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Auditory verbal learning in drug-free Ecstasy polydrug users

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Drug-free Ecstasy polydrug users have shown impairment on tasks of verbal working memory and memory span. Current research aims to investigate how these deficits may affect the learning of verbal material by administration of the Auditory Verbal Learning Task (AVLT) (Rey, 1964). The task provides a learning curve by assessing immediate memory span over multiple trials. Learning strategies are further analysed by tendencies to confabulate as well as demonstrate either proactive or retroactive interference elicited by a novel 'distractor' list. Three groups completed the task: two groups of 14 Ecstasy users (short- and long-term) and one group of 14 polydrug controls. Compared with controls both Ecstasy groups recalled significantly fewer words and made more confabulation errors on the initial three recall trials as well as a delayed recall trial. Long-term users demonstrated increased confabulation on the initial trials and the novel 'distractor' trial, compared with short-term users. Only following repeated presentations were both short- and long-term users shown to perform at control levels. As such, deficits in verbal learning may be more related to storage and/or retrieval problems than problems associated with capacity per se. No interference errors were demonstrated by either of the Ecstasy groups. However, a high level of intrusion errors may indicate selective working memory problems associated with longer-term use of the drug.

KEY WORDS — Ecstasy; AVLT; confabulation; immediate recall; delayed recall

INTRODUCTION

Selective deficits in the cognitive functioning of drug-free recreational Ecstasy polydrug users have been shown (Parrott, 2000). Impairments have been demonstrated in immediate and delayed verbal recall (Parrott *et al.*, 1998; Bolla *et al.*, 1998; Morgan, 1999) and in verbal working memory (Wareing *et al.*, 2000; Fox *et al.*, 2000). Such decrements may reflect the slowed learning of verbal material shown in Ecstasy users (Reneman *et al.*, 2000) and Ecstasy/cannabis users (Gouzoulis-Mayfrank *et al.*, 2000).

Our objectives were to corroborate these findings using the Auditory Verbal Learning Task (AVLT) and to study in greater depth the nature of learning impairment. For example, would reduced performance in Ecstasy users be due to deficits in short-term verbal memory span or working memory processes, or both? The AVLT comprises a repetitive learning paradigm across multiple trials. Whilst performance scores on each trial represented decrements in short-term verbal memory span (immediate or delayed), error analysis and the inclusion of a second 'intrusion' list helped clarify the nature of various working memory control processes, including retroactive and proactive interference and confabulation. It was considered that a more inclusive assessment of learning strategies might help expound the nature of selective cognitive impairment in Ecstasy polydrug users.

We also aimed to assess potential differences in long and short-term Ecstasy polydrug users, compared with a group of polydrug controls who had either never consumed Ecstasy or only used the drug on one or two occasions. As concomitant cannabis use has been deemed a possible confounder in previous Ecstasy research, because of inadequacies in control procedures (Croft *et al.*, 2001), the current study also aimed to use quantity of cannabis consumed as a covariate.

The experimental hypothesis is that Ecstasy polydrug users will demonstrate reduced learning on the AVLT task, which is due either to deficits in short-term verbal memory or in working memory, or both.

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METHOD

Participants

Participants were recruited through advertisements placed in London-based magazines or through the 'snowball technique' (Solowij *et al.*, 1992). Participants were regular Ecstasy users who had consumed the drug either for 5 years or less or for 8 years or more. Data on drug use were obtained by self-report. Participants were administered a questionnaire during an informal interview where they were encouraged to think as clearly as possible about their pattern and quantity of drug consumption over various time periods. Participants were requested to remain free of Ecstasy and other illicit drugs for at least 2 weeks and cannabis for at least 1 day prior to testing.

Participants were asked whether they had a history of psychiatric or neurological illness or alcohol dependence. A positive response to this question was an exclusion criterion. All participants gave written informed consent, and the University of East London's Ethics Committee approved the study. (See Table 1 for demographic and drug use data.)

The auditory verbal learning task (Rey, 1964)

Immediate recall. This comprised five presentations of a 15 word recall list (list A) at a speed of 1 word per second (Trials 1 to 5). Participants were requested to recall as many of the words as possible immediately following each presentation. All responses were taped for subsequent scoring. No time limit was given, and participants were prompted to recall all of the words (in any order) on each occasion, regardless of whether they had recalled them on previous trials. After Trial 5, a new list of 15 words (list B) was presented and recall was requested immediately following presentation. Following the list B trial participants again recalled list A, but without prior presentation (Trial 6).

Delayed recall. Participants recalled list A following a 0.5 h interval (Trial 7). Memory scores were calculated for each individual trial (out of 15). 'Error confabulations' (words unrelated to those in the stimulus list) and 'errors associations' (words semantically or phonetically linked to those in the stimulus list) were also recorded, along with intrusion errors from list A to B and vice versa.

Data analysis

Analysis of variance (ANOVA) was performed on the AVLT data and the Duncan's range was used for post hoc analysis. A χ^2 'goodness of fit' test was used to analyse group variations on the initial five trials (immediate recall). No inferential analyses were performed on error data from either the list B trials or the delayed recall trials, as χ^2 assumptions were violated.

Associations between patterns of drug use and verbal learning were analysed using Pearson's product moment coefficient. The drugs used in the correlational analysis were Ecstasy and those drugs that varied significantly between the long-term Ecstasy users and the controls. Analysis of covariance (ANCOVA) was also conducted in order to control for the consumption of such drugs.

A series of Mann-Whitney U comparisons were performed for drug consumption. One-way ANOVA was performed for the age and IQ variables, and a χ^2 test was applied to gender data. A two-way ANOVA was subsequently performed using gender as a second independent variable in order to account for group variation.

RESULTS

Participant data

Table 1 shows the demographic data of the participants and data on drug use. No significant group differences were shown for age and intelligence. However, a χ^2 test revealed significantly different gender ratios within the polydrug and long-term user groups. Short-term users and controls had consumed similar quantities of all illicit and legal drugs (with the exception of Ecstasy). Long-term users had consumed significantly greater amounts of cannabis, cocaine, LSD and psilocybin mushrooms than the controls. With the exception of Ecstasy, the only drugs that were consumed in significantly different amounts between long- and short-term users were cannabis and LSD: long-term users had consumed greater quantities of both.

Task data

As Figure 1 shows, both Ecstasy groups recalled significantly fewer words than the controls on Trial 1 ($F_{(2,42)} = 17.6$, $p < 0.001$, Trial 2 ($F_{(2,42)} = 17.1$, $p < 0.001$, Trial 3 ($F_{(2,42)} = 7.4$, $p = 0.002$) and Trial 7 (delayed recall) ($F_{(2,42)} = 3.8$, $p = 0.032$). Long-term users also recalled significantly fewer words than the short-term users on Trial 2. No group differences were shown on Trials 4, 5, 6 or on list B. A significant

Table 1. Group demographic and drug use data (means and SDs shown)

	Polydrug controls (14)	Short-term Ecstasy group (14)	Long-term Ecstasy group (14)	p	Kruskall-Wallace analysis		
					C/ST	C/LT	ST/LT
Age (years)	29.1 ± 10.9	26.4 ± 5.9	30.7 ± 4.1	0.31			
Gender	4M/10F	7M/7F	11M/3F	0.03			
Pre-morbid verbal IQ (NART)	113.6 ± 5.2	114.1 ± 6.5	114.1 ± 3.8	0.90			
Pattern of Ecstasy use:							
No. of tablets taken	0.6 ± 0.9	223.9 ± 387.3	811.5 ± 981.8	< 0.001			
Last taken (months)	—	16.6 ± 27.7	4.1 ± 5.1	0.11			
Duration of use (years)	—	3.9 ± 1.8	10.9 ± 0.8	< 0.001			
No. of tablets usually taken	—	2.5 ± 1.9	2.1 ± 1.3	0.57			
Largest no. of tablets ever taken	—	5.3 ± 3.5	5.3 ± 3.6	0.98			
Other drug use:							
Cannabis	447.3 (629.2)	1617.3 (2898.4)	10306.8 (22119.5)	0.004		*	*
Amphetamine	360.9 (1160.2)	127.1 (214.6)	157.5 (222.3)	n.s.			
Cocaine	45.8 (132.5)	123.1 (244.5)	160.0 (254.5)	0.02		*	
LSD	30.6 (105.5)	8.9 (11.1)	75.4 (133.1)	0.001		*	*
Barbiturates	0 (0)	0 (0)	45.0 (155.6)	n.s.			
Opiates	11.4 (42.8)	1.1 (2.2)	124.2 (313.1)	n.s.			
Psilocybin mushrooms	0.8 (2.7)	14.4 (39.8)	34.4 (83.2)	0.002		*	
Solvents	14.3 (53.5)	0 (0)	262.4 (975.0)	n.s.			
Nicotine	9.6 (11.2)	13.1 (13.5)	8.8 (8.3)	n.s.			
Alcohol	10.6 (9.1)	17.9 (22.1)	13.1 (9.9)	n.s.			

*, Significant group differences; C, controls; ST, short-term Ecstasy group; LT, long-term Ecstasy group.

polynomial linear function was shown for Trials 1, 2, 3, list B and Trial 7 (delayed recall).

χ^2 analysis for combined errors on the first five trials (immediate recall) revealed that long-term users made a significantly greater number of errors than the controls ($\chi^2 = 20.1$, $p < 0.001$). Short-term Ecstasy users made fewer combined errors than the long-term users but more than the controls. Although no analysis was performed on the combined errors from list B or the delayed recall trial, Table 2 shows that long-term users made more intrusion and association errors than both short-term users and controls on List B. Short-term users, however, made a greater number of intrusion errors on the delayed recall trial than the other groups.

Gender

Gender was used as a second independent variable after drug group in order to account for the fact that there was a significantly greater number of males in the long-term user group and significantly fewer males in the polydrug control group. The only trials that were sensitive to gender differences were Trials 4 and 5, where females scored significantly higher. These trials were not sensitive to differences between Ecstasy users and controls, and there were no significant interactions.

Patterns of Ecstasy use and verbal learning

Total lifetime consumption of Ecstasy was significantly negatively correlated with memory scores on the first three trials of the AVLT ($p = 0.002$, 0.024; and 0.02, respectively). Lifetime consumption of ecstasy was not correlated with delayed recall. Delayed recall was negatively associated with both the usual and largest number of Ecstasy tablets consumed on any one occasion ($p = 0.016$ and 0.006, respectively). A positive association between delayed recall and the last time Ecstasy had been consumed also approached significance ($p = 0.059$). Memory score on Trial 2 was also associated with lifetime consumption of cannabis ($p = 0.032$) and mushrooms ($p = 0.02$).

Analysis of covariance

When cannabis, cocaine, LSD and mushroom use were treated as covariates, group differences remained significant on Trials 1, 2 ($p < 0.001$ for both) and 3 ($p = 0.007$), as well as on the delayed recall task ($p = 0.023$).

DISCUSSION

Both the Ecstasy user groups recalled significantly fewer words on the initial stages of the task (Trials 1, 2 and 3) and the delayed recall stage

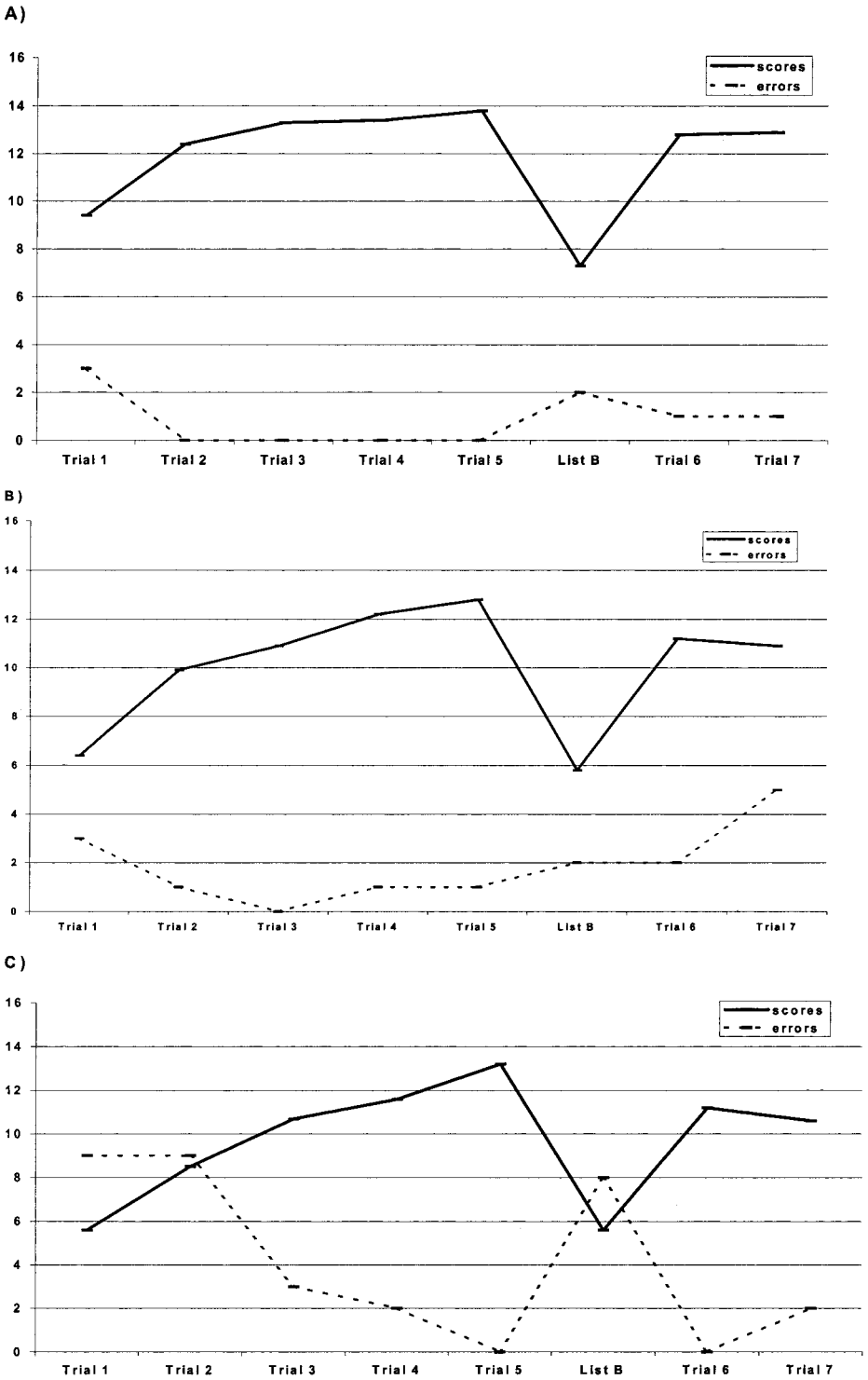

Figure 1. AVLT scores and combined errors for each trial in A) polydrug controls, B) short-term Ecstasy users and C) long-term Ecstasy users. All AVLT scores are out of 15

Table 2. No. of intrusion and association errors across trials

	Polydrug control group	Short-term Ecstasy users	Long-term Ecstasy users
Intrusion errors			
List A, Trial 1	1	3	8
Trial 2	0	1	8
Trial 3	0	0	1
Trial 4	0	1	1
Trial 5	0	1	0
List B	1	2	4
List A, Trial 6	1	2	0
Trial 7	0	5	1
Association errors			
List A, Trial 1	2	0	1
Trial 2	0	0	1
Trial 3	0	0	2
Trial 4	0	0	1
Trial 5	0	0	0
List B	1	0	4
List A, Trial 6	0	0	0
Trial 7	1	0	1

(Trial 7). They performed at similar levels as the controls on Trials 4, 5, 6 and List B (Figure 1). On the immediate recall component of the AVLT the long-term users made a significantly greater number of intrusion and association errors than the controls. They also made more errors in list B, although an inferential statistical analysis was not applied to the data (Table 2).

The significantly lower recall rates and higher number of errors demonstrated by both Ecstasy groups on Trial 1 may be associated with a deficit in 'supraspan', or rather the attentional processes related to the acquisition of information prior to storage. Similarly, list B also involved initial mnemonic processes on a new word list; however, unlike Trial 1, list B assessed participants' supraspan ability immediately following learning. Although List B produced no significant group recall differences, a trend was apparent whereby polydrug users recalled slightly more words than the long-term and short-term Ecstasy users (Figure 1). Long-term users also displayed a higher number of combined errors than the other two groups. The less robust finding in the memory scores may reflect the fact that the previous presentation of five list A trials interfered with the recall ability of the control group (proactive inhibition) but not that of the long-term users, because of initial acquisition problems. This is shown by the fact that the controls scored several points lower on the list B trials than on Trial 1, whereas both groups of Ecstasy users scored equally as low in both trial conditions.

Differences in memory score between the two groups of Ecstasy users were shown only on Trial 2, and correlational analysis indicated that this could have been due to the use of other drugs. However, it is important to note that the trend in means indicated that long-term users scored lower than short-term users on all trials except for trials 5 and 6. Furthermore, long-term users made many more combined errors (intrusion and association) than short-term users on the first four trials of the immediate recall component of the AVLT, as well as on list B. A high number of intrusion errors is usually associated with confabulation, which is often interpreted as a basic failure of memory control processes, or more specifically an inability to accurately evaluate any retrieved information (Burgess and Shallice, 1996). High levels of confabulation are predominantly reported after frontal rather than posterior cortical lesions (Stuss and Benson, 1984; Mayers and Daum, 1997). An increase in association errors is indicative of retrieval problems such as 'tip-of-the-tongue' syndrome, where participants reveal that they know the correct word but are unable to actually recall it (Brown and McNeill, 1966).

Our overall findings are consistent with previous research. On the Verbal Learning and Memory Test (a German standardised equivalent of the AVLT), Gouzoulis-Mayfrank *et al.* (2000) found that Ecstasy/cannabis users recalled significantly fewer words than non-user controls following the first presentation. These users also required more repetitions in order to learn the information, compared with both a cannabis control group and a non-user control group. Immediate recall was associated with cumulative lifetime consumption of the drug. The Ecstasy/cannabis group recalled significantly fewer words than non-users immediately following the presentation of a second 'intrusion' list. In contrast, data from the current study indicated that users showed no recall impairment on Trial 6.

Imaging studies have associated reduced verbal memory performance on the AVLT (and analogous tasks) with modulations of the serotonin system. Reduced performance on the Californian Verbal Learning Task has been associated with a reduction in neocortical serotonin transporter sites (Semple *et al.*, 1999), and poorer recall on the AVLT with an up-regulation of 5-HT receptor density in the occipital cortex (Reneman *et al.*, 2000).

The role of other drugs must not be discounted when considering the implications of the current data. It is possible that the concomitant use of other legal or illicit drugs may have contributed to the deficits in

verbal memory shown in the current study. Various studies have highlighted the fact that the combined use of Ecstasy and cannabis may be responsible for some of the cognitive problems previously seen in Ecstasy users (Croft *et al.*, 2001; Rodgers, 2000). In relation to this, when cannabis (and other drugs) were used as a covariate in the present study, all previously significant group differences remained significant. It is also important to note that the polydrug controls and the short-term Ecstasy users showed similar drug profiles (with the exception of Ecstasy use), despite significant differences in recall and confabulation. However, due to the fact that assessing the use of Ecstasy alone remains a complex issue and that other drugs may influence its toxic effects, data from this study should be regarded as reflecting a profile of Ecstasy polydrug users who consume Ecstasy as a drug of preference.

Other methodological caveats include the fact that no biological assays were taken in order to establish dosage consumed of any drug. Data were therefore reliant solely upon participants' self-report. Attempts were made, however, to improve the accuracy of self-report by means of an informal interview with the participants where they were encouraged to think carefully about their patterns of use over various time periods.

In relation to the original hypothesis, unimpaired performance on Trials 4, 5 and 6 indicate that at least some of the processes needed to acquire verbal information are still intact. However, the Ecstasy users required repeated presentation on these trials in order to achieve control levels. This suggests that verbal learning problems are associated more with deficits in storage and/or retrieval than capacity per se. Impaired delayed recall also suggests that once the material is 'learnt' problems regarding either storage or retrieval prevent access to the information at a later stage. This is consistent with other findings (Morgan, 1999; Parrott *et al.*, 1998).

In relation to working memory, although Ecstasy users did not demonstrate proactive or retroactive interference, long-term users did produce higher levels overall of confabulation than the controls (Table 2). This indicates the possibility of selective executive problems occurring with heavier use of the drug. The appearance of executive problems in heavier users is also consistent with previous research (Wareing *et al.*, 2000; Morgan, 2000).

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