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ORIGINAL INVESTIGATION

Prospective memory impairment in “ecstasy” (MDMA) users

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Abstract
Rationale Considerable research indicates that “ecstasy” users perceive their memory for future intentions (prospective memory) to be impaired. However, only one empirical study to date has directly tested how this capacity is affected by ecstasy use, and this study provided relatively limited information regarding the extent, scope, or implications of problems experienced.
Objectives The present study assessed prospective performance on a laboratory measure of prospective memory that closely represents the types of prospective memory tasks that actually occur in everyday life and provides an opportunity to investigate the different sorts of prospective memory failures that occur (“Virtual Week”).
Method Ecstasy user group (27 current users and 34 nonusers) was between participants, and prospective memory task (regular, irregular, time-check) was within participants. A measure sensitive to specific aspects of psychopathology was also administered.
Results Ecstasy users were significantly impaired on Virtual Week, and these deficits were of a comparable magnitude irrespective of the specific prospective memory task demands. The pattern of results was unchanged after controlling for marijuana use, level of psychopathology, and sleep quality. Further, prospective memory was shown to be significantly impaired for both relatively infrequent and relatively frequent ecstasy users, although for the latter group the magnitude of this deficit was greater.
Conclusions Prospective memory performance is sensitive to regular and even moderate ecstasy use. Importantly, ecstasy users experience generalized difficulties with prospective memory, suggesting that these deficits are likely to have important implications for day-to-day functioning.

Keywords 3,4-Methylenedioxymethamphetamine · Cognitive performance · Prospective memory impairment · Memory for intentions · Substance abuse · MDMA · Ecstasy

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Introduction

There is considerable evidence that 3,4-methylenedioxymethamphetamine (MDMA; a principal ingredient in the popular recreational drug “ecstasy”) is a serotonergic neurotoxin that leads to degeneration of serotonergic axon terminals in animals, including nonhuman primates (Buaumann et al. 2007; Scheffel et al. 1998). The neurotoxic effects of MDMA appear to be long-lasting, with serotonergic depletion in one study shown 7 years after initial administration of the drug (Hatzidimitriou et al. 1999). It has been argued that these neurobiological changes underpin the well-documented neurocognitive deficits associated with MDMA use in humans (Morgan 2000).

Thus, numerous studies have documented that, relative to controls, ecstasy users perform more poorly on a range of measures sensitive to neuropsychological function (Montgomery et al. 2005; Wareing et al. 2004; Yip and Lee 2005; Verbaten 2003). However, deficits in retrospective memory are amongst the most consistently reported findings (Bolla et al. 1998; Morgan 1999, 2000). Indeed, in a recent meta-analytic review, although there was evidence for generalized neurocognitive impairment, with deficits in attention, psychomotor speed, and executive functioning consistently observed, the cognitive domain “verbal learning and memory” was subject to disproportionate impairment (Kalechstein et al. 2007).

Given the evidence for retrospective memory impairment in relation to ecstasy use, deficits in *prospective* memory may also be anticipated. Prospective memory (PM) refers to memory for future intentions (Maylor 1996), such as remembering to take medication and turn off appliances, which is crucial for maintaining health and safety and necessary for independent living. Thus, PM failures may be anticipated in the ecstasy user population because prospective remembering also involves a retrospective component (Cohen et al. 2001; McDaniel and Einstein 1992), that is, successfully performing a PM task requires not only recall of something that is to be done in the future but also retrieval of what it *is* that needs to be done. This latter component clearly implicates retrospective memory. Additionally, PM is considered to impose considerable demands on executive functioning and, in particular, self-initiated retrieval (Craik 1986). As executive dysfunction is also a common feature of ecstasy use (Kalechstein et al. 2007; Quednow et al. 2007), PM deficits may therefore also be expected to arise as a consequence of deficits in this capacity.

However, few studies to date have investigated how PM is affected by ecstasy use, and all but one of these studies has used self-report methodology to do so. These studies have invariably reported that ecstasy users do perceive significant deficits in their PM capacity, with users of ecstasy reporting significantly more errors in prospective remembering relative to non-ecstasy users (Heffernan et al. 2001a, b; Rodgers et al. 2001, 2003).

However, self-perceived PM deficits in the context of ecstasy use may not necessarily reflect objective change in this capacity given that in other populations’ metamemory, one’s knowledge of one’s memory performance, is relatively inaccurate (Burdick et al. 2005; Cook and Marsiske 2006; Grut et al. 1993; Vermuelen et al. 1993). Indeed, of particular relevance to ecstasy users are studies which have shown perceived memory deficits to be associated with physical and psychological stressors (Pearman and Storandt 2005; Roth et al. 2005). Thus, as ecstasy use is associated with both increased psychopathology and sleep disruption (see Montoya et al. 2002), any perceived memory disturbance might not be attributable to real deficits in this capacity but to increased levels of either or both types of stressor.

In the one study to date that has directly investigated how PM is affected by ecstasy use, Zakzanis et al. (2003) tested PM by asking participants to (1) remember to ask for a belonging at the end of the test session, (2) ask a specific question when an alarm sounded, and (3) deliver a message at a specific point during testing. The results indicated that ecstasy users (n=15) were significantly less likely than nonusers (n=17) to remember to execute these delayed intentions. Thus, although the results from these studies are consistent with the possibility that ecstasy users may experience increased difficulty with PM, they are limited by solely relying on a self-report measure of this construct (Heffernan et al. 2001a, b; Rodgers et al. 2001, 2003), or use of a PM task where performance cannot be discriminated beyond correct or incorrect on a limited number of one-off trials (Zakzanis et al. 2003). These studies therefore provide relatively limited information regarding the extent, scope, or implications of problems experienced by ecstasy users. They also do not identify or investigate the conditions under which PM failures are most likely to occur.

Although studies of PM performance in ecstasy users and other clinical groups are very limited, there is considerable research focused on aging and PM (Kliegel et al. in press). While age deficits are generally found on controlled laboratory measures of PM, exceptions have been noted (for a review, see Henry et al. 2004), and in the influential multiprocess model of PM, the finding of variations in age-related differences has been attributed to variation in the processes tapped by different PM tasks (McDaniel and Einstein 2000). Specifically, it has been suggested that PM tasks can be carried out using either automatic monitoring, where cues “pop into mind,” or instead by strategic, effortful monitoring, where cues are actively searched for during the on-going task. In the context of this model, age-related deficits are therefore only anticipated for PM tasks that fall into the latter category. Additionally, other specific distinctions between types of PM task have also been identified, which are considered to differentially load other aspects of cognitive functioning.

Given the noted particular importance ascribed to retrospective memory impairment in the ecstasy user population (Kalechstein et al. 2007), the distinction between *regular* and *irregular* PM tasks is of particular interest in the present study, as the former type of task imposes fewer demands on retrospective memory, (i.e., remembering what it is that needs to be done), and thus permits an assessment of whether difficulties with PM are restricted to the retrospective memory component, or whether these difficulties also extend to the PM component (i.e., the implementation of delayed intentions; see Rendell et al. 2007). Additionally, the contrast between *time*- and *event*-based prospective remembering is of interest. Whereas time-based PM tasks require the participant to perform a specified behavior after the passage of a given amount of time, for event-based PM tasks, the required behavior is prompted by an external cue. Thus, of the two types of PM, time-based is believed to be the most reliant upon internal control mechanisms because, assuming no external mnemonic aid is employed, it is more dependent on self-initiated mental activities, such as active time monitoring. Assessment of different subtypes of PM is therefore important to delineate the mechanisms underpinning any PM failures in the ecstasy user population, as well as the degree to which any observed impairment generalizes across different tasks.

The aim of the present study was to conduct a more comprehensive assessment of how PM is affected by ecstasy (MDMA) use. This will be achieved using "Virtual Week," a laboratory measure of PM that closely represents the types of PM tasks that actually occur in everyday life, and provides an opportunity to investigate the different sorts of PM failures that occur (see Rendell and Craik 2000; Rendell et al. 2007). Thus, using Virtual Week, it will be possible to quantify the nature and magnitude of any PM deficits associated with ecstasy use. It will also be tested whether level of ecstasy use, perceived sleep quality, and psychopathology mediate the level of PM impairment observed. Further, given that a high proportion of ecstasy users also take marijuana and use of this drug has been shown to negatively impact on memory function (see Dafters et al. 2004; Roiser et al. 2007), level of marijuana use will also be entered as a statistical covariate to test whether marijuana use independently contributes to any PM impairment observed in the ecstasy user population.

Materials and methods

Design

A mixed design with ecstasy status (user, nonuser) between participants and PM task (regular, irregular, time-check) within participants was used. These were the task distinctions focused on in previous studies involving Virtual Week (Henry et al. 2007; Rendell and Craik 2000; Rendell et al. 2007). The substantial within-group differences according to these task types shown in these studies is not of interest in the present study. Instead, the primary interest is in whether there is an interaction between ecstasy status and type of task that parallels the age interactions found by Rendell and Craik (2000) with minimal differences on regular and substantial age-related deficits on irregular and time-check tasks. Therefore, within-group differences will not be reported unless there is significant interaction with ecstasy status. The dependent variable was the proportion of correct responses on each of the PM tasks. Measures of background variables such as age, verbal intelligence, and cognitive speed were recorded to characterize participants. Other background variables, such as marijuana use, level of sleep disturbance, and psychopathology were additionally measured for subsequent use as covariates.

Participants

Participants were recruited via information letters posted on community notice boards at several Melbourne universities and via contact with promoters at local nightclubs. Twenty-seven participants (52% men) who reported taking ecstasy on a regular basis were recruited for the ecstasy user group. A nonuser group of 34 participants (44% men) who had never tried ecstasy were also recruited to provide a control group. In the ecstasy user group, 13 were relatively infrequent users (defined as taking ecstasy no more than once a month), and 14 were relatively frequent users (defined as taking ecstasy at least once a fortnight). To ensure participants' responses were not influenced by acute effects of ecstasy, both users and nonusers agreed to abstain from taking ecstasy (or any other drugs) for at least 48 h before testing.

Participants' background details are shown in Table 1. It can be seen that, in addition to being matched for gender, the ecstasy user and nonuser groups did not differ significantly with regard to age, years of education, vocabulary as indexed by the Mill Hill Vocabulary Test (Raven et al. 1988), or self-rated health (all $p>0.05$). However, ecstasy users were significantly impaired relative to nonusers on Digit Symbol (Wechsler 1981), a cognitive task sensitive to attentiveness, persistence, and cognitive processing speed ($p=0.026$) and also reported significantly worse sleep over the last month ($p<0.001$). Ecstasy users were also significantly more likely to be using marijuana ($p=0.027$) and reported significantly higher levels of psychopathology as indexed by an abbreviated measure of the Symptom Checklist-90 Revised ($p<0.001$).

Measures

Psychopathology

Four subscales of the Symptom Checklist-90 Revised (SCL-90-R; Derogatis 1994) were used to index psychopathology and, specifically, the sub-scales that measure obsessive–compulsive characteristics, depression, anxiety, and phobic anxiety. For each item, participants are asked to

Table 1 Background characteristics of the ecstasy user and nonuser groups

Characteristic	Ecstasy user group		Nonuser group		Inferential statistics		
	M	SD	*M*	SD	*t*	*df*	p
Age	21.3	1.96	20.6	1.40	1.42	59	0.160
Years of education	15.4	1.05	15.2	0.86	0.61	59	0.544
Wechsler Adult Intelligence Scale (WAIS) digit symbol[a]	62.3	11.85	68.9	10.77	2.28	59	0.026
Mill Hill Vocabulary Test[a]	13.1	2.35	13.6	2.18	0.88	59	0.88
Self-rated health[b]	2.4	0.84	2.4	0.89	0.86	59	0.39
Self-rated sleep[b]	3.3	1.07	2.4	0.92	3.84	59	<0.001
Marijuana use rating[c]	3.2	1.48	2.4	1.50	2.27	59	0.027
SCL-90-R[d]	45.4	21.94	25.1	17.36	4.03	59	<0.001

[a] Higher score indicates better performance.
[b] Participants were asked to self-rate sleep and health "over the last month". For both of these measures, participants were asked to provide self-rating on a five-point Likert scale where 1=excellent; 2=very good; 3=good; 4=not very good; 5=poor.
[c] Participants were asked to self-rate frequency of marijuana use, as indexed by a six-point rating scale ranging from 1 (never) to 6 (at least once a week).
[d] The abbreviated version of the SCL-90-R that was used consisted of the obsessive–compulsive, depression, anxiety, and phobic anxiety subscales.

indicate on a 5-point Likert scale ranging from "0" (not at all) to "4" (extremely) the degree to which each symptom applies to them. A higher total score collapsed across these four subscales denotes a higher level of psychopathology. The reliability of this measure has been demonstrated (Derogatis 1994).

Prospective memory

Virtual Week was used as the laboratory measure of PM (see Rendell and Craik 2000 for full details of this task). Virtual Week is a board game in which participants move around the board with the roll of a dice. The times of day people are typically awake are marked on the board, with each circuit of the board representing a day. As participants move around the board, they are required to make choices about daily activities and remember to carry out lifelike activities (PM tasks). Each "day" of Virtual Week includes ten PM tasks (four regular, four irregular, and two time-check tasks) and in this study, participants completed five virtual days, permitting the nature of any PM impairment to be precisely identified. The four regular PM tasks simulate the kinds of regular tasks that occur as one undertakes normal duties, two of which are time-based (i.e., triggered by passing a particular time on the board), and two of which are event-based (i.e., triggered by some information shown on an event card). The four irregular PM tasks simulate the kinds of *occasional* tasks which occur in everyday life; again, two of these tasks are time-based, and two are event-based. Finally, the two time-check tasks require the participant to "break set" from the board game activity and monitor real time on the stop-clock that was displayed prominently and indicate when a specified period of time has passed.

Answers on Virtual Week were scored in the following four categories: correct scores indicated the target item was remembered at the correct time (correct time for the time-check task was within 10 s of the target time, and for the other tasks, it was before next roll of the dice); late items were remembered after the correct time criterion but before the end of the virtual day; participants were marked wrong when they recalled the details incorrectly or recalled the correct item at the incorrect time; miss indicated the participant did not remember the target item at any time. The version as set out in Rendell and Craik (2000) was used, except the game was reduced from seven virtual days to five virtual days.

Procedure

Before obtaining written informed consent, all participants were assured confidentiality and informed about the general purpose of the study and the types of measures involved in the study. Each participant was then tested individually in a single session lasting approximately 2 h. Participants completed the brief demographic questionnaire, followed by each of the baseline cognitive measures, Virtual Week, and the self-report measure of psychopathology. After all of the measures were administered, participants were debriefed. This study was approved by the Human Research Ethics Committee of the Australian Catholic University and was in accordance with the ethics standards in the Helsinki Declaration of 1975.

Results

For Virtual Week, the proportion of correct PM responses were analyzed with a 2×3 mixed analysis of variance

(ANOVA) with the between-subjects variable of ecstasy *status* (user, nonuser) and the within-subjects variable of *prospective memory task* (regular, irregular, time-check). The mean proportion of correct responses for the two groups on each of the PM tasks are reported in Table 2. Ecstasy status and PM task did not significantly interact, $F(2, 118)=1.46$, MSE=0.03, $p=0.237$, $\eta^2=0.02$, but the main effect of ecstasy status was significant and indicated that the ecstasy user group ($M=0.56$, SD=0.21) had a significantly smaller proportion of correct responses than the nonuser group ($M=0.76$, SD=0.18); $F(1, 59)=41.38$, MSE=0.05, $p<0.001$, $\eta^2=0.412$. Further analysis of another task distinction, event- versus time-based, also revealed no differential effect of ecstasy use on these different types of PM task (all $p>0.05$). Thus, ecstasy users present with an undifferentiated profile of impairment across the different types of PM task.

Table 2 also reports the proportion of correct responses and different types of error responses made for the two groups (ecstasy user, nonuser). It can be seen that for both groups, the majority of errors on the regular and irregular tasks are missed responses. For the time-check task however, while for the ecstasy user (but not the nonuser) group, a substantial proportion of errors are attributable to missed responses, the predominant source of error for both groups on the time-check task is late responses. Separate 2×3 mixed ANOVAs of late and missed responses with the between-subjects variable of ecstasy *status* (user, nonuser) and the within-subjects variable of PM task (regular, irregular, time-check) revealed similar pattern to analysis of correct responses, significant main effect for ecstasy status [$F(1, 59)=4.97$, $p=0.030$ and 40.25, $p<0.001$, for late and missed responses, respectively] but no evidence of any interaction effects (both $p>0.05$). There were too few error responses made on the regular and time-check tasks to warrant analysis of the third type of error responses, wrong responses.

Covariates of prospective memory deficits in ecstasy users

Correlations between proportion correct on Virtual Week with marijuana use, sleep, and psychopathology ratings were not significant with exception of sleep which was significantly negatively correlated for the user group only ($r=-0.50$, $p=0.009$).

While the use of analysis of covariance (ANCOVA) in nonrandomized designs has been subject to some debate, it has been suggested that this methodology may be useful (despite nonrandom assignment) in the context of exploration of a dataset to understand patterns of shared variance (Huitema 1980; Miller and Chapman 2001). Thus, a series of ANCOVAs were conducted on the total proportion correct on all 50 PM tasks, with the between-subjects variable of ecstasy status and one of the following variables entered as covariate: marijuana use rating, sleep rating, and psychopathology rating (as indexed by the SCL-90-R). For all three analyses, the main effects of group remained significant (all $p<0.001$).

Prospective memory deficits in frequent versus infrequent ecstasy users

As noted previously, 13 users of ecstasy were relatively infrequent users, while 14 were relatively frequent users. To investigate the potential role of ecstasy use, data were reanalyzed using a 3×3 mixed ANOVA with between-subjects variable ecstasy use (nonuser, infrequent user, frequent user) and the within-subjects variable of PM task (regular, irregular, time-check). The mean proportion of correct responses for the three groups on each of the PM tasks are shown in Fig. 1.

The analysis revealed no significant interaction effect, $F(4, 116)=0.93$, $p=0.452$, $\eta^2=0.03$; however, the main effect of ecstasy use was significant, $F(2, 58)=26.42$, $p<0.001$, $\eta^2=0.48$. Tukey post hoc analysis revealed that for PM performance across all three PM tasks, the frequent users ($M=0.50$, SD=0.19) were significantly worse ($p=0.026$) than the infrequent users ($M=0.62$, SD=0.22) who were in turn, significantly worse ($p=0.001$) than the nonusers ($M=0.76$, SD=0.18).

Table 2 Mean proportions of correct responses and different types of error on Virtual Week as a function of ecstasy user status and task type

Measure	Regular task				Irregular task				Time-check task			
	User		Nonuser		User		Nonuser		User		Nonuser	
	M	SD	*M*	SD	*M*	SD	*M*	SD	*M*	SD	*M*	SD
Correct	0.71	0.15	0.85	0.11	0.44	0.14	0.68	0.19	0.53	0.25	0.76	0.20
Late	0.09	0.06	0.06	0.04	0.02	0.04	0.02	0.04	0.28	0.18	0.20	0.16
Wrong	0.05	0.07	0.03	0.05	0.17	0.11	0.11	0.07	<0.01	0.02	0.01	0.02
Missed	0.17	0.11	0.06	0.07	0.36	0.16	0.19	0.16	0.19	0.19	0.04	0.09

Discussion

The present results indicate that ecstasy use is associated with significantly increased difficulties with PM, that the magnitude of this deficit does not vary as a function of task type, and that these deficits are not simply secondary to the effects of marijuana use, increased psychopathology, or disrupted sleep. Further, PM impairment was observed in an ecstasy group that may be regarded as relatively infrequent users of the drug. However, consistent with previous empirical research in which it has been shown that there are dose–response relationships between the extent of exposure to ecstasy and the level of cognitive impairment (Morgan 2000), PM deficits were greatest for relatively frequent users of ecstasy.

The present results are therefore consistent with prior research that has assessed PM function in relation to this population using self-report methodology. Importantly, these self-report studies provided evidence for generalized PM deficits, with perceived deficits extending across short-term habitual, long term habitual, and internally cued PM (Heffernan et al. 2001a, b; Rodgers et al. 2001, 2003). However, as noted, the only prior study to directly measure PM function did not assess performance beyond correct or incorrect on a limited number of one-off trials (Zakzanis et al. 2003). The present results are therefore important, providing evidence of consistent behavioral deficits that parallel the impairment perceived by ecstasy users and suggest that ecstasy use has a relatively generalized negative effect on PM function.

As noted previously, prospective remembering is considered to depend upon both executive functioning and retrospective memory (Cohen et al. 2001; Craik 1986; McDaniel and Einstein 1992), both of which are negatively impacted by ecstasy use (Kalechstein et al. 2007). Indeed, recent meta-analytic reviews have shown that ecstasy use is associated with relatively generalized neurocognitive impairment (Kalechstein et al. 2007; Verbaten 2003). Qualitative observations in the present study suggest that retrospective memory failures are not sufficient to account for the magnitude of the PM impairment observed. Specifically, the regular tasks in Virtual Week impose only minimal demands on retrospective memory and yet were significantly impaired. Further, for PM failures to be attributable to difficulties with retrospective memory, this would predict a substantial proportion of errors being recorded as wrong content (i.e., remembering that *something* should be done, but forgetting what it was), but in the present study the majority of errors were misses (i.e., failures to respond) or late responses. Nevertheless, future research is needed to directly test the degree of overlap between retrospective and PM failures in the ecstasy user population. Further, the present study did not permit any assessment to be made of the potential role of executive dysfunction as a determinant of PM failures in the context of ecstasy use. Thus, further research is needed to directly assess whether the deficits in prospective remembering associated with ecstasy use are simply attributable to more generalized impairment in these other aspects of cognition.

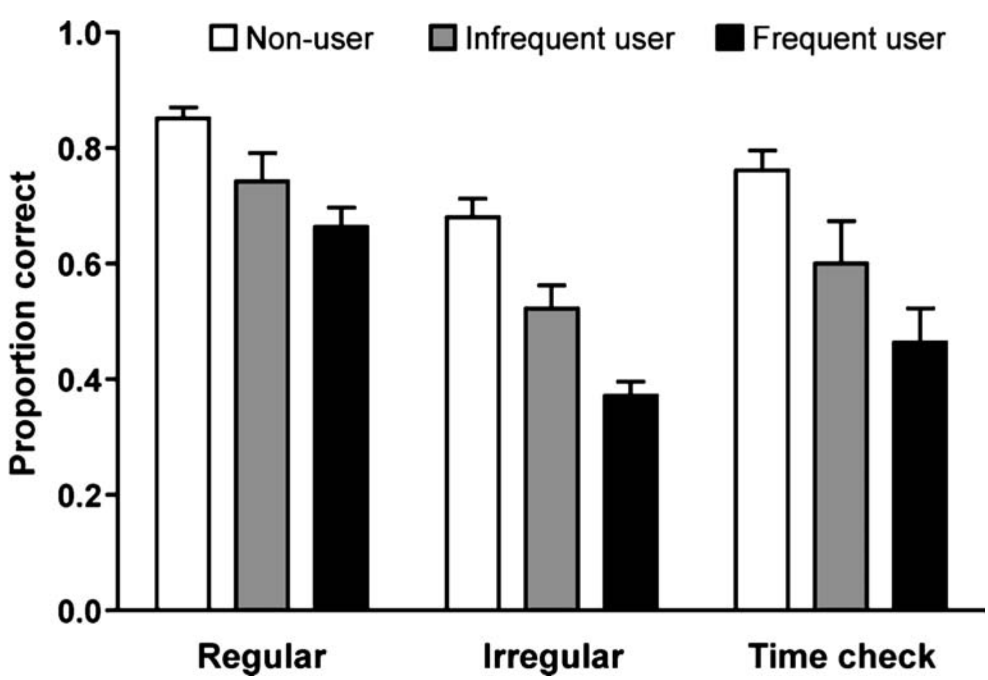

Fig. 1 Mean proportion of correct responses by ecstasy user groups (*non*, *infrequent*, *frequent*) on the three types of prospective memory task. *Bar* represents the standard error

Study limitations and conclusions

There were several methodological limitations to the current study. In particular, standard laboratory tests were not performed to confirm the status of the ecstasy user and nonuser groups. Further, although there were no a priori reasons for believing that participants provided false information related to their history of substance usage, even with accurate self-reporting, little quality control exists for street drugs, and thus the dose or purity of ecstasy taken by participants in the user group is unclear. Nevertheless, it is suggested that the assignment of participants to “frequent” and “infrequent” users of ecstasy is a valid distinction given that, as noted, although deficits in PM were observed for both groups, the level of impairment associated with the former group was significantly greater. Further, the results from the present study showing generalized PM impairment in the context of ecstasy use is consistent with the results from studies involving anonymous self-reporting of PM failures (Heffernan et al. 2001a, b; Rodgers et al. 2001, 2003). Nevertheless, in future research it would be helpful to have more detailed information relating to past ecstasy and other drug use, including usual dose, frequency, duration, and time since last use to more precisely quantify the relationship, and specifically potential mediators of the relationship, between ecstasy use and PM impairment.

In summary, despite the methodological caveats noted, the present results provide the first empirical evidence of generalized PM impairment in both relatively frequent and relatively infrequent users of ecstasy. The absence of an interaction between ecstasy status and PM task provides evidence for a pervasive PM deficit in the context of ecstasy use. Further research is needed to delineate the mechanisms underpinning this impairment.

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