Reduced memory skills and increased hair cortisol levels in recent Ecstasy/MDMA users: significant but independent neurocognitive and neurohormonal deficits

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Objectives The goals of this study were to measure the neurocognitive performance of recent users of recreational Ecstasy and investigate whether it was associated with the stress hormone cortisol.

Methods The 101 participants included 27 recent light users of Ecstasy (one to four times in the last 3 months), 23 recent heavier Ecstasy users (five or more times) and 51 non-users. Rivermead paragraph recall provided an objective measure for immediate and delayed recall. The prospective and retrospective memory questionnaire provided a subjective index of memory deficits. Cortisol levels were taken from near-scalp 3-month hair samples.

Results Cortisol was significantly raised in recent heavy Ecstasy users compared with controls, whereas hair cortisol in light Ecstasy users was not raised. Both Ecstasy groups were significantly impaired on the Rivermead delayed word recall, and both groups reported significantly more retrospective and prospective memory problems. Stepwise regression confirmed that lifetime Ecstasy predicted the extent of these memory deficits.

Conclusions Recreational Ecstasy is associated with increased levels of the bio-energetic stress hormone cortisol and significant memory impairments. No significant relationship between cortisol and the cognitive deficits was observed. Ecstasy users did display evidence of a metacognitive deficit, with the strength of the correlations between objective and subjective memory performances being significantly lower in the Ecstasy users. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—MDMA; cortisol; memory; metacognitive; Ecstasy; 5-HT

The ring-substituted methamphetamine derivative 3,4-methylenedioxymethamphetamine (MDMA) or ‘Ecstasy’ is a powerful central nervous system stimulant, which stimulates serotonin (5-hydroxytryptamine, 5-HT) release through indirect agonistic actions on the serotonergic system. MDMA has been described as neurochemically ‘messy’, because it also affects several other neurotransmitters, including dopamine, noradrenaline and histamine (Ricaurte et al., 2000; Green et al., 2003). MDMA is known for its euphoric and entactogenic properties, because it can induce subjective feelings of happiness and closeness to others (McCann and Ricaurte, 2007; Taurah et al., 2014). The recreational use of Ecstasy/MDMA is associated with a range of neuropsychobiological problems, in memory and higher cognition (Murphy et al., 2009; Piechatzek et al., 2009), neurohormonal activity (Gerra et al., 2003), psychiatric well-being (Soar et al., 2004; Potter et al., 2013), mood state (Hoshi et al., 2006), pain sensitivity (McCann et al., 2011), sleep (Carhart-Harris et al., 2009) and psychomotor ability (Verkes et al., 2001; Wilson et al., 2014). Furthermore, in many of these psychobiological areas, the degree of impairment is associated with lifetime Ecstasy/MDMA usage (Parrott et al., 2000; Soar et al., 2006).

Over the past 25 years, research into Ecstasy/MDMA has attempted to identify the mechanisms through which it causes these neuropsychobiological changes. Neuroimaging studies on 5-HT markers in recreational Ecstasy/MDMA users have identified reduced levels of the 5-HT transporter (serotonin transporter) in many brain areas. For instance, serotonergic damage has been

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identified in the frontal cortex, which is involved with impulsivity and higher cognition, while the hippocampus is closely involved in memory (McCann and Ricaurte, 2003; McCann et al., 2005; Benningfield and Cowan, 2013). Ecstasy/MDMA can also influence neuroendocrine activity, both acutely and chronically (Dumont and Verkes, 2006). An acute dose has stimulatory effects on the hypothalamic-pituitary-adrenal (HPA) axis, leading to increased secretion of the glucocorticoid hormone cortisol (Harris et al., 2002). In laboratory studies, acute MDMA leads to a cortisol increase of 100–200% in sedentary humans, depending on factors such as dosage (Harris et al., 2002; Kuypers et al., 2013) and single or closely repeated administration (Farre et al., 2004). Even greater neurohormonal changes have been found in real-world studies of recreational users, with self-administered Ecstasy/MDMA by dance clubbers leading to an increase in salivary cortisol of around 800% (Parrott et al., 2008; Parrott et al., 2013). This larger increase is hypothesised to result from the combination of drug and environmental stimulation, because dance clubs involve loud music, dense crowding and prolonged periods of dancing. These environmental factors have been incorporated into the bio-energetic stress model, which attempts to explain the variability in neuropsychological, functional and structural consequences of recreational Ecstasy/MDMA (Parrott, 2004, 2012a, 2012b, 2013a, 2013b).

Corticosteroids are essential for normal brain functioning and are involved in neuroadaptive responses to environmental changes; furthermore, low or high levels of corticosteroids can be damaging to various psychobiological functions (Herbert et al., 2006). The exposure to repeated stressors, such as Ecstasy/MDMA consumption in biologically stressful situations, may increase cortisol levels and can be a contributory factor for any associated neurocognitive effects (Parrott et al., 2008). Wetherell and Montgomery (2014) reported significantly greater levels of anxiety and depression and elevated diurnal cortisol profiles, in abstinent Ecstasy/MDMA users. As noted earlier, recreational Ecstasy/MDMA use is associated with memory problems and other neurocognitive deficits (Parrott et al., 1998; Gouzoulis-Mayfrank et al., 2000; Parrott, 2013a, 2013b). Structural damage to brain areas related to memory function, including the fronto-temporal and hippocampal regions (McEwen, 2005), has been observed to be altered in Ecstasy/MDMA users, and this damage may partially reflect a repeated exposure to high levels of cortisol. Further to this, heavy users of Ecstasy/MDMA can display significant neuroendocrine changes in comparison with controls and lesser users of Ecstasy/MDMA—in the form of reduced cortisol response to serotonin agonists (Gerra et al., 2000; Verkes et al., 2001). As such, the repeated exposure to high levels of cortisol through Ecstasy/MDMA exposure may constitute a potential mechanism for the associated memory impairments detected in Ecstasy/MDMA users.

Kuypers and colleagues (Kuypers et al., 2013) investigated this hypothesis by giving participants a cortisol synthesis inhibitor (metyrapone), together with a single dose of MDMA. They reported that the cortisol-inhibiting effect of metyrapone did not prevent the MDMA-induced verbal memory impairment; this allowed them to conclude that the cortisol response to MDMA was unrelated to the memory deficits. This was a single-dose study, and the effects of repeated Ecstasy/MDMA use on cortisol and cognition remain unclear. The bio-energetic stress model predicts that repeated drug usage will lead to chronically increased levels of cortisol (Parrott, 2006, 2009). Furthermore, any basal neurohormonal changes may have adverse practical implications, given the importance of cortisol for homeostasis, neurocognition and psychobiological integrity (Herbert et al., 2006). Initial evidence suggests that drug-free Ecstasy users exhibit altered baseline cortisol and also stress-responsive cortisol secretion (Gerra et al., 2003), although some equivocal evidence exists concerning the longer-term endocrine changes associated with Ecstasy/MDMA usage. For example, Allott and colleagues observed no persistent effect of MDMA use on neuroendocrine functioning with respect to a serotonergic challenge study, with Ecstasy/polydrug, cannabis/polydrug and non-drug using controls not differing in their cortisol responses to citalopram (Allott et al., 2009), whereas Wolff and colleagues examined cortisol samples ‘in the field’ in participants pre-clubbing and post-clubbing (Wolff et al., 2012). They observed changes in cortisol readings to be significantly greater in MDMA-positive clubbers and that these changes were related to the low-activity catechol-O-methyl transferase genotype. They concluded that chronic use of MDMA may lead to HPA axis dysregulation, although this may be moderated by genetic polymorphism. Frokjaer and colleagues (2013) demonstrated an empirical link between cortisol and prefrontal serotonin, hence supporting the putative links between elevated cortisol, serotonergic neurotoxicity and disrupted memory (McCann et al., 2008).

Until recently, the measurement of cortisol levels has been limited to biological markers, such as blood, saliva or urine samples, taken at single time points. Because cortisol is a labile hormone, these measures may be influenced by situational factors and circadian activity (Hellhammer et al., 2007; Stalder et al., 2009). The
assessment of cortisol in hair includes an important methodological advance, because it provides a single index of neurohormonal level over several months (Stalder and Kirschbaum, 2012). In the current study, we utilised this novel procedure to investigate the link between recent Ecstasy/MDMA use and the amount of cortisol deposited in hair over the previous 3 months. The basic findings of significantly higher cortisol in heavier Ecstasy/MDMA users have been fully described elsewhere (Parrott et al., 2014). In the current report, we present the memory test findings from that study and analyse the relationship between the cognitive changes and cortisol levels. We compare the same three groups of light recent MDMA users, heavy recent MDMA users and non-user controls (Parrott et al., 2014). The first hypothesis was that memory performance would be impaired in the recreational Ecstasy/MDMA users. Secondly, we hypothesised that the extent of memory impairment would be greater in those participants with higher levels of hair cortisol.

METHODS

Participant characteristics

One-hundred and one participants (53 men, 48 women and mean ± standard deviation (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 3 months. Recent light users included 27 participants (18 men, 9 women and 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 included 23 participants (7 men (one participant was removed because of multiple outliers across demographic and outcome measures), 15 women and mean ± SD age: 21.48 ± 0.89 years) who had consumed MDMA five or more times in the past 3 months. The control group included 51 individuals (27 men, 24 women and mean ± SD age: 21.20 ± 5.85 years) who had not consumed any MDMA in the past 3 months. The drug usage characteristics for the three subgroups appear in the aforementioned cortisol paper (Parrott et al., 2014).

Written informed consent was provided by all participants. The sign-up form indicated that the University did not condone the use of illicit substances and provided sources of information for advice on drug-related problems. The study was conducted in accordance with the Declaration of Helsinki and was approved by the University ethics committee, and the participants were not compensated for their participation.

Procedure

The unpaid volunteer participants attended Swansea University on a single occasion, and after providing informed consent, the participants completed the demographic, drug use and subjective memory questionnaires (described next). Following this, each participant completed the objective memory assessments in a one-on-one setting in a designated testing room. Finally, each participant provided a hair sample for the cortisol assessment.

Assessment measures

Demographic and hair-related variables. A self-developed questionnaire was used to record sociodemographic and lifestyle variables, such as sex and age, in addition to hair-related characteristics, such as hair colour and washes per week, and hair treatments were assessed (as in Stalder et al., 2012a).

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

Subjective memory. The prospective and retrospective memory questionnaire (Crawford et al., 2003) included 16 questions—eight questions covering prospective memory and eight related to retrospective memory. Responses were evaluated on the following forced-choice scale: never = 1, rarely = 2, sometimes = 3, quite often = 4 and very often = 5.

Objective memory. The Rivermead behavioural memory test (Wilson et al., 1989) involved the reading of two paragraphs, containing 60/61 words and 21 key ideas each. One paragraph was to be recalled immediately, whereas the other was to be recalled following a 5-min delay, in which trail-making test B was administered as a distractor task (Mitrushina, 2005). The standardised scoring was for total ideas correctly recalled.
Based on a hair growth rate of ~1 cm/month (Wennig, 2000), this segment re-
sulted from hair grown over the previous 3 months. Wash and steroid extraction pro-
cedures followed the laboratory protocol described previ-
ously (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 (Professor Clemens Kirschbaum). Intra-assay and inter-assay coefficients of variation of this assay are below 8%.

### RESULTS

#### Cortisol

Group mean cortisol values are presented in Table 1. The between-group analysis of variance showed that non-user controls had the lowest group mean cortisol values and these were marginally higher (nonsignificantly) in recent light Ecstasy/MDMA users. Recent heavy Ecstasy/MDMA users had cortisol values significantly higher (by around 400%) than non-user controls ($p < 0.001$) and significantly higher (by around 300%) than recent light users ($p < 0.001$). The cortisol findings are described more fully in Parrott et al. (2014).

#### Objective and subjective memory

Means and SDs of both objective and subjective memory measures are displayed in Table 1. A higher score on the objective memory tasks indicates better recall performance, whereas a higher score on the subjective memory tasks indicates higher self-reported memory problems. Pearson’s correlation coefficients between each of these measures and cortisol levels are also displayed; the emergent correlations were all nonsignificant. The assessment of possible curvilinear relationships between cortisol levels and memory scores also yielded nonsignificant results. The correlation between performances on the memory tests ($r=0.762$, $p < 0.001$) was significant. Interestingly, the correlation between the memory test performances was noticeably different for each group (control: $r=0.823$, low recent users: $r=0.649$ and high recent users: $r=0.450$). Using the Fisher r-to-Z transformation, we calculated a value of $Z$ that can be applied to assess the significance of the difference between two correlation coefficients. Thus, when comparing the control group with the low recent users, $Z=1.69$, ($p=0.046$, one tailed or 0.091, two tailed). When comparing the control group and the high recent users, $Z=2.58$ ($p=0.005$, one tailed or 0.010, two tailed).

A multivariate analysis of variance revealed a significant effect of recent Ecstasy/MDMA use on recall ($F(4, 212)=3.07$, $p < 0.05$, $g^2=0.06$). Univariate tests of between subject effects demonstrated a nonsignificant group effect for immediate recall ($F(2, 106)=0.21$, $p > 0.05$, ns) but a significant group effect with delayed recall ($F(2, 106)=5.51$, $p < 0.01$, $g^2=0.10$). Comparison tests using Tukey HSD (honest significant difference) test revealed significant differences between the control group and recent Ecstasy/MDMA light users ($p < 0.01$) and the control group and recent heavy Ecstasy/MDMA users ($p=0.01$), with no significant differences between the two Ecstasy/MDMA subgroups.

The retrospective and prospective memory questionnaire revealed a significant multivariate analysis of variance effect across the three drug groups ($F(4, 212)=4.71$, $p < 0.01$, $g^2=0.08$). There were also significant differences between drug groups, for the prospective memory subscale ($F(2, 106)=8.37$, $p < 0.001$).
For retrospective memory, Tukey comparison tests revealed significantly more problems in recent light Ecstasy/MDMA users than the control group ($p < 0.01$) and significantly more memory problems in recent heavy Ecstasy/MDMA users than controls ($p < 0.01$); there were no significant differences between light and heavy Ecstasy/MDMA user groups (Table 1). A similar pattern emerged with self-reported retrospective memory problems. The recent light Ecstasy/MDMA users reported significantly more retrospectively memory problems than the control group ($p < 0.01$), while recent heavy Ecstasy/MDMA users also noted significantly more memory problems than controls ($p < 0.01$); again, there were no significant differences in retrospective memory between the two Ecstasy subgroups.

For the 3-month drug data, a series of stepwise regressions were undertaken to determine which drug type, or combination of drug types, predicted the memory deficits and cortisol values (Table 2). High collinearity and low usage of certain drug types lead to their exclusion from the regression model. Six variables were entered into the stepwise regression—MDMA, cocaine (nasal), mephedrone, tobacco, alcohol and cannabis. The regression-concerning cortisol levels identified two significant predictors, recent cannabis usage and recent Ecstasy/MDMA usage. For the objective memory assessments, alcohol consumption was the only significant predictor of immediate recall (4%), and recent Ecstasy/MDMA and mephedrone consumption significantly predicted delayed recall performance (9%). For prospective memory, there were three significant predictors, recent Ecstasy/MDMA, tobacco and alcohol (Table 2). For self-rated retrospective memory, there were three significant predictors, recent tobacco, recent Ecstasy/MDMA and recent alcohol (Table 2). Stepwise regression analyses were then repeated with the lifetime usage data—for the same six drugs (Table 4). Cortisol levels were predicted by lifetime cannabis usage, while immediate recall was predicted by lifetime alcohol consumption. Delayed recall was predicted by lifetime Ecstasy/MDMA, while prospective memory was also predicted by lifetime Ecstasy/MDMA. Self-rated retrospective memory was statistically predicted by lifetime Ecstasy/MDMA and lifetime alcohol (Table 4).

**DISCUSSION**

This study confirmed the adverse effects of recreational Ecstasy/MDMA on objective memory task performance and self-reported memory deficits. On the Rivermead delayed recall performance test, both groups of recent Ecstasy/MDMA users were significantly impaired, in comparison with non-user controls (Table 1). A similar pattern of deficits was found with the retrospective and prospective memory questionnaires, where both groups of Ecstasy/MDMA users reported significantly more memory problems than the control group (Table 1). The correlation between objective and subjective memory scores significantly differed between the recent high users and controls, indicating a possible metacognitive deficit in the

| Table 2. Stepwise regression of recent 3-month drug usage upon objective and subjective memory assessments |
|-----------------------------------------------|----------------|----------------|------|
| **Step** | **Variable** | **Beta** | ***t*** | **Adjusted R²** |
| Immediate recall | Alcohol | 0.223 | 2.36* | 0.04 |
| Delayed recall | MDMA | −0.257 | −2.73** | 0.06 |
| | MDMA | −0.248 | −2.69** | 0.09 |
| | Mephedrone | −0.213 | −2.31* | 0.09 |
| Prospective memory | MDMA | 0.344 | 3.78** | 0.11 |
| | MDMA | 0.299 | 3.34** | 0.17 |
| | Tobacco | 0.260 | 2.91** | 0.17 |
| | MDMA | 0.259 | 2.87** | 0.17 |
| | Tobacco | 0.255 | 2.89** | 0.17 |
| | Alcohol | 0.185 | 2.08* | 0.19 |
| Retrospective memory | Tobacco | 0.338 | 3.69** | 0.11 |
| | Tobacco | 0.291 | 3.25** | 0.17 |
| | MDMA | 0.264 | 2.94** | 0.17 |
| | Tobacco | 0.286 | 3.24** | 0.17 |
| | MDMA | 0.223 | 2.47* | 0.19 |
| | Alcohol | 0.188 | 2.11* | 0.19 |

MDMA, 3,4-methylenedioxymethamphetamine.

*Significant at the $p < 0.05$ level.

**Significant at the $p < 0.01$ level.
MDMA-using participants. The contributory role of Ecstasy/MDMA was statistically confirmed in the regression analyses. When recent 3-month drug usage was considered, Ecstasy/MDMA was found to be a significant predictor for delayed word recall, for prospective memory problems and retrospective memory problems (Table 2). When the lifetime drug usage values were entered into the regression analysis, lifetime Ecstasy/MDMA consumption was a significant predictor for delayed word recall, the prospective memory questionnaire deficits and also the retrospective memory questionnaire deficits (Table 3). The findings were consistent with the extensive empirical literature on memory deficits in abstinent Ecstasy/MDMA users (Verkes et al., 2001; Taurah et al., 2014). Not every study has identified memory deficits (Parrott 2006, 2013b) and is consistent with the lack of group differences in immediate word recall (Table 1) reported in the current study. The presence of deficits in delayed recall, but not in immediate recall, suggests that time may be an important factor—with Ecstasy/MDMA putatively affecting the key process of information storage.

The second aim of the current study was to examine whether hair cortisol levels would be related to neurocognitive performance. As previously reported (Parrott et al., 2014), the only significant group differences in cortisol hair deposits were found in the recent heavy Ecstasy/MDMA user group. Yet both groups of Ecstasy/MDMA users showed significant memory deficits—recent heavy users and recent light users (Table 1). Hence, there was a general dissociation between the neurohormonal and the neurocognitive findings. The independence of the cortisol and cognitive findings was statistically confirmed in their near zero correlations. Hence, for immediate word recall, delayed word recall, retrospective memory and prospective memory, the 3-month hair cortisol values did not correlate with any memory test score (Table 1). This clearly suggests that the neurocognitive and neurohormonal effects of recreational MDMA are independent. There may be other potential reasons for the lack of any statistical associations here. Firstly, the cortisol values covered the previous 3 months, whereas the cognitive deficits would be primarily related to lifetime usage. Furthermore, longer-term Ecstasy/MDMA users tend to use the drug less frequently than novice users (Parrott, 2005), so that the light current user subgroup may have contained a number of heavy lifetime users. Gerra et al. (2003) observed that cortisol levels returned to baseline after 12 months of abstinence, whereas the cognitive performance of Ecstasy users tends to remain impaired for a period of time after cessation (Morgan et al., 2002; Taurah et al., 2014). This pattern of results may be suggestive of a metacognitive deficit within the drug-using participants, with the strength of the correlations between objective and subjective memory performances being significantly lower in the MDMA users (from r=0.823 in the controls to r=0.450 in heavy users). Thus, greater MDMA usage may impact participants’ ability to self-monitor their own memory performance, making them less aware of their reduced cognitive capacity, even after reducing their MDMA intake in recent times.

The regression analyses identified recent cannabis and recent Ecstasy/MDMA usage as significant predictors of cortisol levels (R^2 = 21%), with higher

Table 3. Lifetime use of illicit drugs (University of East London (UEL) Recreational Drugs Questionnaire, Parrott et al., 2001)

<table>
<thead>
<tr>
<th></th>
<th>Non-user controls Mean times used (SD)</th>
<th>Recent light Ecstasy/MDMA users Mean times used (SD)</th>
<th>Recent heavy Ecstasy/MDMA users Mean times used (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDMA</td>
<td>4.41 (12.08)</td>
<td>21.06 (25.19)**</td>
<td>34.74 (26.44)**</td>
</tr>
<tr>
<td>Amphetamine</td>
<td>0.37 (1.51)</td>
<td>7.87 (20.19)**</td>
<td>2.87 (5.67)**</td>
</tr>
<tr>
<td>Cocaine (nasal)</td>
<td>7.87 (29.77)</td>
<td>2.53 (44.05)</td>
<td>7.78 (8.82)</td>
</tr>
<tr>
<td>Cocaine (crack)</td>
<td>0.00 (0.00)</td>
<td>0.03 (0.17)</td>
<td>0.00 (0.00)</td>
</tr>
<tr>
<td>LSD</td>
<td>0.20 (1.37)</td>
<td>0.26 (0.77)</td>
<td>1.43 (3.68)**</td>
</tr>
<tr>
<td>Mephedrone</td>
<td>12.59 (39.29)</td>
<td>28.48 (57.95)</td>
<td>5.22 (5.22)</td>
</tr>
<tr>
<td>Opiate</td>
<td>0.09 (0.49)</td>
<td>0.10 (0.40)</td>
<td>0.17 (0.39)</td>
</tr>
<tr>
<td>Barbiturate</td>
<td>1.20 (6.92)</td>
<td>1.87 (5.80)</td>
<td>0.65 (2.16)</td>
</tr>
<tr>
<td>Magic mushrooms</td>
<td>0.44 (1.66)</td>
<td>1.26 (1.88)</td>
<td>2.78 (5.44)**</td>
</tr>
<tr>
<td>Steroids</td>
<td>0.02 (0.02)</td>
<td>0.00 (0.00)</td>
<td>0.00 (0.00)</td>
</tr>
<tr>
<td>Solvents</td>
<td>0.46 (2.75)</td>
<td>0.00 (0.00)</td>
<td>0.15 (0.63)</td>
</tr>
<tr>
<td>Poppers</td>
<td>2.15 (8.54)</td>
<td>4.87 (18.01)</td>
<td>5.13 (11.03)</td>
</tr>
<tr>
<td>Ketamine</td>
<td>2.39 (13.68)</td>
<td>3.00 (7.82)</td>
<td>1.87 (4.57)</td>
</tr>
</tbody>
</table>

SD, standard deviation; MDMA, 3,4-methylenedioxymethamphetamine; LSD, lysergic acid diethylamide.

*Tukey HSD—significantly different from control group at p < 0.05 level.

**Tukey HSD—significantly different from control group at p < 0.01 level.
consumption of each drug being related to the increased cortisol deposits (Parrott et al., 2014). Previous research has shown that acute cannabis consumption (Ranganathan et al., 2009), and acute Ecstasy/MDMA consumption (Kuypers et al., 2013), can increase cortisol secretion. Furthermore, the adverse neurocognitive and neuropsychiatric sequelae of chronic cannabis (King et al., 2011), and chronic recreational Ecstasy/MDMA (Parrott, 2013b), have been suggested to be partially mediated through their effects on cortisol. Heavy recreational use of cannabis is associated with executive function deficits, in attentional impairments and reduced mental flexibility (Lindquist, 2010). In a similar fashion, repeated Ecstasy/MDMA usage may lead to neurocognitive difficulties—in encoding memories for long-term retrieval, verbal learning and reduced attentional control of higher cognitive processing (Lindquist, 2010). Deficits in this constellation of cognitive components due to MDMA and/or cannabis usage may have negative impacts upon daily functioning and may be accompanied by alterations in neuroendocrine integrity. Although a significant relationship was not observed between the levels of accumulated cortisol over 3 months and Ecstasy/MDMA usage (Table 2), hence other mechanisms and patterns of licit/illicit drug usage may be contributing to both the disruptions in memory performance and the changes in neuroendocrine activity.

In relation to recent drug use, Ecstasy/MDMA consumption was found to be the strongest predictor of variation in delayed recall performance (along with mephedrone consumption) and self-rated prospective memory (with tobacco use and alcohol consumption) and the second strongest predictor of self-rated retrospective memory behind tobacco usage (Table 2). Lifetime drug use was also associated with the neurocognitive and neurohormonal changes (Table 4). These findings are consistent with previous findings that have illustrated the metabolic deficiencies in brain areas implicated in working memory and lifetime dosage studies of Ecstasy/MDMA users (Gouzoulis-Mayfrank et al., 2000; Benningfield and Cowan, 2013). Given that the participants in this study also consumed alcohol, tobacco and various illicit drugs in addition to Ecstasy/MDMA and the drug usage amounts are based upon self-reporting, the results still need to be interpreted with some caution. The regression analyses also only included six of the drug types that were sampled (given the low usage of some drugs and high collinearity of the usage pattern of the lesser used drugs). While these other drugs may have additive or synergistic effects upon both the psychological and physiological outcomes utilised in this study, it is beyond the scope of this study to attribute their effects.

This leads into another ubiquitous limitation of these types of cross-sectional design studies, where estimates of retrospective drug use may be considered unreliable. Also, we were unable to confirm ‘recent’ use of the target drug types through biological sampling, therefore again relied upon accurate reporting of drug use, and that the declared drugs were what the participants believed they had consumed. With regard to assessment of cortisol, while the accumulated deposits of cortisol in the hair over the 3-month sampling period offer some insight into ‘recent’ stress, it cannot be causatively linked to ongoing memory deficits of the MDMA-using groups in this study. Future study designs could consider a more longitudinal approach to assessing changes in memory performance in alongside hair cortisol changes or consider changes in HPA functionality through daily cortisol profiling, as employed by Wetherell and Montgomery (2014). It is also important to empirically investigate how the different measures of cortisol (saliva, blood and hair) may be interrelated. While future studies should also include subjective indices for self-rated feelings of anxiety or stress.

Further research is also needed to examine the additive or synergistic actions of licit and illicit drugs

<table>
<thead>
<tr>
<th>Step</th>
<th>Variable</th>
<th>Beta</th>
<th>t</th>
<th>Adjusted $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cortisol</td>
<td>0.292</td>
<td>3.02**</td>
<td>0.12</td>
</tr>
<tr>
<td>2</td>
<td>Immediate recall</td>
<td>Alcohol</td>
<td>0.223</td>
<td>2.36*</td>
</tr>
<tr>
<td>2</td>
<td>Delayed recall</td>
<td>MDMA</td>
<td>−0.230</td>
<td>−2.44*</td>
</tr>
<tr>
<td>2</td>
<td>Prospective memory</td>
<td>MDMA</td>
<td>0.398</td>
<td>3.46***</td>
</tr>
<tr>
<td>3</td>
<td>Retrospective memory</td>
<td>MDMA</td>
<td>0.300</td>
<td>3.24***</td>
</tr>
<tr>
<td>3</td>
<td>Retrospective memory</td>
<td>Alcohol</td>
<td>0.255</td>
<td>2.72**</td>
</tr>
</tbody>
</table>

MDMA, 3,4-methylenedioxymethamphetamine.
*Significant at the $p < 0.05$ level.
**Significant at the $p < 0.01$ level.
upon multiple mechanisms that underlie the cellular adaptations, dysfunction and neurotoxic or neuroprotective nature of stimulants and other substances of abuse. Use of these substances has been observed to lead to the variable levels of neurocognitive and psychiatric dysfunction (Downey and Loftis, 2014), and it is an important research question to ascertain just how much of certain drugs alone or in combination can be consumed before irreparable damage to the brain is done. It is also likely that a wide range of factors influence that synergizes with the effects of substances of abuse to impact brain and neuroendocrine function, thus qualifying the molecular changes within the brain and endocrine system with respect to exposure to specifically abused substances like Ecstasy/MDMA, should inform the development of therapeutic approaches to addiction and symptoms of heavy usage.

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

REFERENCES


