Hair MDMA Samples Are Consistent with Reported Ecstasy Use: Findings from a Study Investigating Effects of Ecstasy on Mood and Memory

A.B. Scholey a L. Owen a J. Gates a J. Rodgers b T. Buchanan d J. Ling e 
T. Heffernan c P. Swan a C. Stough a A.C. Parrott f

a Brain Sciences Institute, Swinburne University, Melbourne, Vic., Australia; b Newcastle University and 
c Northumbria University, Newcastle upon Tyne, d Westminster University, London, e Keele University, Keele, and 
f Swansea University, Swansea, UK

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Abstract
Aims: Our group has conducted several Internet investigations into the biobehavioural effects of self-reported recre-ational use of MDMA (3,4-methylenedioxymethamphetamine or Ecstasy) and other psychosocial drugs. Here we re-port a new study examining the relationship between self-reported Ecstasy use and traces of MDMA found in hair samples. Methods: In a laboratory setting, 49 under-graduate volunteers performed an Internet-based assessment which included mood scales and the University of East Lon-don Drug Use Questionnaire, which asks for history and cur-rent drug use. They also provided a hair sample for determi-nation of exposure to MDMA over the previous month. Results: Self-report of Ecstasy use and presence in hair samples were consistent (p < 0.00001). Both subjective and objective measures predicted lower self-reported ratings of happiness and higher self-reported stress. Self-reported Ecstasy use, but not presence in hair, was also associated with decreased tension. Conclusion: Different psychoactive drugs can influence long-term mood and cognition in complex and dynam-ically interactive ways. Here we have shown a good corre-spondence between self-report and objective assessment of exposure to MDMA. These data suggest that the Internet has potentially high utility as a useful medium to complement traditional laboratory studies into the sequelae of recre-ational drug use.

Introduction

The use of Internet questionnaires is a valuable tool for the investigation of illicit substances on cognitive func-tion for several reasons (e.g. the availability of large sam-ple sizes). While the online environment is clearly less controlled than the laboratory, it could be argued that Web-based data collection is more naturalistic, has higher ecological validity and is less likely to induce 'performance anxiety'. Another problem may be the possibility of a ‘memory paradox’ – that is relying on memory of cognitive failures in individuals with impaired memory [1]. Thus care must be taken in the design and implementa-tion of each study and we recommend the procedures outlined in Buchanan et al. [1]. Nevertheless, the Internet
provides a very valuable source of participants for research into legal and illicit drugs and some of the procedures can control for a number of these factors. The very large samples generated have benefits in terms of statistical power, especially for analyzing the complex interactions between drug and non-drug factors [2–5]. The development of objective cognitive performance measures which can be implemented online offers huge potential for collecting data from large numbers of people. This provides a methodology for marrying relatively high levels of control, sensitivity and ecological validity.

There is evidence to suggest that individuals are more willing to disclose information about illegal activities such as drug use when online. On the other hand it is possible that a study may be 'hijacked' by groups of individuals who may want to either underplay or exaggerate drug use and/or drug-related problems. Importantly, the possibility remains that reliance on self-report may lead to spurious data. A recent method of assessing drug exposure objectively is to examine the levels in hair. Drugs and metabolites are incorporated into the hair during the formation of the hair shaft (via diffusion from blood into the actively growing follicle), after the formation (via secretions of the apocrine and sebaceous glands) and after the hair has emerged from the skin [6].

Therefore the primary aim of this study was to assess the extent to which online self-reported Ecstasy use ties in with results from hair analysis of exposure to the drug. The sensitivity of Web-based assessments of self-reported mood and memory measures as outcomes for drug use needs to be established. Recreational users of Ecstasy/MDMA (methylenedioxymethamphetamine) typically have a variety of neuropsychobiological problems, including deficits on laboratory tasks of memory, attention, executive functioning and social intelligence. In one study from our group an Internet site was constructed where unpaid volunteers completed a series of questionnaires related to the use of legal and illegal recreational substances. The questions were based on an earlier, pencil-and-paper version of the University of East London Recreational Drug Use Questionnaire [7]. Initially >700 participants were recruited. Memory was assessed using 2 self-report questionnaires. The Everyday Memory Questionnaire [8] and the Prospective Memory Questionnaire [9]. Both are valid and reliable self-report measures. The Everyday Memory Questionnaire assesses frequency of memory lapses in everyday behaviours such as ‘finding a television story difficult to follow’ and ‘telling someone a story or joke that you have told them once already’. The Prospective Memory Questionnaire provides measures of 3 aspects of prospective memory on a series of 9-point scales measuring frequency of lapses in short-term habitual prospective memory (e.g. ‘I forgot to turn my alarm clock off when I got up this morning’), long-term episodic prospective memory (e.g. ‘I forgot to pass on a message to someone’) and internally cued prospective memory (e.g. ‘I forgot what I wanted to say in the middle of a sentence’). Additionally, the instrument gauges the number of strategies used to aid remembering. In this study typical Ecstasy users were found to report significantly more difficulties in long-term prospective memory and were also observed to make considerably more mistakes while completing the questionnaires than users of other substances and drug-naive controls. Furthermore an overall dissociation between the effects of cannabis and Ecstasy on self-reported memory functioning and on the likelihood of making an error during the completion of the questionnaire was found [3]. These cognitive/memory deficits may possibly reflect impaired hippocampal-frontal associative links [10].

Therefore a secondary aim of this study was to further evaluate the effects of MDMA usage on self-reported prospective and retrospective memory taking into account cannabis use.

Method
Participants
Forty-nine unpaid volunteers (23 female) were recruited by word of mouth and the snowball technique. The age range for participants was 18–42 years (mean = 24.285, SD = 4.425). Volunteers completed online tests in a computer laboratory condition and provided hair samples for assessment of drug exposure. No restriction criteria were applied to the sample in order to obtain a true representation of a typical Internet participant sample. Both self-reported users and non-users of MDMA completed the questionnaire. Of the 49 participants, 20 claimed to have never used MDMA.

Questionnaire Items
Questionnaire items were intended to establish values for a broad range of demographic, lifestyle and consumption variables. All of the questionnaire items were presented as interactive forms on a single Web page. Different response formats (typing in text, clicking on radio buttons or selecting options from a drop-down menu) were used as appropriate. If participants submitted an incomplete form (i.e. left one or more questions blank), they were automatically informed of this and requested to supply the missing data and then resubmit the form. Within these questionnaires the participants were asked about the number of times they had taken the following drugs: cannabis, MDMA, amphetamine, cocaine, LSD, barbiturates, opiates, ‘magic’ mushrooms, steroids and solvents. The participants were required to give a
response between 1 and 5 indicating the number of times they had used these drugs (1 = Never in my life, 2 = 1–9 occasions, 3 = 10–99 occasions, 4 =>100 occasions, 5 = prefer not to answer).

**Visual Analogue Scales.** The participants were asked to complete a computer-adapted version of the caffeine research visual analogue scales (‘relaxed’, ‘alert’, ‘jittery’, ‘tired’, ‘tense’, ‘headache’, ‘overall mood’) that had been extensively used in previous research [11] with an additional 5 items, (‘mental fatigue’, ‘stressed’, ‘calm’, ‘happy’, ‘sad’). The scales were completed by placing a cross on a line that represented a continuum between ‘not at all’ and ‘extremely’ for each of the listed 10 mood states. The scales ranged from 1 to 100.

**Prospective and Retrospective Memory Questionnaire.** The Prospective and Retrospective Memory Questionnaire (PRMQ [31]) was developed to provide a self-report measure of prospective and retrospective memory slips in everyday life. It consists of 16 items, 8 asking about prospective memory failures and 8 concerning retrospective failures including questions such as ‘If you tried to contact a friend or relative who was out, would you forget to try later?’ (prospective memory). The participants were asked to report how often these things happened to them on a 5-point scale (5 = very often, 4 = quite often, 3 = sometimes, 2 = rarely, 1 = never). This measure has demonstrated high reliability [12]. For example, Crawford et al. [13] reported the good reliability of the PRMQ for the total scale (reliabilities between 0.83 and 0.92). They concluded that the PRMQ provides a useful measure of everyday memory for use in clinical research and practice. Furthermore, several studies have shown the PQRM to be a valid tool for the assessment of prospective and retrospective memory [see 12, 14].

**Hair Analysis**

At least 1.5 cm length of approximately a pencil thickness of hair was harvested by cutting as closely as possible (within 0.5 mm) of the scalp, with the experimenter wearing latex gloves to avoid contamination. Each sample was wrapped in aluminium foil at the ‘root’ end to identify orientation and placed in a specially designed container prior to dispatch to the Victorian Institute of Forensic Medicine (VIFM) that performed the hair analysis.

Hair was analysed according to Society of Hair Testing guidelines regarding the examination of drugs in human hair [15]. Hair was collected from the posterior vertex region of the scalp (nape of the neck), in such a manner as to enable identification of the proximal (scalp) to the distal orientation. Hair samples were decontaminated following VIFM procedures which include multiple washes in organic solvents and/or water. Weak acid solution was used as necessary to remove other surface contamination not otherwise removed. Hair was then dried and accurately weighed prior to extraction.

Post-harvesting procedures were designed to eliminate traces on the external surface of the hair [16]. The VIFM has performed research to determine the extent to which their decontamination procedures may remove inappropriate concentrations of drug from the hair, leading to false-negative or false-positive results. Based on their research and other published decontamination methods, the VIFM uses relatively standard decontamination procedures [17]. Threshold detection and quantification values have also been established to ensure appropriate reporting of results.

Hair analysis determined exposure in the previous month to the following substances: 6-monooctylmorphine; alprazolam, 7-aminoclonazepam, 7-aminoflunitrazepam, 7-aminonitrazepam, amphetamine, benzoylgonine, clonazepam, cocaine, co-caethylene, codeine, diazepam, EDDP, ekgonine methyl ester, flunitrazepam, ketamine, methylenedioxasympatetamine, MDMA, methadone, methamphetamine, morphine, nitrazepam, nordiazepam, oxazepam oxycodeone, pethidine, temazepam, Δ9-tetrahydrocannabinol (THC), 11-Nor-Δ9-tetrahydrocannabinol-9-carboxylic acid, tramadol and zolpidem. The current report concentrates on MDMA only.

**Procedure**

The participants were requested to attend a group testing session at a computer laboratory at Swinburne University of Technology. The room was well lit and ventilated with a constant ambient temperature. They sat visually isolated from each other at desktop PCs with the Website opened in a Web browser so the participants could begin immediately when instructed. They were requested to refrain from speaking to others while being tested. The participants were asked to wait until all others booked for the session were present so they were not distracted by others entering or leaving.

The participants gave informed consent, and provided demographic information and information about their drug usage. They then completed the mood visual analogue scales and the PRMQ. Finally the participants provided hair samples for later analysis of presence of various drugs, were thanked and debriefed.

**Data Analysis**

The data were analyzed using Statistical Package for the Social Sciences (SPSS) 16.0 statistical software. The significant relationship between self-reported MDMA usage and the presence of MDMA detected in hair was analyzed using a χ2 test.

To assess the impact of MDMA use, as defined by presence in the hair, on mood and memory measures, the data were evaluated using a univariate analysis in which mood and memory questions were dependent variables and presence of MDMA in hair samples was a fixed factor (2 levels; ‘detected’ and ‘not detected’). To assess the impact of MDMA use, as defined by self-reported use, the data were analyzed using a univariate analysis in which mood and memory questions were dependent variables and self-reported MDMA use was a fixed factor (2 levels; ‘never taken’ and ‘taken’). Data from all participants were analyzed initially. However, given the potential confounding effects of co-use of cannabis with Ecstasy, a secondary analysis was conducted following the removal of 6 participants where THC was detected in the hair.

**Results**

**Self-Report and Hair Analysis Measures of MDMA Usage**

MDMA was detected in 22 of the 49 individuals who took part in the study. A χ2 analysis assessing the self-reported usage of MDMA and actual MDMA detected in hair samples demonstrated highly significant differential
distribution of groups \([\chi^2(2) = 20.689, p = 0.000032]\), consistent with an association between whether MDMA was present in hair and self-reported Ecstasy use (table 1). By and large the results of the hair analysis confirm that the self-reported measure of MDMA usage is a relatively accurate indication of participants’ previous MDMA intake.

**Self-Report Mood and Memory**

In terms of mood and memory questionnaires, comparisons were made between the participants in whom MDMA was detected in the hair samples compared with those in whom MDMA was not, and between whether individuals self-reported that they had used Ecstasy or not.

Those with MDMA in hair rated themselves as significantly less happy and more stressed than the MDMA non-users (table 2). Compared with non-users, self-reported Ecstasy users had a similar pattern – with users reporting significantly lower ‘happy’ and greater ‘stress’ scores. The self-reported Ecstasy user group were also significantly less tense and more likely to report mislaying an item from the PRMQ.

A secondary analysis excluded individuals with THC detected in hair from the analysis (6 people). The main effect on stress was maintained with self-reported Ecstasy users having greater stress levels than non-users \([F(1,41) = 6.763, p = 0.013]\). Furthermore, MDMA users reported significant deficits on specific PRMQ items. MDMA users indicated that they were more likely to mislay objects \([F(1,41) = 5.724, p = 0.021]\), to forget things that had happened in the past few days \([F(1,41) = 4.307, p = 0.044]\), and to forget something they had watched on television \([F(1,41) = 4.424, p = 0.042]\). The last 2 of these questions make up the measure for long-term self-cued retrospective memory.

**Discussion**

The focus of the current study was to compare self-report and objective measures of Ecstasy/MDMA use. The findings demonstrated that in the present sample there was a strong relationship between self-reported drug use and MDMA detected in hair samples of individuals. These findings validate the use of the self-report drug measure applied in a series of Internet studies from our group. A further aim of the study was to assess the effects of MDMA on self-reported mood and memory. The data suggest that for mood, MDMA users (both defined by hair analysis and self-reported usage where MDMA was detected in the hair) report feeling significantly less happy and more stressed than non-users. When cannabis users were excluded from the analysis, the significant effect on self-reported happiness was no longer significant. However, MDMA users were still observed to feel more stress than non-users.

Moreover in terms of memory, following exclusion of cannabis users, significant detriments in self-reported retrospective memory were observed in MDMA users compared with non-users.

**Table 1.** Frequencies of self-reported Ecstasy usage and MDMA detected in hair samples of participants

<table>
<thead>
<tr>
<th></th>
<th>Never used</th>
<th>Used 1–9 times</th>
<th>Used 10–100 times</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Detected</td>
<td>8</td>
<td>13</td>
<td>1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Not detected</td>
<td>19</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2.** Effects of subjective report and presence of MDMA in hair samples on mood and memory

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Hair analysis</th>
<th>Self-report</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MDMA not present</td>
<td>MDMA present</td>
</tr>
<tr>
<td>Happy</td>
<td>31.44 (23.52)</td>
<td>18.863 (16.45)</td>
</tr>
<tr>
<td>Stressed</td>
<td>44.04 (21.10)</td>
<td>58.945 (23.06)</td>
</tr>
<tr>
<td>Tense</td>
<td>36.333 (28.75)</td>
<td>26.636 (23.613)</td>
</tr>
<tr>
<td>Mislay item</td>
<td>2.70 (0.91)</td>
<td>3.272 (1.24)</td>
</tr>
</tbody>
</table>

Values are means with standard deviations in parentheses. Summary statistics from analyses of variance are also shown.

* p < 0.05, ** p < 0.001.
An important methodological issue when considering qualitative measures of drug use is the validation of self-report measures, particularly with the growing availability of objective and sensitive urine and hair analysis [18].

The study reported here used hair assessment to complement self-reported MDMA usage. Hair analysis to confirm drug use is a relatively new methodology and is currently applied as an option for epidemiological studies on drug use as well as in other settings (e.g. private-sector workplace programmes, criminal justice applications, court systems). There are a number of advantages of hair as a specimen matrix, including its ease of collection, transport and storage.

In addition, hair is less likely to transmit bio-organisms than, for example, urine and it is less susceptible to tampering. After the hair has undergone sample preparation steps, the same analytical methods commonly used for screening and confirmatory urine tests (i.e. immunoassay, chromatography and mass spectroscopy, respectively) can be used for most drugs of abuse testing in hair. Perhaps the most important advantage in the context of validating self-report is that hair has a longer drug detection window than urine. Many drugs of abuse are detected in urine only up or even years after use. Although these characteristics make hair an attractive option for drug testing, researchers must be aware of the limitations imposed by the testing methodology and the biological specimen [19]. The main issues involved in hair analysis are that the ability to distinguish drug use from external contamination remains unknown (although stringent steps were taken to minimise this possibility in the present study). Furthermore, drug dose and time relationships for drugs in the hair are not clear. Some studies (e.g. self-report) may be less robust in a smaller sample size. It should be noted, however, that the direction of any causal relationship is unclear. Changes in hypothalamic-pituitary-adrenocortical axis function and drug usage have been observed in individuals with stimulant addictions [22] as well as in MDMA users [23]. The finding that MDMA users report feeling significantly more stressed than non-users provides further qualitative support for hypothalamic-pituitary-adrenocortical axis dysregulation and also demonstrates that these individuals experience real stress symptoms. It should be noted, however, that the direction of any causal relationship is unclear. Changes in hypothalamic-pituitary-adrenocortical axis function may either reflect long-term feelings of stress that contribute to drug intake on the one hand or elevated cortisol levels on the other or may be a consequence of long-lasting exposure to MDMA or reflect a pre-existing condition, such as addictive behaviour [24]. A number of clinical neuro-psychological studies have previously reported negative moods associated with persistent use of MDMA. These include elevated self-reported depression and anxiety, impulsiveness and aggression [4, 25, 26]. However, the evaluation of self-reported stress has been largely neglected, despite emerging reports of elevated cortisol in Ecstasy users. Also reduced reactivity to stressful stimuli in MDMA users has been observed [27]. This may reflect the serotonergic dysregulation caused by MDMA.

In the present study it was observed that MDMA users were significantly less happy than non-users, but this effect did not remain once cannabis users were removed from the analysis. It is possible that either cannabis use or combined use of both cannabis and Ecstasy may lead to a more negative effect. Alternatively this effect may simply be less robust in a smaller sample size. Impairment of memory performance still appeared to be associated primarily with Ecstasy rather than cannabis use. However, Rogers et al. [3] previously observed dissociation between the effects of Ecstasy and cannabis, with cannabis being associated with significantly more everyday memory problems (as assessed using the Everyday Memory Ques-
tinctionnaire), whereas MDMA/Ecstasy use was statistically related to long-term prospective memory deficits. The authors suggest that users of both MDMA and cannabis might be particularly vulnerable to memory deficits. Therefore further analysis was conducted excluding the cannabis users. Contradictory to previous findings, it appeared that greater self-reported memory deficits were actually still observed following the removal of individuals with THC present in hair, suggesting that MDMA use is the primary determinant of memory deficit.

After removal of cannabis users, MDMA users reported deficits of self-cued retrospective memory. This finding was somewhat unexpected since previous research has indicated prospective memory deficits associated with MDMA use. Dissociation of the prospective and retrospective memory components has been clearly established [28]. Prospective memory requires the formation of an intention to act and subsequent remembering to ‘act’ in the future. Retrospective memory involves episodic memory and is related to the memory of events in the past. Both prospective and retrospective memories may be triggered by environmental cues or may be self-initiated. Self-initiated memory is thought to be more effortful than environmentally-cued memory [29]. Here we observed self-reported retrospective self-cued memory detriments in MDMA users. This kind of memory may also be considered as demanding episodic memory.

Previous research has demonstrated impaired verbal memory even in subjects with fairly moderate patterns of Ecstasy use. Given previous findings that MDMA use impacts significantly on self-reported prospective memory, it seems likely that deficits associated with Ecstasy use are not specific to one domain but rather exert more global effects on memory. It is generally accepted that activation of the serotonin system has effects on large areas of the brain with axons of neurons in the rostral raphe nuclei terminating in the thalamus, striatum, hypothalamus, nucleus accumbens, neocortex, cingulate gyrus, cingulum, hippocampus and amygdala. MDMA acts as a potent and selective serotonergic neurotoxin affecting serotonergic axon degeneration and reduction in serotonin uptake sites. More recently, neuroimaging efforts have focused on markers of serotonergic integrity. McCann et al. [30] found significant reductions in 5-HTT binding in Ecstasy users in areas of the amygdala, hippocampus, thalamus and cortical regions. Prospective memory function has been postulated to depend heavily on frontal lobe areas, while retrospective memory may rely more heavily on medial temporal areas including the hippocampus (e.g. [31]). Since serotonergic axons terminate in these areas, axonal loss theoretically may target a number of memory domains pertaining to these areas. Fractionation of MDMA deficit on memory may be more complex than simply domain selectivity. It seems likely that MDMA effects on memory may be modulated by brain region and individual differences in axonal loss, which may be due to the amount of MDMA used, as well as duration and concomitant use of other substances which act on serotonergic pathways.

In conclusion, the current study has shown that measurable exposure to MDMA is consistent with self-reports of Ecstasy use. These findings add weight to previous studies into the effects of Ecstasy which have relied on the University of East London Drug Use Questionnaire and similar instruments.

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