MDMA, cortisol, and heightened stress in recreational ecstasy users

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Stress develops when an organism requires additional metabolic resources to cope with demanding situations. This review will debate how recreational 3,4-methylenedioxymethamphetamine (MDMA, 'ecstasy') can increase some aspects of acute and chronic stress in humans. Laboratory studies on the acute effects of MDMA on cortisol release and neurohormone levels in drug-free regular ecstasy/MDMA users have been reviewed, and the role of the hypothalamic–pituitary–adrenal (HPA) axis in chronic changes in anxiety, stress, and cognitive coping is debated. In the laboratory, acute ecstasy/MDMA use can increase cortisol levels by 100–200%, whereas ecstasy/MDMA-using dance clubbers experience an 800% increase in cortisol levels, because of the combined effects of the stimulant drug and dancing. Three-month hair samples of abstinent users revealed cortisol levels 400% higher than those in controls. Chronic users show heightened cortisol release in stressful environments and deficits in complex neurocognitive tasks. Event-related evoked response potential studies show altered patterns of brain activation, suggestive of increased mental effort, during basic information processing. Chronic mood deficits include more daily stress and higher depression in susceptible individuals. We conclude that ecstasy/MDMA increases cortisol levels acutely and subchronically and that changes in the HPA axis may explain why recreational ecstasy/MDMA users show various aspects of neuropsychobiological stress. *Behavioural Pharmacology* **00:000–000 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

3,4-Methylenedioxymethamphetamine (MDMA) is used as a recreational drug under the street name 'ecstasy' (Solowij *et al.*, 1992; McCann *et al.*, 1996, 1998; Schifano, 2000, 2006; Parrott, 2001, 2004, 2013a; McCardle *et al.*, 2004; Scholey *et al.*, 2004, 2011; Montgomery *et al.*, 2005, 2010; Taurah *et al.*, 2014). Compared with other psychostimulants, its mechanism of action is wide-ranging, causing the release of serotonin, dopamine, and norepinephrine, and also affecting other neurotransmitter systems including acetylcholine and histamine (McDowell and Kleber, 1994; Green *et al.*, 2003; Capela *et al.*, 2009). In addition to its effects on neurotransmission, ecstasy/MDMA also stimulates neurohormonal activity. In preclinical research, MDMA was found to increase plasma levels of prolactin in Rhesus monkeys (Murnane *et al.*, 2010, 2012), and the increase in oxytocin levels following MDMA administration in rats is associated with increased prosocial behavior (Morley *et al.*, 2005). Release of vasopressin (antidiuretic hormone) is also notably higher after MDMA administration in animal models (Forsling *et al.*, 2002), and this may contribute to hyponatremia in both animals and humans. In humans, the effects of acute ecstasy/MDMA administration on neurohormonal functions were reviewed by Dumont and Verkes (2006). They reported that cortisol levels were significantly increased on acute ecstasy/MDMA administration in 11 of 12 published studies and prolactin levels were elevated in five of nine studies; in both cases, the null results were associated with lower doses of ecstasy/MDMA. Empirical evidence on its effects on other neurohormones in humans is limited, although there are indications of increased levels of testosterone, progesterone, and oxytocin (McGregor *et al.*, 2008; Parrott *et al.*, 2008).

Changes in cortisol secretion are also seen after the administration and chronic use of other drugs of abuse. In a drug-administration study, Heesch *et al.* (1995) found that after administration of 2 mg/kg cocaine intranasally, cortisol levels were elevated relative to placebo, suggesting that cocaine increases cortisol levels acutely. Another study found that after intravenous administration of 40 mg cocaine, levels of cortisol were elevated, whereas levels of prolactin were not, suggesting that the effects of ecstasy on neurohormone function are more wide-ranging than those of cocaine (Baumann *et al.*, 1995). Following chronic recreational use or abuse, cocaine appears to dysregulate the stress system. Fox

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et al. (2009) found that cocaine-dependent patients exhibited elevated cortisol levels and elevated perceived stress relative to control participants. The cocaine-dependent participants also had deficits in learning and memory, which were significantly associated with elevated cortisol levels. Importantly, individuals with poorer learning and memory (and elevated cortisol levels) showed higher cocaine use after treatment, suggesting a direct link between chronic use, elevated cortisol levels, impaired memory, and treatment outcomes.

The use of methamphetamine has also been associated with changes in neurohormone levels (Carson *et al.*, 2012). Individuals who abused methamphetamine had lower basal plasma cortisol levels, although there were no significant differences in the plasma levels of oxytocin and vasopressin compared with controls. Levels of cortisol were correlated with levels of other neurohormones in controls but not in methamphetamine users. This suggests that, compared with cocaine, methamphetamine use is associated with lower levels of basal cortisol. The effects of alcohol on cortisol secretion have been studied in a range of populations. In heavy drinkers, there is a relationship between units of alcohol consumed in a week and cortisol levels, with heavy users showing a dose-dependent increase in cortisol levels (sex specific to men). In addition, the diurnal cortisol profile for heavy drinkers is flatter, indicating reduced responsiveness of the hypothalamic–pituitary–adrenal (HPA) axis in heavy drinkers. Among female drinkers, the cortisol awakening response (CAR) was greater in heavy drinkers; as participants were abstinent on the day of testing, these results suggest chronic changes in HPA axis function (Badrick *et al.*, 2008). King *et al.* (2006) provide some tentative evidence of the link between hyporesponsiveness of cortisol to alcohol administration and drinking levels. Alcohol administration produced an attenuated cortisol response in the downward slope of blood alcohol concentration in heavy drinkers, but not in light drinkers. This suggests a possible link between heavy drinking and reduced cortisol response to alcohol administration, which the authors suggest could be linked to chronic alcohol use. In support of this, Thayer *et al.* (2006) found that heavy male drinkers had higher cortisol levels than moderate and light drinkers, suggestive of impaired inhibitory control of the HPA axis induced by alcohol. In summary, other drugs of abuse are also associated with short-term and long-term changes in neurohormone levels; however, we believe the effects of ecstasy to be more wide ranging than those of other psychostimulants such as cocaine, because of the mechanism of action of ecstasy and the top–down control of 5HT on basal HPA axis function (Frokjaer *et al.*, 2013).

Compared with other drugs of abuse, one of the main concerns about ecstasy/MDMA is the neuropsychobiological effects of chronic repeated usage (McCann *et al.*, 1996; Reneman *et al.*, 2002; Kish *et al.*, 2010; Erritizoe *et al.*, 2011). Preclinical research has shown that ecstasy/MDMA can be a 'serotonergic neurotoxin', in that it reduces functional levels of the key neurotransmitter serotonin, although the exact nature of the underlying neural changes remains a matter of active debate. In particular, there is debate over whether the changes to the serotonergic system represent permanent damage or neuroadaptive changes that are potentially reversible (Biezonski and Meyer, 2011; Benningfield and Cowan, 2013; Parrott, 2013b). In animal studies, the structural and functional effects of MDMA, including the extent of serotonergic damage, are heightened under stimulatory environmental conditions, which heighten energy expenditure (Huether *et al.*, 1997; Malberg and Seiden, 1998; Sanchez *et al.*, 2004; Hargreaves *et al.*, 2007). In humans, there is extensive neuroimaging evidence for reduced levels of the serotonin transporter, along with deficits in a wide range of functions known to be modulated by serotonin, such as memory, higher cognition, psychiatric well-being, sleep, and vision (McCann *et al.*, 1998, 2008; Parrott, 2001, 2006, 2013a, 2013b; Fox *et al.*, 2002; Morgan *et al.*, 2002; Montgomery *et al.*, 2005, 2010; Reneman *et al.*, 2006; Cowan, 2007; Murphy *et al.*, 2009; Kish *et al.*, 2010; Erritizoe *et al.*, 2011; Taurah *et al.*, 2014). These neuropsychobiological effects are dependent on factors such as acute dosage taken, time since last usage, cumulative lifetime usage, and the environmental conditions. For example, light users often show no deficits, or minimal changes (Fox *et al.*, 2001), whereas heavy lifetime users show more pronounced structural and functional deficits (Janssen, 1997; Topp *et al.*, 1999; Kish *et al.*, 2010).

In an earlier review, it was noted that cortisol is important for a wide variety of psychobiological functions and that it may be involved in the acute and chronic effects of recreational ecstasy/MDMA (Parrott, 2009). Since then a number of further studies have been undertaken. Hence, a core aim of this review was to summarize these more recent developments in empirical knowledge and theoretical understanding. To undertake this review, we performed a systematic search of the relevant databases for studies addressing the relationship between ecstasy, psychological stress/distress, cortisol, and memory functioning in nonclinical participant samples. The databases searched were PsycINFO, Medline, PubMed, and Embase. Non-English language publications were excluded to avoid translation bias. Our strategy, therefore, was to initially identify electronically a relatively large pool of studies that had examined the relationship between ecstasy, psychological stress/distress, cortisol, and memory functioning, and then to identify those studies within that pool that had recruited from the population of interest. The initial sections of this paper will summarize the earlier findings, whereas the latter sections will cover the latest research in more detail. Finally, we will debate the practical and theoretical

implications, and suggested topics for future investigation. Throughout this review, we will focus on Hans Selye's original notion of stress as an adaptive coping response to potential overload (Selye, 1956; Wilson, 2006). In stressful situations, an automated series of adaptive coping responses is initiated, based around the HPA axis, which includes enhanced cortisol release. This releases further energetic resources, which are normally replenished during rest and recuperation. Under repeated stressors, these periods of recovery are reduced, explaining why regular stress is cumulatively damaging to the organism. In this article, we will examine whether this situation of repeated stressors is applicable to those who regularly take the recreational stimulant drug ecstasy/MDMA.

Hans Selye's concept of stress

The concept of stress proposed by Hans Selye was based around Cannon's (1935) notion of physiological stability and homeostasis. Selye (1956) was interested in how the human body coped with extreme physical conditions, such as living in hot or cold environments, surviving under low oxygen at high altitudes (hypoxia), or marathon running with continuous physical exertion. Under these demanding situations, Selye (1956) found that a general adaptation syndrome was initiated, which led to the release of additional metabolic resources necessary for continued physical functioning. In subsequent writings, the general adaptation syndrome evolved into the broader concept of stress (Jackson, 2006). The precise chain of psychophysiological responses in this acute stress response is described more fully in numerous textbooks and articles (Selye, 1956; Lovallo, 1997; Jackson, 2006; Parrott, 2009; Wetherell and Montgomery, 2014). They all note that a core response to stress is the increased production and secretion of the glucocorticoid hormone cortisol.

Cortisol can affect every organ throughout the body, is essential for everyday functioning, and is involved in predictive and reactive homeostasis (Herbert *et al.*, 2007). Predictive homeostasis facilitates the body's regular pattern of waking, alertness, and sleep, with cortisol release following the well-established circadian rhythm, peaking in the period after awakening (Lovallo, 1997; Wetherell and Montgomery, 2014). The release of cortisol can also be initiated by physical or psychological stressors, a phenomenon termed reactive homeostasis. The increase in cortisol comprises one aspect of a more general sympathetic nervous system activation, which heightens glucose release for increased energy, and suppresses immunoreactivity, hence preparing the body for fight or flight. Selye (1956) noted that cortisol reactivity and homeostasis were impaired when the body was subjected to repeated stressors. The physical nature of the bodily damage caused by chronic stress is evident in the terms used by Selye: 'being under strain', 'feeling overloaded', or 'suffering a breakdown'. Under repeated stressors, the ability to cope is impaired, and this is reflected in aberrant patterns of cortisol activity and deficits in core psychological functions, including memory, cognition, sleep, and well-being (Selye, 1956; Lovallo, 1997; Herbert *et al.*, 2007). Repeated stressors can therefore be very damaging to the organism, with Selye referring to stress as the 'wear and tear of life' (Jackson, 2006).

MDMA and cortisol: acute effects in the laboratory

The first empirical studies on the effects of MDMA on cortisol release were placebo-controlled acute-dose laboratory studies. Mas *et al.* (1999) administered oral doses of 75 and 125 mg MDMA to human volunteers and found significant dose-related increases in cortisol, peaking around 1.5–2 h after administration. In a pilot study, Pacifici *et al.* (1999) found increased cortisol levels following acute MDMA administration, although the samples sizes were very small ($n = 2$). However, this finding was replicated in a larger follow-up study (Pacifici *et al.*, 2001), in which 100 mg oral MDMA again led to a significant increase in cortisol levels. They also found that two closely-spaced doses of ecstasy/MDMA led to similar significant increases in cortisol levels. De la Torre *et al.* (2000) compared 75, 100, and 125 mg oral MDMA and also found significant increases in plasma cortisol levels, which again peaked at 2 h after administration. In most studies, the data have been presented as changes from baseline; however, Harris *et al.* (2002) also presented baseline values, which allowed the percentage increase to be calculated. They found that acute administration of 0.5 mg/kg oral MDMA led to a cortisol increase of around 100%, whereas 1.5 mg/kg MDMA led to a mean percentage increase of 150%, compared with predrug baseline. These and other early findings were reviewed by Dumont and Verkes (2006), who concluded that acute MDMA caused a 'robust' increase in circulating cortisol levels.

MDMA and cortisol: acute effects in recreational users

The effects of recreational ecstasy/MDMA use on cortisol levels have also been investigated in the real-world environment. This is particularly relevant for the energetic stress model (Parrott, 2006), as ecstasy/MDMA is generally taken at clubs or house parties, where the music is loud, the environmental conditions are hot, and dancing typically occurs over prolonged time periods (Parrott and Lasky, 1998; Suy *et al.*, 1999; Curran, 2000; Parrott, 2001, 2004; Winstock *et al.*, 2001). These stimulatory conditions can make considerable demands on energy expenditure and thus act as potential metabolic stressors. Three prospective studies have measured baseline cortisol levels in recreational ecstasy/MDMA users before they go dance clubbing, then during clubbing or immediately afterwards (Table 1). In the study by Parrott *et al.* (2008), two subgroups of young ecstasy/MDMA users

Table 1 Prospective changes in cortisol levels in recreational ecstasy/MDMA users before, during, and after dance clubbing

Parrott *et al.* (2008): within-group design	Predrug baseline	1 h after drug	2.5 h after drug	48 h after drug	72 h after drug	ANOVA session
On MDMA	0.3 ± 0.3	0.9 ± 0.5***	2.2 ± 1.1***	0.5 ± 0.7	0.4 ± 0.5	***
Off MDMA	0.2 ± 0.1	0.3 ± 0.2	0.4 ± 0.4	0.4 ± 0.4	0.2 ± 0.2	NS
Parrott *et al.* (2007): within-group design	Pre-drug baseline	2 h after drug	4 h after drug	6 h after drug	24 h after drug	ANOVA session
On MDMA	0.3 ± 0.1	1.0 ± 0.7*	2.3 ± 1.3***	1.5 ± 0.9*	0.7 ± 0.7	***
Off MDMA	0.3 ± 0.3	0.4 ± 0.3	0.3 ± 0.2	0.5 ± 0.8	0.4 ± 0.5	NS
Wolff *et al.* (2012): between groups design	Predrug baseline			After clubbing		ANOVA group
On MDMA group	See article			736 ± 83***		***
Nonuser group	See article			350 ± 34		

Parrott *et al.* (2007, 2008) used a within-group design, with users tested twice: during on-MDMA and off-MDMA weekends. Wolff *et al.* (2012) used a between-group design, where MDMA users were compared with a nonuser controls at the same club venue.
Cortisol units for saliva samples in the study by Parrott *et al.* (2007, 2008) are in μg/dl. Cortisol units for blood plasma samples in the study by Wolff *et al.* (2012) are in nmol/l.
Two-tailed significance levels for ANOVA session effect, and Tukey's paired-comparison tests with predrug baseline (Parrott *et al.*, 2007, 2008).
Two-tailed significance levels for ANOVA group effect (Wolff *et al.*, 2012).
ANOVA, analysis of variance; MDMA, 3,4-methylenedioxymethamphetamine.
*$P < 0.05$.
**$P < 0.01$.
***$P < 0.001$.

were prospectively assessed before, during, and after clubbing (Table 1). They were monitored over successive weekends. On one weekend they danced/partied as usual, whereas on the other they abstained from taking ecstasy/MDMA or any other central nervous system stimulant drug. Saliva sampling indicated the presence of MDMA in all 12 volunteers during the 'normal' weekend, and confirmed its absence during the abstinence weekend (hence off-MDMA). The ecstasy/MDMA weekend led to a peak increase of around 800% in salivary cortisol levels, which was significantly higher than both the predrug baseline and clubbing during abstinence levels. In contrast, partying when free from ecstasy/MDMA generated no significant changes in cortisol levels (Table 1). In the study by Parrott *et al.* (2008), it was noted that an increase in the cortisol level by 800% was far greater than that found in routine psychophysiological research. For instance, Davis *et al.* (1981) assessed a group of volunteers on the standard psychophysiological test of 'cycling to exhaustion', using a static exercise bicycle in the laboratory. Cortisol levels rose significantly after exercise, but the extent of this increase was comparatively smaller. Experienced athletes showed a 78% acute increase in cortisol, whereas the normal volunteers showed a 138% increase in cortisol following severe physical exercise.

The next study (Parrott *et al.*, 2007) involved a similar design, with more experienced ecstasy/MDMA users at a house party. Cortisol levels on ecstasy use were significantly increased by a group mean of around 800%, whereas when partying without ecstasy/MDMA the cortisol levels were statistically unchanged (Table 1). Intriguingly, the more experienced users in the second study were taking higher doses of ecstasy/MDMA than the more novice users in the first study, yet generating similar peak levels of cortisol. This suggests that the more experienced users were self-titrating with higher doses to achieve the same neurohormonal/subjective effect; these data are consistent with those on chronic pharmacodynamic tolerance (Parrott, 2005). The third real-world prospective study involved cortisol samples from dance clubbers before and after they went dance clubbing (Wolff *et al.*, 2012). The study had an independent-group design, with clubbers divided into 21 MDMA users and 18 nonusers, on the basis of postclubbing urine analyses. Postclubbing cortisol levels were 110% higher among MDMA users than among nonusers ($P < 0.001$; Table 1). Unfortunately the preclubbing cortisol samples from the two groups were not fully tabulated, as only those values above a certain threshold were presented. Hence, the overall changes from baseline for each group were not shown. However, the authors did present changes from baseline in several subanalyses that investigated genetic factors. These revealed significant associations between low activity in the COMT genotype (Met/Met) and heightened cortisol response, both for the overall sample and for the MDMA subgroup. There was also an association between CYP2D2 and heightened cortisol levels in the MDMA subgroup only; there were no associations with 5-HTTLPR genotyping [for further debate on these cortisol findings in dance clubbers, see Parrott *et al.* (2013) and Wolff and Aitchison (2013)].

MDMA and cortisol: initial studies on chronic changes

Given that ecstasy/MDMA can increase cortisol levels acutely, its regular use may lead to more enduring changes. This notion was first examined in a series of studies by Gerra *et al.* (1998, 2000, 2003). Gerra *et al.* (1998) assessed a group of recreational ecstasy/MDMA users with minimal lifetime use of other recreational drugs 3 weeks after ecstasy/MDMA discontinuation. They found a significantly reduced cortisol response to a dexfenfluramine challenge, along with significantly higher depression, hostility, and dysphoric experiences. In a follow-up study, Gerra *et al.* (2000) replicated their earlier findings of reduced cortisol response to

dexfenfluramine challenge in regular ecstasy/MDMA users 3 weeks after last usage. They also investigated whether the HPA axis had recovered after 12 months of abstinence from ecstasy/MDMA. In their subgroup of former users, cortisol responses to dexfenfluramine challenge were similar to control group values, indicting neuropsychobiological recovery.

Verkes *et al.* (2001) compared subgroups of moderate and heavy ecstasy/MDMA users, with a control group of regular dancers/ravers who had never taken ecstasy/MDMA, hence controlling for the important factor of all-night dancing. They found significantly reduced cortisol responses to a dexfenfluramine challenge in both ecstasy/MDMA subgroups, compared with nonuser controls. Further, the extent of reduction in cortisol responses correlated significantly with the lower task performance on some cognitive measures. Gerra *et al.* (2003) investigated cortisol responses to the psychosocial stressors of public speaking and performing mental arithmetic calculations in front of an audience. They found significantly higher baseline cortisol values in the drug-free ecstasy/MDMA users, along with reduced cortisol reactions under stress. This pattern emerged with both cortisol and adrenocorticotropic hormone (see Figs 1 and 2 in Gerra *et al.* 2003). It was concluded that regular ecstasy/MDMA use led to a complex pattern of neuroendocrine dysfunctioning, with hyperactivation of basal HPA axis activity and reduction in cortisol reactivity to psychosocial stressors.

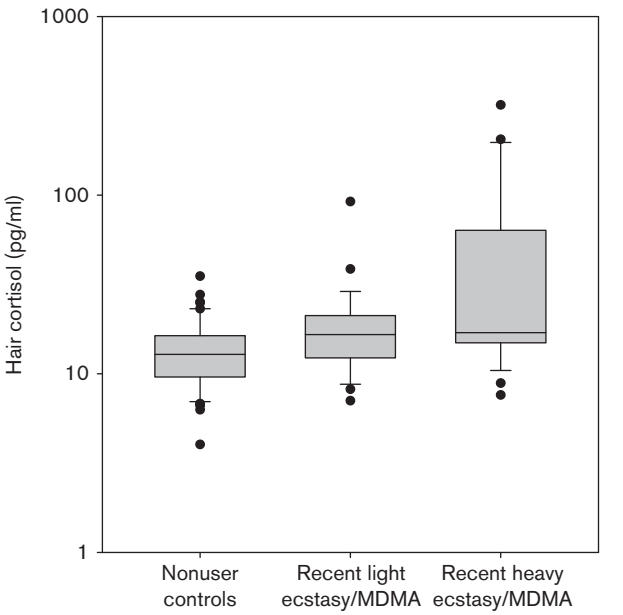
Cortisol in 3-month hair samples of ecstasy/MDMA users

Until recently, cortisol measures have been restricted to saliva, urine, or blood samples taken at individual time points. An important development in cortisol research has been the measurement of cortisol levels in hair (Broderick *et al.*, 2004). As cortisol is incorporated into the living hair, the mean cortisol levels from an extended time period can be calculated by analyzing standard-length hair samples. The cortisol values obtained through hair sampling have been shown to be both valid and reliable (Broderick *et al.*, 2004; Kirschbaum *et al.*, 2009; Stalder *et al.*, 2012). This novel procedure was used to investigate neurohormonal aspects of recent ecstasy/MDMA usage (Parrott *et al.*, 2014a). A total of 101 participants (53 male, 48 female; mean age 22 years) completed the University of East London recreational drug usage questionnaire for the most recent 3-month period of drug use (Parrott *et al.*, 2001). The three subgroups comprised 32 light recent ecstasy/MDMA users (one to four times in the past 3 months), 23 recent heavy MDMA users (more than five times in the past 3 months), and 54 nonuser controls. The cortisol levels in the past 3 months were significantly higher in recent heavy ecstasy/MDMA users (55.0 ± 80.1 pg/mg), compared with both recent light ecstasy/MDMA users (19.4 ± 16.0 pg/mg, $P = 0.015$) and nonuser controls (13.8 ± 6.1 pg/mg, $P < 0.001$). Hence regular ecstasy/MDMA usage was associated with an almost four-fold greater level of cortisol, in comparison with nonusers (Fig. 1). It remains unclear whether these increases are only due solely to the acute periods of usage or whether cortisol levels are heightened in a more enduring manner. Time series analyses are required to investigate this important question.

Diurnal cortisol rhythms

Cortisol shows a typical diurnal rhythm, with a peak around 30–45 min after waking, followed by a gradual decrease over the rest of the day (Lovallo, 1997; Wetherell *et al.*, 2012). To investigate whether these diurnal rhythms are maintained in ecstasy/MDMA users, Wetherell and Montgomery (2014) compared the cortisol secretion patterns of heavy and light users, compared with nonuser controls. The diurnal patterns were assessed on two consecutive days, first a normal day of everyday activities and second a high-stress day requiring performance on a multistressor laboratory task (see the section Cognitive Performance below). Cortisol samples were taken after waking, 30 min after waking, between 14.00 and 16.00 h, and finally before bedtime. Light and heavy ecstasy/MDMA users exhibited significantly elevated anxiety and depression levels compared with controls, although the two ecstasy subgroups did not differ from each other. On the low-stressor day, all groups showed typical diurnal cortisol profiles, and the overall profiles did not differ significantly between groups,

Fig. 1



Cortisol levels in 3-month hair samples taken from light and heavy recent ecstasy/MDMA users and from nonuser controls (after Parrott *et al.*, 2014a). MDMA, 3,4-methylenedioxymethamphetamine.

although light users had slightly elevated cortisol levels at bed time. On the high-stress day, heavy ecstasy/MDMA users showed significantly higher cortisol levels on waking, and both heavy and light users showed higher cortisol levels before bedtime.

The elevations in psychological distress were in line with those in previous studies (Wetherell *et al.*, 2012), although this was the first study to show significant dysregulation of diurnal cortisol rhythms in abstinent users. Similarly, Frokjaer *et al.* (2014) assessed MDMA-abstinent MDMA users compared with healthy controls. Again, MDMA users showed an elevated CAR; MDMA users also reported significantly greater levels of perceived stress (on the basis of Cohen's perceived stress scale). Prefrontal serotonin binding (measured using [^{11}C]DASB PET scanning) was a significant predictor of CAR in the regression model after controlling for variance in a number of demographic and background variables (age, sex, BMI, perceived stress), suggesting the same top–down control of CAR by serotonin as seen in healthy participants (Frokjaer *et al.*, 2013). These findings provide further evidence for raised cortisol values in abstinent ecstasy/MDMA users, and a tentative link between serotonin deficiency and the aberrant CAR, which needs further investigation.

These findings are a cause for concern as they indicate that abstinent users may be errant in anticipating future demands (see later), whereas HPA dysregulation is also associated with psychological morbidity (Gold *et al.*, 1998; Lupien *et al.*, 1998; Edwards *et al.*, 2003; Lovell *et al.*, 2011, 2012). More specifically, Wetherell *et al.* (2012) provide empirical evidence consistent with modified HPA activity by showing that recreational users exhibit mood dysregulation on waking and increased perceived effort/workload during a multitasking stressor. These findings are suggestive of continued HPA dysregulation when drug-free. In relation to potential functional implications, deviations from the normal cortisol awakening response are associated with chronic stress (Scholtz *et al.*, 2004), work overload (Schulz *et al.*, 1998), uncontrollable distal stressors (Miller *et al.*, 2007), and informal caregiving stress (Lovell *et al.*, 2011, 2012).

Self-rated feelings of stress and clinical aspects

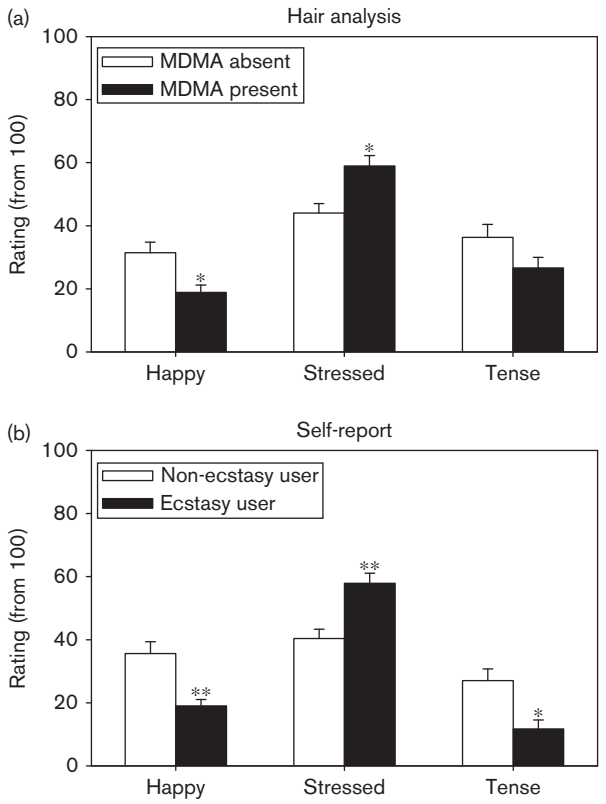
The above findings of increased stress (Wetherell *et al.*, 2012) are consistent with many earlier indications of psychological distress in abstinent ecstasy/MDMA users. The earliest reports emerged from clinical case studies (review: Soar *et al.*, 2001), but these were followed by more systematic clinical surveys. Schifano *et al.* (1998) found increased levels of depression, panic attack, bulimia, and psychotic disorder in a survey of 150 young recreational ecstasy/MDMA users who were seeking help for drug-related problems. Raised psychiatric symptom profiles have also been reported in more general population surveys. Parrott *et al.* (2000) found significantly higher levels of self-rated anxiety and phobic anxiety in a nonclinical survey of heavy MDMA users compared with nonuser controls. Significantly higher levels of SCL-90 self-reported anxiety, phobic anxiety, and other problems were also noted in a larger follow-up study of moderate and heavy ecstasy/MDMA users (Parrott *et al.*, 2001). Although the respondents were extensive polydrug users, Milani *et al.* (2000) showed that lifetime ecstasy use was associated with both higher anxiety and phobic anxiety.

Scholey *et al.* (2011) examined the effects of ecstasy/MDMA use on aspects of self-reported cognitive function and mood. Forty-nine undergraduate volunteers underwent an online assessment while at the laboratory. Unipolar visual analog scales were used to assess feelings of being relaxed, alert, jittery, tired, tense, stressed, calm, happy, and sad; headache, mental fatigue, and overall mood were also assessed. Participants completed the UEL Drug Use Questionnaire evaluating history of drug use and current drug use. They also provided a hair sample for determination of exposure to ecstasy/MDMA over the previous month, using gas chromatography–mass spectroscopy (Villamor *et al.*, 2005). This allowed the categorization of ecstasy/MDMA users and nonusers, both objectively (presence in hair) and subjectively (self-reported usage). Three of the 10 mood scales differed as a function of ecstasy/MDMA group (Fig. 2). Compared with their respective controls, both the ecstasy/MDMA-positive hair group and the self-reported ecstasy users reported higher 'stress' and lower 'happy' ratings. Self-reported ecstasy use, but not presence in hair, was also associated with decreased tension. A secondary analysis was completed after excluding data from six participants with detectable cannabis in their hair samples. Despite the reduced *N*, the main effect of ecstasy/MDMA on stress was maintained – emphasizing the link between ecstasy/MDMA and stress. The most robust finding was that both objectively and subjectively defined ecstasy/MDMA users reported significantly more self-rated stress than nonusers. Although physiological measures of stress were not collected, similar relationships between HPA axis function and drug use have been observed in stimulant-addicted individuals (Goeders, 2003). The finding that ecstasy/MDMA users report feeling significantly more stressed than nonusers provides further empirical evidence consistent with the notion of HPA axis dysregulation. It also indicates that the individuals are aware of their personal stress.

Cognitive stress

Recreational users of ecstasy/MDMA can show significant deficits in various neurocognitive tasks, in areas such as memory, learning, executive control, and thinking and reasoning (Krystal *et al.*, 1992; Parrott and Lasky, 1998; Fox *et al.*, 2002; Fisk *et al.*, 2005; Reay *et al.*, 2006;

Fig. 2



Mood states (mean ± SEM) of abstinent MDMA/ecstasy users and nonuser controls. Self-rated moods were recorded for participants (a) characterized as having ecstasy/MDMA in hair samples or (b) self-reporting ecstasy use (from Scholey *et al.*, 2011). $^{*}P < 0.05$, $^{**}P < 0.01$. MDMA, 3,4-methylenedioxymethamphetamine.

Zakzanis and Campbell, 2006; Murphy *et al.*, 2009; Taurah *et al.*, 2014). The deficits in laboratory performance tasks may translate into real-world impairments in everyday cognitive activities, particularly those that are more demanding. This has been subjectively confirmed through surveys of recreational users who report problems with memory and cognition, which they attribute to their own ecstasy/MDMA usage (Parrott *et al.*, 2002; Rodgers *et al.*, 2003, 2006). Performance deficits have also been found in laboratory tasks designed to be representative of everyday activities. For example, significant performance detriments have been observed in time-based and event-based memory recall tasks, when assessed using video films (Hadjiefthyvoulou *et al.*, 2011). Rendell *et al.* (2007) found significant impairments in a 'virtual week' task that involved multiple memory requirements. Further, although infrequent ecstasy/MDMA users were significantly impaired, frequent users were even more impaired. Deficits have also been found in a virtual reality task designed to mimic everyday office work (Montgomery *et al.*, 2010); again, the drug-free ecstasy/MDMA users were significantly impaired compared with nonuser controls.

Most laboratory assessments involve single tasks, and the findings may therefore be extrapolated to everyday activities that utilize similar cognitive domains. Most everyday activities, however, involve simultaneous attention and response to multiple stimuli. It is therefore important to assess how individuals cope in these more complex situations. The Multitasking Framework is a laboratory technique that requires users to respond to several cognitive tasks simultaneously. In normal volunteers it elicits feelings of being stressed, through the manipulation of workload intensity and task difficulty (Wetherell and Sidgreaves, 2005). In common with everyday demanding situations, the Multitask Framework elicits psychobiological responses indicative of heightened stress. These include increased neuroendocrine and immune activation, subjective feelings of stress and anxiety, and perceptions of greater cognitive demand, increased effort, and frustration (Kennedy *et al.*, 2004; Wetherell and Sidgreaves, 2005; Scholey *et al.*, 2009; Wetherell and Carter, 2014). This task therefore provides a valid and reliable laboratory analog, for stressful multitasking in the real world.

As ecstasy/MDMA usage is associated with increased anxiety and depression (Rodgers *et al.*, 2006; Wetherell *et al.*, 2012) and self-reported stress (Scholey *et al.*, 2011), it was predicted that abstinent users would find it particular difficulty to cope with the Multitask Framework and its high level of cognitive demand. Wetherell *et al.* (2012) found that recreational ecstasy/MDMA users perceive significantly greater levels of mental demand and time pressure compared with nonuser controls following a short (10–20 min) period of laboratory multitasking. Whereas cognitive performance was not assessed in this study, in addition to increases in perceived levels of mental demand, ecstasy users also reported greater levels of frustration and lower feelings of contentment and calmness while engaged with the task. These findings are consistent with the nonpharmacological literature on cognitive deficits (Gonzalez, 2007). They suggest that ecstasy/MDMA users may be experiencing reduced neurocognitive capacity and hence need to work harder to maintain task performance.

This hypothesis is supported by some event-related potential (ERP) research findings, where abstinent users show aberrant patterns of brain activation during standard information processing tasks. A review of this ERP literature by Parrott (2013b, section 4.2), concluded that many different ERP studies had found different patterns of brain activation in abstinent ecstasy/MDMA users performing various cognitive tasks (Croft *et al.*, 2001; Mejias *et al.*, 2005; Burgess *et al.*, 2011; others). More recently, Roberts *et al.* (2013a) investigated ERPs during a Go/NoGo response inhibition task. They found

a significantly enhanced P2 wave in abstinent ecstasy/MDMA users, accompanied by levels of performance similar to those in nonuser controls. They suggested that the increased ERP waveform may reflect the recruitment of additional processing resources to facilitate normal performance. In a follow-up study assessing semantic retrieval (Roberts *et al.*, 2013b), performance levels did not differ between groups, but again there were significant differences in evoked potentials. Roberts *et al.* (2013b) suggested that this pattern of findings was 'suggestive of compensatory mechanisms or reallocation of cognitive resources'.

In summary, deficits in tasks requiring declarative memory, thinking and reasoning, planning, and higher cognitive skills are well established (Krystal *et al.*, 1992; Fox *et al.*, 2002; Fisk *et al.*, 2005; Parrott, 2006, 2012b, 2013a; Reay *et al.*, 2006; Zakzanis and Campbell, 2006; Murphy *et al.*, 2009; Montgomery *et al.*, 2010; Taurah *et al.*, 2014). The recognition by users of their own suboptimal performance can comprise a broad source of stress throughout each day (Wetherell *et al.*, 2012). Indeed these deficits in memory and higher cognitive skills, as well as complex visual information processing, will make many professional occupations more difficult to perform. Using a virtual reality paradigm, Montgomery *et al.* (2010) showed that the daily performance of an office worker was significantly impaired. Parrott (2013b) debated how these deficits may adversely affect skilled occupations such as aircraft pilot, surgeons, social workers, and teachers. More subtly, even with basic cognitive skills that are unimpaired in terms of performance, ERP studies have found different patterns of brain activation. The authors of these ERP articles have suggested that extra cognitive resources and attentional effort may be required for this processing (Roberts *et al.*, 2013a, 2013b); if confirmed, this would comprise another potential source of stress. Given the diversity of these neuropsychobiological effects, Parrott (2013b) concluded: 'It is difficult to think of any human occupational activity which would not be impaired by recreational ecstasy/MDMA'.

Sleep and sex

Many psychobiological functions can be impaired in abstinent ecstasy/MDMA users, and some of these deficits may be modulated through cortisol or other hormones controlled through the HPA axis. When administered acutely, ecstasy/MDMA can result in impaired sleep for several days thereafter (Jones *et al.*, 2008). In a comprehensive sleep review, McCann and Ricaurte (2007) summarized the empirical evidence for sleep deficits in abstinent users, assessed through all-night EEG profiling or standardized sleep questionnaires. In a subsequent sleep questionnaire survey, Carhart-Harris *et al.* (2009) observed that ecstasy/MDMA users with little experience of other illicit drug use reported selective sleep deficits, including lower sleep quality, greater sleep time, and more night-time awakenings. In another large survey, Ogeil *et al.* (2011) reported that 69.5% of ecstasy/MDMA users had Pittsburgh Sleep Quality Index scores indicative of disturbed sleep. Taurah *et al.* (2014) also found significantly higher Pittsburgh Sleep Quality Index scores in both current and former ecstasy/MDMA users, in comparisons with several control groups, including cannabis users and polydrug users. These enduring sleep deficits may be damaging to everyday well-being and may contribute indirectly to the other forms of psychobiological distress (McEwan, 2006). In addition, immunocompetence is impaired (Connor, 2004), markers for oxidative stress are increased (Zhou *et al.*, 2003), and regular ecstasy/MDMA users report an increased incidence of coughs and colds (Parrott *et al.*, 2002). These health problems may provide a further source of everyday stress.

Some regular ecstasy/MDMA users also report sexual problems. In an extensive survey of over 700 young people from four cities in Italy and UK, Milani *et al.* (2001) found that heavy ecstasy/MDMA users reported significantly higher rates of 'loss of sexual interest or pleasure', in comparison with non-drug users and polydrug user controls. Soar *et al.* (2005) also reported a higher incidence of self-reported sexual difficulties; these included a decrease in sexual desire, physical problems with sex, and difficulty achieving an orgasm. Whether these problems are related to serotonergic dysfunction, neurohormonal problems, or both needs to be further studied. Whatever the underlying causes, this loss of sexual desire/interest/ability will comprise another source of stress.

Dance clubs and environmental overstimulation

The theoretical rationale behind the interaction between recreational ecstasy/MDMA and environmental conditions in clubs was debated by Parrott (2004), who observed the following: 'Animal research shows that heat and crowding potentiate the effects of ecstasy/MDMA, with loud noise and physical activity also contributing to the general overarousal. Furthermore, ecstasy/MDMA impairs homeostatic thermal control in laboratory rats, leading them to overheat in hot environments. The human implications of these findings are that the hot, noisy, and overcrowded conditions at raves may be providing the ideal environment to heighten the acute drug response'. This review concluded that environmental factors may be heightening the acute and chronic effects of recreational ecstasy/MDMA. Later reviews have debated the underlying biological mechanisms (Parrott, 2009, 2013b). The contributory roles of neurohormones were debated by Parrott (2009), who noted the following: 'The energizing hormone cortisol is involved in the psychobiology of ecstasy/MDMA, probably via its effects

on energy metabolism. Acute cortisol release may potentiate the stimulating effects of ecstasy/MDMA in dance clubbers. Nonpharmacological research has demonstrated that cortisol is important for many psychological functions including memory and cognition, sleep, impulsivity, depression, and neuronal damage. These same functions are often impaired in recreational ecstasy/MDMA users, and cortisol may be an important modulatory cofactor'. The present review has suggested the involvement of cortisol in both the acute and the chronic effects of recreational ecstasy/MDMA. However, the nature of this involvement is likely to be complex and multifactorial.

Acutely, cortisol release may contribute toward general activation and may hence make ecstasy/MDMA positively rewarding for users. It should be emphasized that the acute mood effects of ecstasy/MDMA are far more variable than is popularly believed. In the laboratory, acute ecstasy/MDMA can intensify both positive moods (e.g. elation, euphoria) and negative moods (e.g. anxiety, loneliness; Bedi *et al.*, 2010; Parrott *et al.*, 2011; Kirkpatrick *et al.*, 2012). Recreational users also describe a range of positive and negative moods, and although positive moods generally predominate, they are often mixed with negative mood elements, and some users occasionally experience quite negative overall reactions [mood studies were reviewed by Parrott (2007)]. Further, the nature of these mood changes may vary between individuals. Parrott (2010) noted that novice users who had ceased using reported far weaker positive mood changes to their first ecstasy/MDMA experience than those who were continuing to use. This variance in acute mood reactions may be due to differences in neurohormonal responses (serotonin, dopamine, oxytocin, and other neurohormones), psychosocial factors such as personality/expectancy, and neurohormonal activation. With regard to the latter, the extent of acute cortisol release may be a contributory factor. It may be hypothesized that individuals with milder cortisol reactions may experience weaker general activation and comparatively slight mood state changes, whereas those with stronger acute cortisol reactions may experience more intensive mood state changes. This hypothesis needs to be empirically investigated.

Medical abreactions and sex issues

Recreational ecstasy/MDMA can engender a range of acute medical abreactions, including hyperthermia, hyponatremia, and rhabdomyolysis (Hall and Henry, 2006; Halpern *et al.*, 2011). These medical emergencies are generally related to overheating (Parrott, 2012a), and the profound overstimulation may occasionally prove fatal (Schifano *et al.*, 2006). Hospital emergency teams are now well trained in the importance of rapid cooling and electrolyte stabilization (Hall and Henry, 2006; Prator, 2006). Many abreactions are related to the serotonin syndrome, and the degree of acute cortisol activation may help explain why some individuals are more susceptible to these than others. Parrott (2002) observed that many ecstasy/MDMA users at clubs/raves showed mild signs of serotonin syndrome, but only a small minority developed more extreme reactions. The extent of these acute abreactions may be related to the extent of cortisol release, as they typically occur under hot and crowded conditions, when cortisol release is pronounced (Table 1). However, this hypothesis needs to be medically/empirically investigated.

Sex differences in adverse psychological and physiological effects also merit discussion. Van Dijken *et al.* (2013) collected blood/plasma samples from Dutch ravers, with MDMA presence confirmed through urine analysis. Mild hyponatremia was evidenced in 3% of male users, compared with 25% of female users. It was also observed that 'the number of pills ingested by the female users who developed hyponatremia was not different from that ingested by those who did not develop this complication'. Hyponatremia following recreational ecstasy/MDMA use is well established (Parrott, 2002; Hall and Henry, 2006), and this finding confirms an earlier report of greater female susceptibility to MDMA-induced hyponatremia (Rosenson *et al.*, 2007). Sex differences have been noted in the subjective and longer term mood effects of ecstasy (Liechti *et al.*, 2001; Verheyden *et al.*, 2002; Milani *et al.*, 2004); hence, sex differences in neurohormonal response are of particular importance for elucidating the mechanisms underlying both these differences and differences in adverse medical outcomes. Women who regularly take MDMA during the first trimester of pregnancy give birth to children with impaired psychomotor development (Singer *et al.*, 2012a, 2012b). High levels of stress and maternal cortisol during pregnancy are known to be damaging to fetal development and birth outcomes (Reynolds, 2013). The possible contribution of neurohormonal factors to the adverse birth outcomes of ecstasy/MDMA in pregnant women has been debated by Parrott *et al.* (2014b).

Hypothalamic–pituitary–adrenocortical axis

The HPA axis is crucially important for homeostasis and everyday health. These health aspects of ecstasy/MDMA users are under-researched, although various deficits in health have been noted (Connor, 2004; see above). Dysregulation of the HPA axis may be one mechanism through which atypical stress responding could lead to impairments in immune function in ecstasy/MDMA users. The magnitude of cortisol secretion and the frequency at which these increases occur are likely to exert a significant challenge to allostasis. More specifically, they may affect the basal functioning of the HPA axis and influence the secretion of cortisol. When the HPA axis is repeatedly and unnecessarily activated, as is the case in ecstasy/MDMA users, it can sometimes lead to

dysregulation of diurnal rhythm, which explains the higher levels of baseline cortisol in ecstasy/MDMA users in some studies (Gerra *et al.*, 2003; Wolff *et al.*, 2012; Frokjaer *et al.*, 2014). Further, the increased perceptions of workload and increased psychological distress following multitasking are associated with reduced immunocompetence (Wetherell *et al.*, 2004). This poorer immune function may contribute to the increases in somatic symptoms experienced by ecstasy/MDMA users (Parrott *et al.*, 2002; Verheyden *et al.*, 2003), with female users occasionally at greater risk (Milani *et al.*, 2004).

The HPA axis is involved in various aspects of psychiatric well-being, with life stressors making the individual more susceptible to psychiatric abreactions (Strohle and Holsboer, 2003; Nemeroff and Vale, 2005). As noted earlier, increased psychiatric distress has been reported in many cross-sectional surveys, with higher levels of depression and other problems (Schifano *et al.*, 1998; Parrott *et al.*, 2000, 2001; MacInnes *et al.*, 2001; Roiser and Sahakian, 2004). Prospective research on teenage schoolchildren in Canada has shown that starting to use ecstasy/MDMA recreationally leads to increased depression 1 year later (Brière *et al.*, 2012). Recreational users also report that quitting ecstasy/MDMA leads to improved mental health (Verheyden *et al.*, 2003). Prospective research on pregnant drug-using mothers (Singer *et al.*, 2012a, 2012b) has also shown that quitting ecstasy/MDMA is associated with reduced levels of depression 18 months later (Turner *et al.*, 2014).

Herbert *et al.* (2007) noted that cortisol was involved in various central nervous system functions, including memory, cognition, sleep, mood state, and psychiatric well-being. Hence, any chronic changes in baseline cortisol levels, or cortisol reactivity, could have a range of functional consequences. Parrott (2009) noted that many of the functions affected by cortisol were also impaired in recreational ecstasy/MDMA users (see Table 2 in Parrott, 2009); hence, any chronic changes in cortisol may well contribute to some of these psychobiological deficits. In theoretical terms, most explanatory models have focused on the contributory role of serotonin, more specifically serotonergic neurotoxicity (McCann *et al.*, 2008; Kish *et al.*, 2010; Biesonski and Meyer, 2011; Di Iorio *et al.*, 2012; Benningfield and Cowan, 2013; Parrott, 2013b). However, the actions of serotonin and cortisol are closely interlinked (Chaouloff, 2000); hence, any explanatory model should debate their cofunctions and interrelationships. However, the nature of this relationship remains a matter of speculation. MDMA has different effects on the serotonin system, acutely versus chronically (White *et al.*, 1996; Reneman *et al.*, 2002). Its chronic effects also vary according to how it is administered acutely: dosage level, frequency of use, cumulative lifetime usage, and environmental cofactors. These may be modulated through cortisol, with prolonged dancing/exercise and thermal stress, leading to stronger psychobiological changes (Parrott *et al.*, 2006; Parrott, 2009, 2012a). Currently, it remains unclear whether the longer-term effects on neurocognition and behavior are explained solely by changes in the serotonin system (and other neurotransmitters) or whether the neurohormonal system has a contributory role (Chaouloff, 2000; McCann *et al.*, 2008; Kish *et al.*, 2010; Parrott, 2013b). Future studies should measure neurotransmitter and neurohormonal activities in parallel to investigate how they are associated with any neurobehavioral changes. MDMA has also been trialed as a drug-adjuct for psychotherapy with some success (Oehen *et al.*, 2013). However, its acute effects are wide-ranging at both the neurotransmitter and neurohormonal levels, and the changes in cortisol need to be debated in relation to both its targeted clinical effects and any unwanted side-effects (Parrott, 2007, 2014b).

Methodological limitations

Despite the compelling evidence for acute and chronic changes in HPA axis function reported in this review, the findings need to be treated with a degree of caution. Because of the limited resources and logistical issues when testing participants on drugs, some studies investigating cortisol in drug users have used minimal sampling protocols. Although it may be advantageous for future research to use more intensive sampling protocols, the studies reported here did, on the whole, use recommended sampling protocols (Hellhammer *et al.*, 2007); hence, this should not detract from the findings of this review. Because of the desire to use a naturalistic sample in many of the studies reported here, a quasiexperimental design was used. Thus, we cannot rule out the possibility that the ecstasy/MDMA users may have differed in premorbid factors other than ecstasy use. Many of the studies reported have accounted for factors such as IQ, sex, socioeconomic status, alcohol use, and sleep quality in their analyses (e.g. Wetherell and Montgomery, 2014), and we believe that the reliance on naturalistic samples that are typical of the drug-using community enhances the ecological validity of the findings. Most studies have also relied on self-reports of previous drug use, with control groups that include polydrug users (Parrott *et al.*, 2014a). The more sophisticated studies have used both objective and subjective estimates of recent drug use and have shown a good correlation between the two. For example, Scholey *et al.* (2011) found that self-reports of ecstasy use were consistent with the amount of ecstasy/MDMA found in hair samples. Finally, these studies do not tell us about the direction of causality. Changes in HPA axis function may be a consequence of long-lasting exposure to ecstasy/MDMA or an expression of preexisting stress that contributes to a predisposition to take drugs (Majewska, 2002).

Theoretical overview

This review has shown how recreational ecstasy/MDMA is associated with various forms of stress (Table 2). Acute

MDMA administration increases the secretion of cortisol in the quiet laboratory, whereas recreational dance clubbers experience far more pronounced increases in cortisol levels (Table 1). The resulting psychophysiological overactivation can have a range of adverse physiological and medical consequences. This may contribute to the mild serotonin syndrome that develops in many users and may exacerbate the more severe acute medical abreactions in a small minority of users (Hall and Henry, 2006). The metabolic stress caused by acute and prolonged overstimulation of serotonin neurones, over many hours of on-drug dance clubbing, may have more enduring adverse consequences. In particular, it may impair cellular recovery and contribute to the gradual development of serotonergic neurotoxicity (Parrott, 2009). Regular ecstasy/MDMA users also show raised levels of cortisol in their hair (Parrott *et al.*, 2014a), and experience a heightened cortisol awakening response under high-stress situations (Wetherell and Montgomery, 2014). Subjectively, regular users report heightened levels of daily stress (Scholey *et al.*, 2011) and increased stress and tension when performing demanding cognitive tasks (Wetherell *et al.*, 2012). There are many other adverse consequences, including impaired sleep and psychiatric distress in susceptible individuals.

However, many of these indices of heightened stress are quite subtle. Throughout this review, various indications for heightened stress have emerged through the use of sensitive psychological and neurohormonal measures: cortisol levels in saliva/serum/hair, mood state questionnaires, simple and complex cognitive performance tasks, the multistressor task, and ERP waveforms during cognitive processing (Table 2). Yet, although these empirical measures are comparatively subtle, they are indicative of frequent and repetitive 'everyday' stress. Seyle (1956) focused on pronounced stress during extreme environmental situations. The heightened stress in drug-free ecstasy/MDMA users may be comparatively milder, but it is very pervasive; take the example of prospective memory or remembering to undertake prearranged tasks. In the review by Parrott (2013b, section 3.3), every study on prospective memory showed significant impairments in the drug-free ecstasy/MDMA users (e.g. Heffernan *et al.*, 2001; Rodgers *et al.*, 2003; Rendell *et al.*, 2007; Hadjiefthyvoulou *et al.*, 2011; others). Similarly, in terms of higher cognition and problem-solving, empirical studies using a range of performance tasks have shown that these skills are often disrupted (Fox *et al.*, 2002; Fisk *et al.*, 2005; Reay *et al.*, 2006; Montgomery *et al.*, 2010; others; review Parrott, 2013b, section 3.4). Higher cognitive skills are routinely required in modern society, and the extra mental effort they require may comprise a potent source of repetitive stress in ecstasy/MDMA users (Wetherell *et al.*, 2012; Wetherell and Montgomery, 2014). Further sources of daily stress are also added by disturbed sleep, disrupted homeostasis, and reduced immunocompetence (Connor, 2004; Jones *et al.*, 2008; McCann and Ricaurte, 2007; Parrott, 2009; Ogeil *et al.*, 2011; Taurah *et al.*, 2014; Table 2). These individual stresses may be comparatively mild or moderate, but cumulatively they provide a repetitive source

Table 2 An overview of neurohormonal stress, psychobiological/medical stress, and cognitive stress in recreational ecstasy/MDMA users

Area of interest	Main effects	References
Acute aspects: neurohormonal	MDMA can increase cortisol levels by 150% in the laboratory and by 800% in dance clubbers. This may facilitate serotonin and dopamine release, given the close interrelationship between neurohormonal and neurotransmitter systems	Harris *et al.* (2002) Pacifici *et al.* (1999, 2001) Parrott *et al.* (2007, 2008) Wolff *et al.* (2012)
Acute aspects: psychobiological and medical	Increased cortisol may contribute to acute mood intensification, both positive and negative. The nature of the mood changes may reflect expectancy and psychosocial factors. HPA overstimulation may contribute to hyperthermia, serotonin syndrome, and medical abreactions	Greer and Tolbert (1986) Parrott (2002, 2004, 2007) Kirkpatrick *et al.* (2012) Hall and Henry (2006) Halpern *et al.* (2011)
Acute aspects: cognitive	High levels of cortisol may affect cognitive functioning. Low doses may speed up basic task performance due to increased alertness, but can impair more complex skills. Recreational users typically show cognitive impairments and mental confusion	Oei *et al.* (2006) Ramaekers *et al.* (2006) Parrott and Lasky (1998) Davison and Parrott (1997)
Chronic aspects: neurohormonal	Baseline cortisol values of abstinent users are unchanged in some studies, but increased in others. The cumulative cortisol level in 3-month hair samples was increased by 400% in regular users. Reduced cortisol response to a tryptophan challenge	Gerra *et al.* (1998, 2000, 2003) Verkes *et al.* (2001) Parrott *et al.* (2014a)
Chronic aspects: psychobiological and clinical	Higher baseline cortisol levels, and reduced cortisol response to a psychological stressor (mental arithmetic). Circadian cortisol levels significantly greater during a high-stress day, but normal during a low-stress day. Subjective self-reports of higher daily stress. Clinical self-rating scales indicate higher anxiety and higher phobic anxiety. Fetal damage during pregnancy	Gerra *et al.* (2003) Wetherell and Montgomery (2014) Scholey *et al.* (2011) Wetherell *et al.* (2012) Parrott *et al.* (2000, 2001, 2014b)
Chronic aspects: cognitive	Cognitive deficits in retrospective and prospective memory, complex problem solving, and aspects of working memory. Many of these deficits are associated with reduced serotonin transporter markers. However, the HPA axis and cortisol levels may be cofactors. Evoked potential studies show altered brain reactivity when performing simple unimpaired tasks, with suggestions of increased mental effort to maintain performance	McCann *et al.* (2008) Kish *et al.* (2010) Parrott (2006, 2009, 2013a, 2013b) Montgomery *et al.* (2010) Wetherell *et al.* (2012)

HPA, hypothalamic–pituitary–adrenal; MDMA, 3,4-methylenedioxymethamphetamine.

of disruption to everyday well-being. From a broader perspective, recent research over the past 10 years has revealed a wide range of neuropsychobiological deficits associated with the recreational use of ecstasy/MDMA (Parrott, 2013a, 2013b). This review has shown that heightened stress, modified cortisol rhythms, and related changes in the HPA axis (Table 2) now need to be added to this list of deficits.

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Conflicts of interest

There are no conflicts of interest.

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