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Assessing the functional significance of ecstasy-related memory deficits using a virtual paradigm.

Catharine Montgomery¹; Nicholas P. Hatton¹; John E. Fisk², Ruth S. Ogden¹, Ashok Jansari³.

1. School of Natural Sciences and Psychology, Liverpool John Moores University
2. School of Psychology, University of Central Lancashire
3. School of Psychology, University of East London

Running head: functional significance of ecstasy-related impairment.

Corresponding author:

Dr Catharine Montgomery

School of Natural Sciences and Psychology,

Tom Reilly Building,

Byrom St,

Liverpool,

Merseyside, UK,

L3 3AF.

Tel 44 (0) 151 2314072

Fax 44 (0) 151 2314245

e-mail: c.a.montgomery@ljmu.ac.uk

Abstract

Rationale/Objectives: Previous research shows that the use of ecstasy results in working memory and executive impairments in some users. The present study sought to assess the functional significance of such deficits using a virtual reality task. *Methods:* Twenty-three ecstasy-polydrug users and 26 nonusers were recruited. Individuals completed a drug use questionnaire measures of sleep quality and fluid intelligence. Participants also completed a virtual reality executive function task in which they play the role of an office worker for the day completing predefined tasks such as prioritising different activities according to their importance, organising the physical office environment and managing the outgoing mail in accordance with a delivery schedule. *Results:* MANOVA revealed that ecstasy users performed worse on the virtual reality task overall, and this was due to poorer performance on the planning and selection subscales. Contrary to expectations, ecstasy-polydrug users performed better on the time-based prospective memory subscale. Indices of ecstasy use were correlated with the planning subscale of the virtual task. *Conclusions:* The present study provides further support for ecstasy/polydrug related deficits in executive functioning. As it is possible that this task is more ecologically valid and relevant to day-to-day activities of many users, previous research finding null results on executive function tasks may have underestimated the impact of ecstasy-polydrug use on executive functioning.

Keywords: ecstasy, MDMA, cannabis, cocaine, executive function, polydrug, virtual reality.

Introduction

There is extensive evidence that the recreational use of ecstasy is associated with working memory and executive deficits on self-report and laboratory tests in humans (e.g. Rodgers, 2000; Parrott & Lasky 1998; Morgan 2000; Montgomery et al. 2005; Montgomery et al. 2007). The present paper assesses the functional significance of such deficits, using a virtual reality task with greater ecological validity.

The theories and methods of contemporary cognitive psychology have proved particularly useful in detecting the effects of chronic recreational ecstasy (MDMA) use on human memory ever since animal studies suggested the drug to be neurotoxic in sufficiently high doses (Battaglia et al. 1987; Ricaurte et al. 1992). Neuroimaging has allowed the structure of the human brain in recreational users to be analysed in great detail. However, the greater sensitivity (Reneman et al. 2001), as well as better ecological validity of cognitive measures has led to their continued usage in this area (Rogers, 2009). In addition, advances in theoretical models of the central executive based on Baddeley's (1986) working memory model have given researchers greater understanding of the exact mechanisms affected by the drug (Wareing et al. 2000; Montgomery et al. 2005; Fisk & Montgomery, 2009), with Miyake et al's (2000) fractionated model of the Central Executive providing a particularly useful framework for psychologists wishing to tap in to precise functional consequences of extended use of the drug (Montgomery & Fisk, 2008).

While executive deficits have been observed in a number of domains, a recent review of the literature (Murphy et al. 2009) suggests that tasks requiring high levels of executive control will be particularly affected, with deficits in verbal and visuospatial updating of information being one of the most consistent findings. However, deficits in executive switching of attention, inhibitory control and access to long-term memory were not present or generally not well replicated. Furthermore a meta-analytic review of studies on neurocognitive deficits in ecstasy users found that the use of ecstasy was consistently associated with impairment of executive function (Kalechstein et al. 2007). Zakzanis et al. (2007) similarly concluded that deficits in learning and memory, including

executive functioning are a robust finding in ecstasy users. Prospective Memory, one's ability to remember to perform actions at a certain timepoint in the future, is thought to rely on Central Executive resources (Heffernan et al. 2001). Heffernan et al. (2001) utilised the Prospective Memory Questionnaire (PMQ) self-report scale and found statistically significant links between ecstasy use and impaired PM that could not be explained by users' propensity to exaggerate failures. Zakzanis (2003) found that deficits in prospective memory persisted even in abstinent users. Most pertinent to the current study, Rendell et al. (2007) found significant impairments of prospective memory in drug users using the "Virtual Week" virtual reality task.

In Summary, previous research has shown that users of ecstasy are impaired on laboratory and self-report tasks of working memory, prospective memory and executive function. In studies utilising such laboratory tasks it is inferred that the processes that lead to impaired performance in the lab will also lead to impaired performance in everyday situations, i.e. we assume that these tasks have ecological validity. However, studies assessing the ecological validity of laboratory assessments have mixed findings. Some studies investigating the relationship between laboratory and everyday executive function have found little to support a relationship between the two (e.g. Amieva et al. 2003; Chan, 2001; Ready et al. 2001; Wilson, 1993); and while a number of studies have shown that impairments in laboratory tasks and everyday situations are related, the relationship is generally modest (Chaytor & Schmitter-Edgecombe, 2003). Recently the use of laboratory tasks to infer impaired everyday **function** in users of ecstasy has come under criticism, as such tasks may not have "functional significance" (ecological validity) for users of the drug (Newcombe 2006). The present study sought to investigate this using a virtual reality executive function task.

Advances in technology have proved a useful addition to the tools of cognitive psychologists, with virtual reality environments addressing many of the methodological shortcomings of traditional laboratory tasks (Rizzo & Buckwalter, 1997). Early attempts at using VR technology to measure executive function included a computerised version of the Wisconsin

Card Sorting Task (Pugnetti et al. 1995). The group found significantly more errors in a sample of neurologically impaired patients compared to a healthy control sample (Pugnetti et al. 1998). In recreational ecstasy users, VR studies have yielded some surprising results, with Turner et al. (1998) finding that ecstasy users performed better in a virtual object recognition task than nonusers. Rendell et al. (2007) utilised VR technology to examine prospective memory and found that ecstasy users were significantly impaired on a number of time based tasks, even when controlling for cannabis use, sleep quality and psychopathology in their “Virtual Week” task. However, there are no studies currently known to the authors that have utilised Virtual Reality technology in order to assess executive functioning of recreational ecstasy users. The present study sought to address this using a task developed by Jansari et al. (2004)- the JAAM- and used extensively in individuals with frontal lobe damage. As mentioned above, some individuals with frontal lobe damage frequently perform normatively on classic executive functioning tasks, yet it is clear that they have problems in day to day functioning (e.g. Eslinger & Damasio, 1985; McGeorge et al. 2001), suggesting that for this group of individuals such tasks lack ecological validity. JAAM was developed as an ecologically valid measure of executive function to address this problem, and has been successful in documenting EF deficits in individuals with frontal lobe damage. The task has 8 subscales: planning, prioritisation, selection, adaptive thinking, creative thinking, time-based prospective memory, event-based prospective memory and action-based prospective memory. Given that previous research in ecstasy users suggests that the updating of working memory may be affected, in addition to tasks requiring high executive load (Murphy et al. 2009), it seems reasonable to expect that the subscales requiring the manipulation and updating of information will be most affected. Thus one would imagine that the prioritisation and adaptive thinking subscales which require the updating of information during the task (see the method section for a more detailed description) would be most affected. In addition research has shown that ecstasy users are also impaired in some aspects of prospective memory functioning (e.g. Heffernan et al. 2001; Rendell et al. 2007), especially time-based PM.

It was hypothesised that the ecstasy-polydrug users in the present study would perform worse than the nonusers on the JAAM task overall, and this would be due to poorer performance on the prioritisation, adaptive thinking and time-based prospective memory subscales.

Method

Design

A between groups design was used with user group (ecstasy polydrug user vs. non ecstasy polydrug user) as the independent variable. Dependent variables were the scores on the JAAM task. JAAM scores were analysed using a MANOVA, with background variables incorporated as covariates where appropriate.

Participants

Forty-nine participants were recruited from the Liverpool John Moores University undergraduate student population and participation panel. Twenty-three were ecstasy polydrug users (13 male; mean age 23) and 26 non-ecstasy polydrug users (9 male; mean age 22) took part. Participants were recruited via the online research participation scheme (SONA Experiment Management System) and via snowballing (Solowij et al. 1992). Participants were requested not to use ecstasy in the 7 days prior to testing, and to abstain from the use of other drugs for at least 24 hours.

Materials

Drug Use (Montgomery et al. 2005)

Previous drug and alcohol use was assessed via a drug use questionnaire previously used extensively in our research. Participants are asked about the frequency and intensity of ecstasy, cannabis, alcohol, cocaine, amphetamine and other drug use, and the data is used to calculate scores for frequency of use, total lifetime dose, average weekly dose, abstinence, length of use and recent use.

Sleep Quality- Epworth Sleepiness Scale (Johns 1994) and Karolinska sleepiness scale (Gillberg et al. 1994).

As it has been suggested that sleep may be an important mediating factor of ecstasy-polydrug

related memory impairment (Cole et al. 2002; Cole & Sumnall 2003), accordingly measures of sleep quality were also collected.

JAAM (Jansari et al. 2004)

The JAAM is a virtual reality assessment which involves the participant playing the role of someone working for a day in an office environment helping to set up a meeting. The assessment was created to tap various abilities that individuals with dysexecutive syndrome seem to have difficulties with, and has previously been used to show impairments in executive functioning in individuals with frontal lobe damage relative to “normal” individuals (e.g. Jansari et al. 2004; 2007; 2008), and to assess the effects of licit drugs on executive functioning (Edginton et al. 2008). Participants read the scenario, which describes their virtual environment and role and are then shown how to navigate around the environment. They are given a list of tasks that need to be completed for the office manager, including arranging for items of post to be collected, setting up tables and chairs for a meeting, turning on the coffee machine when the first person arrives for the meeting. In addition to tasks that the participant is aware of at the beginning of the task, they are also handed a number of memos (virtual and hard copy) during the task which require them to perform additional tasks or amend a current task. The JAAM assessment has 8 constructs:

In the Planning subscale, participants are required to order items in a logical manner and not due to their perceived importance. Therefore they have to decide which tasks would logically be carried out first, for example writing a plan of action based the tasks left for them by their manager.

For the Prioritisation subscale, participants have to order items according to their relative importance, for example ordering the items on the agenda so that the important ones will be discussed first.

In the Selection subscale, participants have to choose between two or more alternatives by drawing on knowledge. For example the participant has items of post which need to be sent to various

destinations and with differing urgency. They must select the appropriate postal service to collect the letters and parcels based on their relative urgencies and destinations.

In the Creative Thinking subscale, participants must look for solutions to problems using non-specified ways. For example they must find a way to cover graffiti which is written in permanent ink.

For Adaptive thinking, participants must achieve their goals in changing conditions of success. This requires them to propose suitable solutions to new problems as they arise.

The three remaining subscales measure prospective memory. For Action-Based Prospective memory, participants must remember to execute a task cued by a stimulus in the task they are already engaged with. For example, they receive a message about new items of post to be sent, and must update the post diary accordingly.

In the Event-based prospective memory subscale, participants must remember to perform a task cued by an event, for example noting the time of fire alarms on their notes for the manager.

In the Time-based prospective memory subscale, participants must remember to perform an action at a certain time point. For example participants must turn on the Overhead Projector 10 minutes before the start of the meeting.

Overall the JAAM task takes 40 minutes to complete. Participants receive a score of 0 (no attempt made), 1 (satisfactory performance) or 2 (perfect performance) for each sub-task of each construct. The scores for subtasks of each construct are then summed and a total percentage score is calculated for each construct. A total performance percentage score is calculated for the JAAM by summing raw scores for each construct, dividing total possible score and multiplying by 100.

Procedure

The tests were administered in a quiet laboratory in isolation. Participants were informed of the general purpose of the experiment, gave informed consent and then completed the drug

questionnaire, Epworth Sleepiness Scale, and Karolinska sleepiness scale (Time 1). Next participants completed the JAAM, followed by Raven's Progressive Matrices (Raven et al. 1998) and the Karolinska Sleepiness scale (Time 2). Participants were debriefed, given drugs education leaflets and granted research credits for their participation, or paid £20 store vouchers if they were not a Psychology student. The research was approved by the Liverpool John Moores University Research Ethics Committee and adhered to the ethical guidelines of the British Psychological Society.

Results

Table 1 shows the background variables for ecstasy-polydrug users and nonusers. Mean age was comparable between the groups, $t(31.44) = 1.23, p > .05$, as were subjective daytime sleepiness measured by the ESS, $t(48) = 0.70, p > .05$ and Karolinska sleepiness scores at the beginning and end of testing, $t(48) = -0.30; 1.13, p > .05$ respectively. Ecstasy-polydrug users did however rate their health as significantly worse than nonusers, $t(48) = -2.15, p < .05$, and also scored significantly lower on Raven's Progressive Matrices, $t(39.45) = -3.10, p < .01$. The ecstasy-polydrug users also drank significantly more units of alcohol per week $t(47) = 2.54, p < .05$.

<<Insert Table 1 About Here>>

The ecstasy-polydrug users reported regular use of cannabis and cocaine in addition to ecstasy. The ecstasy-polydrug users reported moderate use of ecstasy (total lifetime dose 258 tablets), and frequent use of ecstasy (once a month), cannabis (4 times per week), and cocaine (about once per month). Indices of drug use for the ecstasy users are displayed in Table 2.

<<Insert Table 2 About Here>>

For the JAAM task, the score profile of ecstasy users and nonusers is shown in Figure 1. Ecstasy-polydrug users scored lower than nonusers on all subscales with the exception of time-based prospective memory. The scores for JAAM were analysed using MANOVA. There was a significant main effect of ecstasy-polydrug use on JAAM performance indicating that overall ecstasy-polydrug users were impaired $F(8,40) = 2.75, p < .05$ (Partial Eta squared of 0.355, overlap percentage of 62-66%). Univariate analyses revealed that this was due to ecstasy-polydrug users performing significantly worse on the planning subscale $F(1,47) = 12.80, p < .001$ (Partial Eta Squared of 0.214 (overlap percentage of 58%) and selection subscale $F(1,47) = 3.88, p < .05$ (Partial Eta Squared of 0.076; overlap percentage of 54%)). Given the significant between group difference in fluid intelligence, Raven's Progressive Matrices scores were included as a covariate. The main effect of ecstasy polydrug use on JAAM performance remained significant $F(8,39) = 1.79, p < .05$ (one-tailed), Partial Eta Squared 0.268 (overlap percentage of 62%). Although slightly attenuated,

the effects of ecstasy-polydrug use on the planning subscale remained significant $F(1,46) = 7.50$, $p < .01$ (Partial Eta Squared 0.140; Overlap percentage of 54-58%). However, the effects on the selection subscale were reduced to below statistical significance after control for Raven's scores. Homogeneity of regression was achieved with respect to all ANCOVAs, $p > .05$ for the group x covariate interaction.

<<Insert Figure 1 About Here>>

Correlations between measures and drug use: Due to the nature of polydrug use, it is possible that the use of cannabis and cocaine may contribute to the deficits observed in the ecstasy-polydrug group. Correlations were performed between the JAAM measures and indices of drug use. To account for multiple comparisons, a partial Bonferroni correction was applied with all correlations being evaluated at $p < .01$ (Sankoh et al. 1997). Table 3 shows the correlation coefficients. For the JAAM planning subscale, total lifetime use, frequency of use and average dose of ecstasy were significantly correlated with performance, as was frequency of cannabis use, and amount smoked in the last 30 days. For the time-based prospective memory (TBPM) subscale, total lifetime dose, average dose and frequency of use of cocaine were all significantly correlated with TBPM. Contrary to expectations, for the TBPM measure, all correlations were positive, indicating that higher cocaine use was related to higher scores (i.e. better performance) on TBPM.

<<Insert Table 3 about Here>>

Discussion

The present study found that ecstasy-polydrug users were impaired on a virtual-reality task of executive functioning. Correlations between ecstasy use and JAAM planning were significant (with higher ecstasy use associated with poorer performance), and correlations between time-based prospective memory and adaptability and cocaine use were strongest (with higher cocaine use associated with better performance).

The ecstasy polydrug-related difference on JAAM performance provides further support for ecstasy-polydrug related deficits in executive functioning. Contrary to expectations, ecstasy-polydrug users did not perform more poorly on the prioritisation and adaptive thinking subscales (although the lack of predicted differences on specific subscales could reflect the better ecological validity of the JAAM task). Ecstasy-polydrug users performed significantly worse on the planning subscale. Previous research on planning abilities has been equivocal with some studies reporting ecstasy-related deficits and others no deficits. For example, Fox et al. (2001) found that ecstasy users who reported cognitive problems had significantly longer TOL planning times than non-problem users, and heavy users had significantly longer TOL planning times than medium and light users. Similarly Alting von Geusau et al. (2004) found that relative to controls, ecstasy users were impaired on the TOL. However, Morgan (1998) and Fox et al. (2002) reported no group differences on planning ability. In the planning subscale of the JAAM, participants had to write a plan of action based on a list of tasks left for them from the manager. Participants who performed well on this aspect were better able to group the tasks according to whether they related to the meeting, dispatching the mail, or whether they were time-based, then going on to perform the grouped tasks together. Participants also had to arrange the furniture in the meeting room for this subscale, and scored well if all individuals at the meeting would have been able to see the whiteboard, and desks and chairs were arranged appropriately.

Ecstasy-polydrug users were also impaired on the selection subscale requiring them to draw on their knowledge of the task at hand to select appropriate responses. For example participants had

to select the appropriate mail companies for a variety of parcels and letters based on their importance and size. Subsequently they received a memo that a new item was to be added, and that the company postman had failed to collect one bundle of letters. Participants then had to select an alternative mail company. Thus in terms of functional significance, the ecstasy-polydrug related deficits on these subscales suggest that such individuals will have difficulty with logically ordering tasks, completing tasks in a logical order, and selecting appropriate responses from a range of alternatives.

While the ecstasy/polydrug group were clearly impaired on JAAM planning and selection, it is difficult to attribute this deficit solely to ecstasy use given the polydrug nature of the sample. The correlations suggest that other drugs may play a key role. On the JAAM planning subscale, total lifetime dose, frequency of use and average weekly dose of ecstasy, and frequency of cannabis use were significantly correlated with performance. On the TBPM subscale and adaptability subscale of the JAAM task, indices of cocaine use were significantly positively correlated with performance, indicating that higher self-reported cocaine use actually resulted in better performance. Again, this is problematic as it would be expected that higher levels of cocaine use would result in poorer performance. One tentative explanation relates to the effects of heavy cocaine use. Studies in humans (e.g. Bartzokis et al. 2000) and animals (Paine et al. 2003) suggest that impulsivity can be a consequence of as well as a precedent to chronic cocaine use, resulting in delay discounting on psychological tasks (choosing immediate rewards rather than waiting for possible larger rewards). Accordingly the improved performance on the TBPM subscale may reflect a slight increase in impulsivity associated with cocaine use, although further research is needed to support this. In summary, it may be that the effects were a product of polydrug use. Specifically, since all of the cocaine users also used ecstasy, and only 6 of the nonusers had used cannabis, it remains possible that the correlations observed relate to the joint use of the substances. Equally while the present study suggests that there is a relationship between cocaine use and TBPM performance, this has only been demonstrated among ecstasy users. It remains to be seen whether the same pattern of

associations apply among non-ecstasy users.

There were a number of limitations in the present study. The study was quasi-experimental and it is possible that the groups may have differed on some other variable than their ecstasy use. Nonetheless we have attempted to control for some of these differences, namely sleep quality and fluid intelligence. In addition we have had to rely on self-reports of drug use, and it has been noted that these individuals are memory impaired and may not be able to accurately recall amounts of illicit substances consumed. Given the legal status of these drugs, this is the most appropriate way to investigate memory and executive function in ecstasy users, and the majority of published papers in this area rely on self-reports of drug use (e.g. Montgomery et al. 2005, Fox et al. 2001; Rodgers 2000; Heffernan et al. 2001). However, we cannot guarantee the purity of ecstasy tablets taken by our participants or of cannabis and cocaine used, and we had to rely on self-reports of drug use, although it has been reported that analysis of ecstasy tablets from nightclub amnesty bins suggests that tablets approach 100% in purity (Parrott 2004). In addition, *if* the purity of the ecstasy used in the present sample was low, then this raises additional concerns about the magnitude of deficits had the sample used “purer” ecstasy.

The present paper provides further support for executive function deficits in ecstasy polydrug users, and the functional significance of such deficits. In terms of real-world functioning, ecstasy users are impaired on tasks that require logical planning and selection of stimuli from a range of alternatives. Future research should seek to clarify the link between traditional measures of executive function and performance on the JAAM task.

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Table 1

Background scores

	Ecstasy users		Non Ecstasy Users	
	Mean	S.D.	Mean	S.D.
Age (years)	23.22	4.56	21.92	2.27
Raven's Progressive Matrices (maximum 60)	46.87	6.13	51.51	4.45
Epworth Sleep Scale (Maximum 24)	7.39	4.84	6.52	3.99
Self Report Health	3.61	0.78	4.04	0.76
Karolinska Time 1	4.30	1.66	4.44	1.60
Karolinska Time 2	5.26	2.11	4.67	1.61
Average Weekly Alcohol Use	13.57	9.32	7.56	7.24

Table 2

Indices of drug use in ecstasy polydrug users

	Ecstasy-polydrug Users		
	Mean	SD	N
Total Lifetime Dose			
Ecstasy (tablets)	257.67	428.82	23
Cannabis (joints)	2910.71	5662.44	21
Cocaine (grams)	126.18	261.20	11
Frequency (times/week)			
Ecstasy	0.28	0.47	19
Cannabis	4.02	5.46	20
Cocaine	0.18	0.20	10
Use in last 30 days			
Ecstasy (tablets)	1.60	2.89	20
Cannabis (joints)	11.64	23.62	22
Cocaine (grams)	0.34	0.65	17
Average dose			
Ecstasy (tablets)	1.81	2.77	19
Cannabis (joints)	3.60	4.20	16
Cocaine (grams)	0.62	0.95	9

Table 3 Correlations between performance and indices of drug use

	JPlan	JPri	JSel	Jcre	Jada	Jabpm	Jebpm	Jtbpm
Total								
Ecstasy	-.458*	-.044	-.187	-.088	-.034	.105	-.101	.264
Cannabis	-.337	.021	-.274	.017	.071	.233	-.085	.293
Cocaine	-.335	.023	-.229	.056	.233	.182	-.120	.472*
Frequency								
Ecstasy	-.602*	-.029	-.223	-.155	-.006	.031	-.112	.255
Cannabis	-.425*	-.014	-.190	-.063	.108	.081	.027	.268
Cocaine	-.370	-.183	-.296	-.095	.311	.049	-.064	.520*
Average								
Ecstasy	-.499*	-.008	-.163	-.132	-.018	.158	-.138	.212
Cannabis	-.381	.002	-.179	-.077	.108	.156	-.081	.287
Cocaine	-.349	.029	-.138	.018	.326	.072	-.126	.500*
Current								
Ecstasy	-.331	.139	-.080	-.176	.128	-.120	-.040	.295
Cannabis	-.388*	.151	.004	.054	.118	.062	-.186	.317
Cocaine	-.308	.000	-.182	-.071	.156	-.167	.011	.320

*Correlation significant at $p < .01$

Figure 1
JAAM scores profile

