Increased cortisol levels in hair of recent Ecstasy/MDMA users

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Abstract

Previous research has revealed an acute 8-fold increase in salivary cortisol following self-administered Ecstasy/MDMA in dance clubbers. It is currently not known to what extent repeated usage impacts upon activity of the hypothalamic-pituitary-adrenal axis over a more prolonged period of time. This study investigated the integrated cortisol levels in 3-month hair samples from recent Ecstasy/MDMA users and non-user controls. One hundred and one unpaid participants (53 males, 48 females; mean age 21.75 years) completed the University of East London recreational drug use questionnaire, modified to cover the past 3-months of usage. They comprised 32 light recent Ecstasy/MDMA users (1-4 times in last 3 months), 23 recent heavy MDMA users (>5 times in last 3 months), and 54 non-user controls. Volunteers provided 3 cm hair samples for cortisol analysis. Hair cortisol levels were observed to be significantly higher in recent heavy MDMA users (mean=55.0±80.1 pg/mg), compared to recent light MDMA users (19.4±16.0 pg/mg; p=0.015), and to non-users (13.8±6.1 pg/mg; p<0.001). Hence the regular use of Ecstasy/MDMA was associated with almost 4-fold raised hair cortisol levels, in comparison with non-user controls. The present results are consistent with the bio-energetic stress model for Ecstasy/MDMA, which predicts that repeated stimulant drug use may increase cortisol production acutely, and result in greater deposits of the hormone in hair. These data may also help explain the neurocognitive, psychiatric, and other psychobiological problems of some abstinent users. Future study design and directions for research concerning the psychoneuroendocrinological impact of MDMA are also discussed.

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1. Introduction

The amphetamine derivative 3,4-methylenedioxymethamphetamine (MDMA) is associated with a wide range of central nervous system effects, particularly through its indirect
agonistic actions on the serotonergic and dopaminergic systems (Green et al., 2003). MDMA is most widely known for its euphoriant properties, when it is used as an illicit recreational drug under the street name of ‘Ecstasy’ (Schifano, 2000; Parrott, 2004a, 2013a). The activating effects of MDMA are not limited to positive moods, since negative moods such as anxiety can also be increased (Kirkpatrick et al., 2012; Parrott et al., 2011). The regular use of Ecstasy/MDMA is associated with a range of neurocognitive and other psychological problems, including deficits in memory, higher executive processing, sleep and psychiatric well-being (Fox et al., 2002; Laws and Kokkalis, 2007; McCann et al., 2008; Montgomery et al., 2010; Parrott, 2012a, 2013b; Zakzanis and Campbell, 2006).

MDMA also stimulates the hypothalamic-pituitary-adrenal (HPA) axis, with increased secretion of the glucocorticoid hormone cortisol (Mas et al., 1999; Paci et al., 2001; Harris et al., 2002). Following acute doses of MDMA in the laboratory, the increase in cortisol can range from 100% to 150% over baseline, depending on factors such as dosage level (Harris et al., 2002), and repeated administration (Farré et al., 2004). Stronger endocrine changes have been reported in real world studies of recreational drug users. In two independent studies, the acute use of Ecstasy/MDMA in combination with dancing and partying induced an almost 8-fold acute increase in salivary cortisol levels (Parrott, 2004b). Importantly, no significant increases in cortisol were observed in either study on the control weekends, when participants went partying as usual, but without taking Ecstasy/MDMA. The marked cortisol increase in Ecstasy/MDMA-using party-goers may result from the combination of drug and environmental stimulation, with dance clubs typically involving loud music, crowding, and physical exertion (Parrott, 2004b).

Although the short-term neuroendocrine effects of MDMA are well established, the longer-term effects of repeated drug use on HPA axis activity and cortisol remain unclear. Initial evidence suggests that drug-free Ecstasy users exhibit altered baseline and stress-responsive cortisol secretion (Gerra et al., 2003). Until recently, the measurement of chronic cortisol levels was limited to blood, saliva, or urine samples, ideally taken repeatedly at several time points (Evans et al., 2012; Helhammer et al., 2007). Cortisol in hair provides a methodological advance, since it generates a cumulative index of hormone secretion over several months (Stalder and Kirschbaum, 2012). The underlying theory is that the hormone is incorporated into the growing hair, and that the hair cortisol index may provide a valid (Broderick et al., 2004; Kirschbaum et al., 2009; Thomson et al., 2010; Manenschijn et al., 2011), and reliable (Stalder et al., 2012b) measure of longer-term neurohormonal secretion. In the current study we utilised this novel procedure, to investigate the links between Ecstasy/MDMA use and cortisol secretion over the previous 3 months. Our prediction was that more frequent and repeated Ecstasy/MDMA usage would lead to higher levels of cortisol in the hair.

2. Experimental procedures

2.1. Participant characteristics

One-hundred and one participants (53 males, 48 females, mean±SD age: 21.75±4.23 years) were recruited via advertisements concerning MDMA usage. Study inclusion was restricted to participants who had hair longer than 3 cm at the posterior vertex region of the scalp, and who did not suffer from any chronic medical or psychiatric conditions. Participants were divided into three subgroups depending on their self-reported Ecstasy/MDMA usage over the prior three months. Recent light users comprised 27 participants (18 male, 9 female, mean±SD age: 21.15±1.09 years) who had consumed MDMA between one and four times in the past 3-months. Recent heavy users comprised 23 participants (8 male, 15 female, mean±SD age: 21.48±0.89 years) who had consumed MDMA more than five times in the past 3-months. The control group

Table 1  Recent 3-month drug consumption: self-reported by recent light MDMA users, recent heavy MDMA users, and non-user controls (modified University of East London Recreational Drug Usage Questionnaire; Parrott et al, 2001).

<table>
<thead>
<tr>
<th></th>
<th>Non-user controls</th>
<th>Recent light users</th>
<th>Recent heavy users</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of users</td>
<td>Times used (S.D.)</td>
<td>Number of users</td>
</tr>
<tr>
<td>MDMA</td>
<td>0</td>
<td>0 (0)</td>
<td>32</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>1</td>
<td>1 (0)</td>
<td>7</td>
</tr>
<tr>
<td>Cocaine (Nasal)</td>
<td>2</td>
<td>5.5 (66.3)</td>
<td>12</td>
</tr>
<tr>
<td>Cocaine (Crack)</td>
<td>0</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>LSD</td>
<td>1</td>
<td>1 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Mephedrone</td>
<td>7</td>
<td>8.4 (6.6)</td>
<td>12</td>
</tr>
<tr>
<td>Opiate</td>
<td>0</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Barbiturate</td>
<td>2</td>
<td>1.5 (2.1)</td>
<td>2</td>
</tr>
<tr>
<td>Magic Mushrooms</td>
<td>0</td>
<td>0 (0)</td>
<td>1</td>
</tr>
<tr>
<td>Steroids</td>
<td>0</td>
<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Solvents</td>
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<td>0 (0)</td>
<td>0</td>
</tr>
<tr>
<td>Poppers</td>
<td>1</td>
<td>1 (0)</td>
<td>2</td>
</tr>
<tr>
<td>Ketamine</td>
<td>0</td>
<td>0 (0)</td>
<td>2</td>
</tr>
<tr>
<td>Tobacco/day</td>
<td>19</td>
<td>7.5 (4.7)</td>
<td>27</td>
</tr>
<tr>
<td>Alcohol/week</td>
<td>54</td>
<td>13.4 (11.8)</td>
<td>32</td>
</tr>
<tr>
<td>Cannabis/month</td>
<td>20</td>
<td>19.6 (11.2)</td>
<td>27</td>
</tr>
</tbody>
</table>
2.2. Assessment measures

2.2.1. Demographic and hair-related variables
A self-developed questionnaire was used to record socio-demographic and lifestyle variables, such as sex, age, smoking status, medication intake, and oral contraceptive use. In addition, hair-related characteristics, such as hair colour, washes per week, and hair treatments were assessed (Stalder et al., 2012a).

2.2.2. Recreational drug use questionnaire
This self-rating questionnaire covered recreational drug-use during the previous 3-months (Parrott et al., 2001). It covered all the main types of drug, both legal (alcohol, tobacco/nicotine), and illegal (cannabis, Ecstasy/MDMA, amphetamine, cocaine, and others; see Table 1).

2.2.3. Hair cortisol
Hair strands (~3 mm diameter) were carefully cut as close as possible to the scalp from the posterior vertex region at the back of the head. The scalp-near 3 cm hair segment was used for analyses. Based on a hair growth rate of ~1 cm/month (Wennig, 2000), this segment reflects hair grown over the previous three months. Wash and steroid extraction procedures followed the laboratory protocol described in Stalder et al. (2012b, study II), with 10 mg of whole, non-pulverised hair being used for analyses. After extraction, cortisol concentrations were determined using a commercially available immunoassay with chemiluminescence detection (CLIA, IBL-Hamburg, Germany) in the Biopsychology Laboratory, University of Dresden, Germany (Prof. Clemens Kirschbaum). The intra-assay and inter-assay coefficients of variation of this assay are below 8%.

2.3. Statistical analysis
The data were analysed by one way Analysis of Variance (ANOVA), followed by Tukey paired comparison tests between drug conditions. Probability levels were two-tailed. Since the cortisol values were not found to be normally distributed and showed unequal group variances, the data were subjected to log-transformation. Statistical analyses were performed using SPSS version 20.

3. Results
Drug usage for the three groups are reported in Table 1, with the ANOVA group effect for amphetamine usage in the past three months (F(2, 106) = 4.46, p = 0.014), tobacco use per day (F(2, 106) = 4.56, p = 0.013), alcohol use per week (F(2, 106) = 3.90, p = 0.023) and cannabis use per month (F(2, 106) = 5.04, p = 0.008) being significant. Tukey paired comparisons revealed that the light recent Ecstasy/MDMA users reported higher amphetamine (p < 0.05), tobacco (p < 0.01) and cannabis (p < 0.01) consumption than the non-user controls who did consume more alcohol weekly (p = 0.05) than the light recent Ecstasy/MDMA users.

4. Discussion
Recent Ecstasy/MDMA users who had taken the drug on five or more occasions during the past 3-months, demonstrated an almost 4-fold increase in hair cortisol levels compared to non-user controls, and an almost 3-fold increase compared to light Ecstasy/MDMA users. Lighter recent Ecstasy/MDMA users, who had taken the drug on less than 4 occasions in the past 3-months, showed group mean cortisol levels...
slightly higher than controls, although the difference was not significant. There was a marked difference in the variances of cortisol values across groups. Non-user controls had the lowest variance, whereas heavy recent Ecstasy/MDMA users showed the highest group variance. This variation in scores is illustrated by the box-plot distributions, where the exponential Y-axis for the cortisol values should be noted (Figure 1). Non-user controls showed a tight clustering of scores at the low end of the scale, with most cortisol values under 15 ug/dl, and the highest single value of 35 ug/dl. In contrast, heavy Ecstasy/MDMA users showed far greater variance, with comparatively few cortisol values under 15 ug/dl, and five values over 90 ug/dl. The distribution of scores for the light-recent Ecstasy/MDMA users was in between the other two groups, with the majority of users providing mid-range cortisol values.

Although the current data are cross-sectional and technically no causation can be inferred, it may be assumed that the high chronic cortisol values for the heavier users are a result of the neuroendocrine effects of acute MDMA use. In placebo-controlled laboratory studies, MDMA administration causes a significant cortisol release (Mas et al., 1999; Harris et al., 2002), while repeated dosing leads to further rises in cortisol (Pacifici et al., 2001; Farré et al., 2004; Dumont and Verkees, 2006). In real world studies of recreational users, acute self-dosing with Ecstasy/MDMA can generate an even stronger cortisol release, with peak values around 750-800% higher than baseline (Parrott et al., 2007, 2008). Gerra et al. (2003) reported that baseline cortisol levels were significantly higher in drug-free Ecstasy users than non-user controls, and displayed a heightened cortisol response to a psychosocial stressor. This may suggest that in addition to the increased deposits of cortisol in hair in heavy MDMA users from repeated stimulant drug use may also alter basal and cortisol responses to stressful environments. Interestingly, Scholey et al. (2011) have also observed that abstinent Ecstasy/MDMA users reported significantly higher feelings of daily stress than non-user controls. Wetherell et al. (2012) too, observed that drug-free Ecstasy/MDMA users required to perform a laboratory stress task, reported feeling significantly ‘less calm’ than non-user controls. Whether these subjective mood responses to laboratory induced stressors are causally related to the higher cortisol values found both here (Figure 1), and by Gerra et al. (2003) in MDMA users is worthy of future investigation.

Cortisol is important for acute metabolic activation and energy mobilisation, especially under conditions of high physical demand (Selye, 1956; Lovallo, 1997). MDMA is a powerful central nervous system stimulant and metabolic activator, and cortisol release may contribute to the stimulatory effects of Ecstasy/MDMA in recreational users (Parrott, 2009). MDMA is commonly consumed at dance clubs and raves (Winstock et al., 2001) where the prolonged periods of dancing and hot-crowded conditions may help to boost the reinforcing effects of MDMA - possibly through greater cortisol release (Harris et al., 2002; Parrott, 2002, 2009). A potential cause of the neurohormonal variation in our Ecstasy/MDMA users may be individual differences in rates of dancing or sympathetic activation (Parrott et al., 2006). Recreational users also report that the positive effect of MDMA are enhanced or reinstated by heat (Bedi and Redman, 2006; Parrott, 2004, 2012b), and this may be another factor contributing to the variance in neurohormonal response recorded in hair samples. There may also be endogenous differences in HPA or hormonal reactivity to MDMA. All these putative factors need to be empirically studied. In chronic terms, the recreational use of MDMA is associated with many functional problems, including neurocognitive deficits and an increased propensity for psychiatric distress (Brière et al., 2012; Laws and Kokkalis, 2007; McCann et al., 2008; Montgomery et al., 2010; Parrott, 2006, 2012a; Verkes et al., 2001; Zakzanis and Campbell, 2006). The heightened levels of cortisol may contribute to these neurophysiological effects (Parrott, 2009); furthermore the variance in neuroendocrine responses may help explain any variation in functional findings with chronic users.

These findings need to be interpreted in light of the various study limitations, some of which are inherent to many observational drug usage studies. Firstly, our study relied upon the self-reporting of recreational drug users to detail their recent usage of MDMA (or not for the non-using drug control group), and their recent usage of MDMA was not qualified via biological sampling. Concerning the levels of cortisol assessed in the current study, the differences in the levels of hair cortisol are mainly prescribed to the greater consumption of MDMA by the ‘heavy usage’ group. No assessment of trait or state stress levels was administered within the current study, possibly not accounting for any chronic ‘stress induced’ effect upon cumulative cortisol levels. Assessment of any differences in levels of intense exercise undertaken by the sample, their body-to-mass ratio, or the relative amount of intense dancing (common for this age group and amongst MDMA users) for example, are other possible contributors to the cumulative cortisol index provided by hair samples that could be considered in future research of this kind. Future research could also consider the stability of group assignment, given ‘heavier’ or ‘lighter’ users assignment in groups may be affected by the timeframe or the study and whether the heavier users for example were consuming MDMA closer to the hair sampling within the study.

Another potentially important topic for future research is the ‘homeostatic integrity’ of abstinent Ecstasy/MDMA users. Herbert et al. (2007) noted that cortisol was involved in both predictive and reactive homeostasis. Predictive homeostasis is based around circadian rhythms, with cortisol involved in everyday patterns of sleep, waking and alertness (Halberg, 1963). Yet cortisol is a labile and reactive hormone, and its release is also stimulated by physical and psychological stressors. Gerra et al.’s (2000, 2003) earlier cortisol findings are consistent with deficits in reactive homeostasis. This could help explain why abstinent Ecstasy/MDMA users reported feeling more stressed and less calm, than non-user controls (Scholay et al., 2011; Wetherell et al., 2012). Future research needs to investigate predictive and reactive homeostasis within a unified design. The core hypothesis for future empirical investigation is that both aspects of homeostasis may be adversely affected in recreational Ecstasy/MDMA users.

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None.
Increased cortisol levels in hair

Contributors

Authors Parrott, Sands, Jones, Clow, Evans, Stalder, designed the study and wrote the protocol. Authors Sands and Downey completed the data analysis. All authors managed the literature searches and prepared the manuscript for publication. All authors contributed to and have approved the final manuscript.

Conflict of interest

The authors declare no conflicts of interest.

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References


