond to ecstasy/MDMA in different ways, some more emotionally, others more cognitively, and this will increase the random/error variance for any grouped data. Other potential explanatory factors might include group differences in ethnicity or sex, perceived stresses during testing, while genetic factors also need to be studied. Nevertheless, given the extensive preclinical and other evidence for oxytocin and prosocial behaviours (Kovacs *et al.*, 1998; McGregor *et al.*, 2008; McGregor and Bowen, 2012; Churchland and Winkielman, 2012; Broadbear *et al.*, 2014), the absence of the expected association in human MDMA research (Table 1) does remain somewhat surprising.

Turning to cortisol, here the empirical findings are clear. An acute dose of MDMA can increase cortisol levels both in the laboratory (Dumont and Verkes, 2006) and in the real world of dance clubbers (Parrott *et al.*, 2008). Cortisol is involved in basic metabolic activation and is integral to the sympathomimetic alertness caused by stimulant drugs. It increases the delivery of increased energy supplies to the muscles and facilitates prolonged dancing. However, excessive stimulation is also a factor in the acute hyperthermia and other acute medical problems that develop in some recreational uses (Hall and Henry, 2006). MDMA can impair hypothalamic thermoregulation and lead to increased body temperature, both in the laboratory (Freedman *et al.*, 2005) and in recreational users (Morefield *et al.*, 2009; Parrott and Young, 2014). In placebo-controlled laboratory studies the degree of overheating is related to MDMA dosage (review: Parrott, 2012), whereas in real-world studies it can be quite variable, with some studies showing slight changes and others revealing large thermal increases. Morefield *et al.* (2009) reported a group mean peak body temperature increase of +1.1°C in 41 Australian party-goers on MDMA. Parrott and Young (2014) reported a group mean peak increase of +1.2°C in 32 Welsh dance clubbers on ecstasy/MDMA. Hyponatraemia, or low sodium levels in the blood, is another commonly observed abreaction. In a biochemical study of Dutch ravers (Van Dijken *et al.*, 2013), hyponatraemia was found in 25% of female MDMA users, compared with 3% of male users. This indicates an interesting sex difference in reactivity to MDMA. Whether this reflects a broader influence of sex on the HPA axis remains to be empirically determined.

In relation to chronic drug effects, Herbert *et al.* (2007) noted that 'Corticosteroids are an essential component of the body's homeostatic system', and that the regular experience of psychobiological overactivation and stress was cumulatively damaging to the organism, citing Hans Selye's classic studies into cortisol and stress (Selye, 1956). The bioenergetic stress model for recreational ecstasy notes that the regular experience of overactivation and biological stress may be cumulatively damaging to the organism (Parrott, 2006). Furthermore, the degree of psychophysiolgical overactivation will depend on both the extent of drug stimulation and environmental costimulation. Hence, 'Dances and raves may help to boost the acute effects of ecstasy/MDMA. But however, this may also make them more problematic in the longer term' (Parrott, 2006, 2009). The multifactorial types of psychobiological and neurocognitive damage caused by recreational ecstasy/MDMA were summarized earlier. Cortisol may play a key modulatory role by altering the HPA axis, damaging homeostasis, and exacerbating any underlying serotonergic changes (Parrott, 2013a, 2013b).

Future research

In future research, the functional aspects of oxytocin should be investigated using a wider battery of assessment measures. Current research has focussed almost exclusively on prosocial measures. This needs to be widened by including measures of more negative moods and behaviours. It was earlier noted that placebo-controlled studies have found that acute MDMA can generate significant feelings of anxiety, loneliness and

depression (Liechti *et al.*, 2001; Bedi *et al.*, 2010; Parrott *et al.*, 2011; Kirkpatrick *et al.*, 2012), whereas recreational ecstasy/MDMA users occasionally experience feelings of anxiety and panic (Cohen, 1998). Furthermore, recreational users who reported taking the drug only a few times described weak mood gains with their first experience (Parrott, 2010). This helps explain why they did not take it again, and confirms that the mood reactions to MDMA are more variable than is commonly portrayed (extensive literature review in Parrott, 2007). It is widely accepted that oxytocin is involved in affiliative behaviours (McGregor *et al.*, 2008; Broadbear *et al.*, 2014). Yet, does oxytocin selectively boost only positive mood states, or might it also be involved in the intensification of negative moods? Might differences in oxytocin reactivity help explain some of the variation in mood reactions to MDMA? Indeed, there may be many factors that influence these mood state changes.

Two further areas for future research are potential effects of MDMA on sex and pregnancy through alterations in oxytocin or other neurohormones. Emanuele *et al.* (2006) suggested that the increased oxytocin levels revealed by Wolff *et al.* (2006) might account for the increased libido and sexual behaviours of MDMA users. The recreational use of MDMA is associated with enhanced sexual pleasure and increased sexual riskiness (Theall *et al.*, 2006; May and Parrott, 2015). In a laboratory study of reactions to erotic stimuli, increased sexual arousal was found after 40 mg oral methylphenidate, although surprisingly this did not occur after 75 mg oral MDMA (Schmid *et al.*, 2015) (note, however, the low dose of 75 mg MDMA, as significant effects might have occurred after a higher dose). Another potential area for future research is human pregnancy, given that oxytocin has important functions in birth. Oxytocin promotes uterine contractions during labour, and milk ejection during lactation (McGregor *et al.*, 2008). Hence, another key question is whether MDMA leads to chronic changes in oxytocin following repeated drug usage. Chronic oxytocin changes have been demonstrated in laboratory animals, and human research is clearly needed (McGregor and Bowen, 2012). Women who regularly used ecstasy/MDMA during their first trimester of pregnancy gave birth to babies with significant psychomotor impairments (Singer *et al.*, 2013, 2016). Future human studies should monitor levels of oxytocin, cortisol and other neurohormones during pregnancy and following birth. Cortisol levels normally increase during the third trimester (Kirschbaum *et al.*, 2009); hence, the extent of this increase should also be investigated in drug-using mothers. Incidentally, the recreational MDMA-using mothers in the studies of Singer *et al.* (2012, 2016) reported heightened depression when taking MDMA, which reduced to normal levels after ecstasy cessation (Turner *et al.*, 2014). Hence, it would be interesting to replicate this prospective pregnancy study using a full battery of neurohormonal measures.

Another topic for future research is whether oxytocin might prove useful as pharmacotherapy for drug dependency. McGregor and Bowen (2012) reviewed the evidence for oxytocin modulation of acute and chronic drug effects, especially those related to affiliative behaviours and reinforcement/reward. Most evidence was preclinical, although they noted supportive human research findings. The core suggestion was that oxytocin might facilitate the treatment of alcohol, opiate and other forms of drug dependency. McGregor and Bowen (2012) noted that oxytocin 'Has fascinating potential to reverse the corrosive effects of long-term drugs abuse on social behaviour and to perhaps inoculate against future vulnerability to addictive disorders'. Another potential research area is oxytocin-assisted pharmacotherapy for post-traumatic stress disorder. Some studies of MDMA-assisted pharmacotherapy have been undertaken, and they have debated the putative role of oxytocin (Greer and Tolbert, 1986; Mithoefer *et al.*, 2011; Doblin *et al.*, 2014). In critiques of this venture, I have raised several psychobiological concerns over the clinical usage of MDMA (Parrott, 2007, 2014a, 2014b, 2016). If oxytocin is involved in the increase in prosocial feelings, then nasal oxytocin might provide a safer alternative for drug-assisted psychotherapy (McGregor and Bowen (2012); Parrott, 2014a, 2016).

There are many intriguing questions regarding the psychobiological functions of cortisol. In relation to acute effects, how is this master neurohormone related to energetic stress and overstimulation in recreational users? How does it contribute to medical abreactions, such as hyperthermia and hyponatraemia? More specifically, is cortisol related to the degree of psychophysiological overstimulation, and can this help to explain why some users cope with the drug robustly and others develop abreactions? Another area is the functional roles of other neurohormones such as prolactin, vasopressin, progesterone and testosterone. Although they have been investigated in several studies (Wolff *et al.*, 2016; Parrott *et al.*, 2007, 2008; Hysek *et al.*, 2014; Schmid *et al.*, 2014; Seibert *et al.*, 2014), the empirical data are very limited. The role of cortisol for everyday homeostasis and well-being was noted earlier, with many suggestions for future research. Another key question is the extent of functional/structural recovery following drug cessation. This is important for both neurotransmitters and neurohormones. Frokjaer *et al.* (2014) noted that 'Future longitudinal studies are needed to determine the time course of potential recovery of HPA axis function after withdrawal from MDMA use'.

Finally, we need to investigate the dynamic interrelations among neurohormones. In neuropharmacology research, there are extensive animal and human data on

hormonal interactions (Carson *et al.*, 2013; Evans *et al.*, 2014), and this information can be used to guide future MDMA research. For the current topic, how are the changes in cortisol related to those of oxytocin? Do they alter in parallel, or are they more independent? If social enhancement was due to synergistic increases in both cortisol and oxytocin, this might explain why positive moods tend to be optimized in socially arousing venues such as dance clubs or raves (Parrott, 2014a, 2014b). Is there variation in the ways they coalter, and, if so, might these be reflected in their differing functional effects? How are they influenced by the psychosocial situation (Evans *et al.*, 2014). One key hypothesis for future research is that the prosocial effects of oxytocin may depend on the degree of psychophysiolgical activation induced by cortisol.

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Conflicts of interest

There are no conflicts of interest.

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